IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ALLERGAN, INC., **Plaintiff,** **v.** **FAMY CARE LIMITED,** **Defendant.**	**Civil Action No. 2:16-cv-401** **JURY TRIAL DEMANDED**

ALLERGAN, INC.'S COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Allergan, Inc. ("Allergan" or "Plaintiff"), for its Complaint against Defendant Famy Care Limited ("Famy Care") by its attorneys, alleges as follows:

The Nature of the Action

1. This is an action for infringement of United States Patent Nos. 8,629,111 ("the '111 Patent"), 8,633,162 ("the '162 Patent"), 8,642,556 ("the '556 Patent"), 8,648,048 ("the '048 Patent"), 8,685,930 ("the '930 Patent"), and 9,248,191 ("the '191 Patent) under the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*, relating to Allergan's treatment for chronic dry eye, Restasis®.

2. This is also an action under 35 U.S.C. §§ 2201-02 for a declaratory judgment of infringement of the '111, '556, and '930 Patents under 35 U.S.C. § 271 (a), (b), and (c), and for a declaratory judgment of infringement of the '162, '048, and '191 Patents under 35 U.S.C. § 271 (b) and (c).

The Parties

3. Allergan is a corporation organized and existing under the laws of the State of Delaware with a place of business at 2525 Dupont Drive, Irvine, California 92612.

4. Allergan operates a facility in Waco, Texas where it manufactures and distributes numerous pharmaceutical products, including RESTASIS® (cyclosporine ophthalmic emulsion, 0.05%). Allergan coordinates the nationwide distribution of RESTASIS® from Texas. Allergan employs over 800 individuals in Texas, more than in any other state except California.

5. On information and belief, Famy Care is organized and exists under the laws of the Republic of India and has a principal place of business at 3rd Floor, Brady House, 12/14, Veer Nariman Road, Fort, Mumbai – 400 001, Maharashtra, India.

6. On its Paragraph IV Notification, Famy Care lists its attorney, William Rakoczy as its agent in the United States authorized to accept service of process. On information and belief, Famy Care has no physical location in the United States.

Venue and Jurisdiction

7. This action arises under the patent laws of the United States of America, 35 U.S.C. § 1, *et seq.* This Court has subject matter jurisdiction over the action under 28 U.S.C. §§ 1331 and 1338.

8. This Court has personal jurisdiction over Famy Care by virtue of its systematic and continuous contact with this jurisdiction, as alleged herein, and because of the injury to Allergan in this forum arising from Famy Care's ANDA filing and the causes of action Allergan raises, as alleged herein. *See Acorda Therapeutics Inc. et al. v. Mylan Pharmaceuticals Inc. et al.*, No. 2015-1456 (Fed. Cir. March 18, 2016).

9. Alternatively, if this Court does not have jurisdiction over Famy Care because of its contacts with this jurisdiction as described below, this Court has personal jurisdiction over Famy Care under Federal Rule of Civil Procedure 4(k)(2).

10. On information and belief, Famy Care submitted ANDA No. 208469 under section 505(j) of the FDCA, 21 U.S.C. § 355(j), seeking FDA approval to engage in the commercial manufacture, use, importation, sale, or offer for sale of Cyclosporine Ophthalmic Emulsion, 0.05%, a generic version of Allergan's RESTASIS® product.

11. On information and belief, Famy Care is in the business of researching and developing generic drug products.

12. On information and belief, Famy Care has engaged in continuous and systematic contacts with the United States by, among other things, entering into an exclusive partnership with Mylan, Inc. that dates back to 2008 to file ANDAs for generic contraceptive products and to supply such products to customers in the United States. *See* Exhibit 1.

13. On information and belief, in the United States, Famy Care and Mylan Inc. have a portfolio of 12 approved products. As of November 2015, Famy Care and Mylan Inc. had ANDAs for 30 drugs pending the approval of the FDA. *See* Exhibit 1.

14. On information and belief, Famy Care partners with Mylan Inc. for the purposes of marketing, selling, and distributing the generic drug products that Famy Care develops throughout the United States, including in this judicial district.

15. On information, and belief, Mylan Pharmaceuticals is an agent of Mylan Inc. and works in active concert with Mylan Inc. to market, sell, and distribute pharmaceutical products.

16. On information and belief, Mylan Pharmaceuticals is a licensed drug distributor of prescription drugs sold in the State of Texas.

17. On information and belief, Mylan Pharmaceuticals is actively registered with the Texas Secretary of State to conduct business in Texas.

18. On information and belief, Mylan Pharmaceuticals has a registered agent in Texas located at 211 East 7th Street, Suite 620, Austin Texas 78701-3218.

19. On information and belief, Mylan Inc. markets and sells numerous generic drugs in Texas. On information and belief, since 2014 Mylan Inc. has sold over $1.3 billion worth of products in Texas, over $460 million of which were sold in this judicial district.

20. Texas is the second largest market for prescription drugs in the United States and thus a lucrative target for sale of Famy Care's proposed Cyclosporine Ophthalmic Emulsion, 0.05% described in ANDA No. 208469.

21. In view of the lucrative Texas market for generic RESTASIS®, on information and belief, Famy Care knows and intends that its proposed Cyclosporine Ophthalmic Emulsion, 0.05% described in ANDA No. 208469 will be distributed and sold in Texas, including through the extensive distribution networks established by Famy Care's distribution partner, Mylan Inc. and/or Mylan Pharmaceuticals.

22. On information and belief, Famy Care knows and intends that sales of its proposed Cyclosporine Ophthalmic Emulsion, 0.05% described in ANDA No. 208469 will displace sales of Allergan's RESTASIS® product causing injury to Allergan in Texas.

23. Venue is proper in this Court under 28 U.S.C. §§ 1391(c) and 1400(b).

Factual Background

A. Patents-In-Suit

1. U.S. Patent No. 8,629,111

24. On January 14, 2014, the ’111 Patent, titled “Methods of Providing Therapeutic Effects Using Cyclosporin Components,” was duly and legally issued by the United States Patent and Trademark Office (“USPTO”) to inventors Andrew Acheampong, Diane D. Tang-Liu, James N. Chang, and David F. Power. A true and correct copy of the ’111 Patent is attached to this complaint as Exhibit 2.

25. Allergan, as assignee, owns the entire right, title, and interest in the ’111 Patent.

26. Allergan is the holder of approved New Drug Application (“NDA”) No. 50-790 for Cyclosporine Ophthalmic Emulsion, 0.05%, sold under the RESTASIS® trademark.

27. The ’111 Patent is listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the “Orange Book”) for RESTASIS®.

28. RESTASIS® and/or methods of using RESTASIS® are covered by at least one claim of the ’111 Patent.

2. U.S. Patent No. 8,633,162

29. On January 21, 2014, the ’162 Patent, titled “Methods of Providing Therapeutic Effects Using Cyclosporin Components,” was duly and legally issued by the USPTO to inventors Andrew Acheampong, Diane D. Tang-Liu, James N. Chang, and David F. Power. A true and correct copy of the ’162 Patent is attached to this complaint as Exhibit 3.

30. Allergan, as assignee, owns the entire right, title, and interest in the ’162 Patent.

31. Allergan is the holder of approved New Drug Application (“NDA”) No. 50-790 for Cyclosporine Ophthalmic Emulsion, 0.05%, sold under the RESTASIS® trademark.

32. The ’162 Patent is listed in the Orange Book for RESTASIS®.

33. RESTASIS® and/or methods of using RESTASIS® are covered by at least one claim of the ’162 Patent.

3. U.S. Patent No. 8,642,556

34. On February 4, 2014, the ’556 Patent, titled “Methods of Providing Therapeutic Effects Using Cyclosporin Components,” was duly and legally issued by the USPTO to inventors Andrew Acheampong, Diane D. Tang-Liu, James N. Chang, and David F. Power. A true and correct copy of the ’556 Patent is attached to this complaint as Exhibit 4.

35. Allergan, as assignee, owns the entire right, title, and interest in the ’556 Patent.

36. Allergan is the holder of approved New Drug Application (“NDA”) No. 50-790 for Cyclosporine Ophthalmic Emulsion, 0.05%, sold under the RESTASIS® trademark.

37. The ’556 Patent is listed in the Orange Book for RESTASIS®.

38. RESTASIS® and/or methods of using RESTASIS® are covered by at least one claim of the ’556 Patent.

4. U.S. Patent No. 8,648,048

39. On February 11, 2014, the ’048 Patent, titled “Methods of Providing Therapeutic Effects Using Cyclosporin Components,” was duly and legally issued by the USPTO to inventors Andrew Acheampong, Diane D. Tang-Liu, James N. Chang, and David F. Power. A true and correct copy of the ’048 Patent is attached to this complaint as Exhibit 5.

40. Allergan, as assignee, owns the entire right, title, and interest in the ’048 Patent.

41. Allergan is the holder of approved New Drug Application (“NDA”) No. 50-790 for Cyclosporine Ophthalmic Emulsion, 0.05%, sold under the RESTASIS® trademark.

42. The ’048 Patent is listed in the Orange Book for RESTASIS®.

43. RESTASIS® and/or methods of using RESTASIS® are covered by at least one claim of the ’048 Patent.

5. U.S. Patent No. 8,685,930

44. On April 1, 2014, the ’930 Patent, titled “Methods of Providing Therapeutic Effects Using Cyclosporin Components,” was duly and legally issued by the USPTO to inventors Andrew Acheampong, Diane D. Tang-Liu, James N. Chang, and David F. Power. A true and correct copy of the ’930 Patent is attached to this complaint as Exhibit 6.

45. Allergan, as assignee, owns the entire right, title, and interest in the ’930 Patent.

46. Allergan is the holder of approved New Drug Application (“NDA”) No. 50-790 for Cyclosporine Ophthalmic Emulsion, 0.05%, sold under the RESTASIS® trademark.

47. The ’930 Patent is listed in the Orange Book for RESTASIS®.

48. RESTASIS® and/or methods of using RESTASIS® are covered by at least one claim of the ’930 Patent.

6. U.S. Patent No. 9,248,191

49. On February 2, 2016, the ’191 Patent, titled "Methods of Providing Therapeutic Effects Using Cyclosporin Components," was duly and legally issued by the USPTO to inventors Andrew Acheampong, Diane D. Tang-Liu, James N. Chang, and David F. Power. A true and correct copy of the ’191 Patent is attached to this complaint as Exhibit 7.

50. Allergan, as assignee, owns the entire right, title, and interest in the ’191 Patent.

51. Allergan is the holder of approved New Drug Application ("NDA") No. 50-790 for Cyclosporine Ophthalmic Emulsion, 0.05%, sold under the RESTASIS® trademark.

52. The ’191 Patent is listed in the Orange Book for RESTASIS®.

53. RESTASIS® and/or methods of using RESTASIS® are covered by at least one claim of the ’191 Patent.

B. Acts Giving Rise to This Action

54. On information and belief, Famy Care submitted ANDA No. 208469 to the FDA under section 505(j) of the FDCA, seeking FDA approval to engage in the commercial manufacture, use, importation, sale, or offer for sale of Cyclosporine Ophthalmic Emulsion, 0.05%, a generic version of Allergan’s RESTASIS® product.

55. On information and belief, pursuant to § 505(j)(2)(A)(vii)(IV) of the FDCA, Famy Care included with its ANDA No. 208469 a Paragraph IV certification alleging that the claims of patents listed in the Orange Book as covering RESTASIS® are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Famy Care’s Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469. Plaintiff received written notification of ANDA No. 208469 and its § 505(j)(2)(A)(vii)(IV) allegations with respect to the ’111, ’162, ’556, ’048, ’930, and ’191 patents on or about March 1, 2016.

56. On information and belief, the FDA has not yet approved Famy Care’s ANDA No. 208469.

57. On information and belief, Famy Care has made, and continues to make, substantial preparation in the United States to manufacture, offer to sell, sell, and/or import a generic version of Allergan’s RESTASIS® product before expiration of the patents-in-suit.

58. On information and belief, Famy Care continues to seek approval of ANDA No. 208469 from the FDA and intends to continue in the commercial manufacture, marketing, and sale of its proposed generic version of Allergan’s RESTASIS® product.

59. On information and belief, following FDA approval of its ANDA No. 208469, Famy Care will sell the approved generic version of Allergan's RESTASIS® product throughout the United States, including in Texas and this judicial district.

Count I
(Infringement of the '111 Patent Under 35 U.S.C. § 271(e)(2) by Famy Care's Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

60. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

61. Famy Care submitted ANDA No. 208469 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product throughout the United States. By submitting this application, Famy Care has committed an act of infringement of the '111 Patent under 35 U.S.C. § 271(e)(2)(A).

62. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care's proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will constitute an act of direct infringement of the '111 Patent.

63. On information and belief, Famy Care became aware of the '111 Patent no later than the date on which that patent was listed in the Orange Book.

64. On information and belief, Famy Care knows or should know that the commercial offer for sale and sale of Famy Care's proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, will constitute an act of induced infringement and will contribute to actual infringement of the '111 Patent.

65. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made for or especially adapted for an infringement of the '111 Patent, and is not a

staple article or commodity of commerce suitable for substantial non-infringing use, and that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively contribute to the actual infringement of the ’111 Patent.

66. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 in violation of Allergan’s patent rights will cause harm to Allergan for which damages are inadequate.

Count II
(Declaratory Judgment of Infringement of the ’111 Patent Under 35 U.S.C. § 271(a) by Famy Care)

67. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

68. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

69. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

70. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will constitute an act of direct infringement of one or more claims of the ’111 Patent.

71. On information and belief, Famy Care will engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 immediately and imminently upon approval of ANDA No. 208469.

72. The foregoing actions by Famy Care will constitute infringement of the ’111 Patent.

73. Famy Care will commit those acts of infringement without license or authorization.

74. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will infringe the ’111 Patent.

75. Unless Famy Care is enjoined from infringing the ’111 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

Count III
(Declaratory Judgment of Infringement of the ’111 Patent Under 35 U.S.C. § 271(b) and (c) by Famy Care’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

76. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

77. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

78. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

79. Famy Care has actual knowledge of the ’111 Patent.

80. On information and belief, Famy Care became aware of the ’111 Patent no later than the date on which that patent was listed in the Orange Book.

81. On information and belief, Famy Care has acted with full knowledge of the ’111 Patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’111 Patent.

82. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will induce the actual infringement of the ’111 Patent.

83. On information and belief, Famy Care knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively induce the actual infringement of the ’111 Patent.

84. On information and belief, Famy Care will encourage another’s infringement of the ’111 Patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which is covered by certain claims of the ’111 Patent.

85. Famy Care’s acts of infringement will be done with knowledge of the ’111 Patent and with the intent to encourage infringement.

86. The foregoing actions by Famy Care will constitute active inducement of infringement of the ’111 Patent.

87. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made or especially adapted for use in an infringement of the ’111 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

88. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product will contribute to the actual infringement of the '111 Patent.

89. On information and belief, Famy Care knows or should know that its offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the '111 Patent.

90. The foregoing actions by Famy Care will constitute contributory infringement of the '111 Patent.

91. On information and belief, Famy Care intends to, and will, actively induce and contribute to the infringement of the '111 Patent when ANDA No. 208469 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

92. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will induce and/or contribute to the infringement of the '111 Patent.

93. The commercial manufacture, use, offer for sale, sale and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which will actively induce and/or contribute to infringement of the '111 Patent, in violation of Allergan's patent rights, will cause harm to Allergan for which damages are inadequate.

94. Unless Famy Care is enjoined from actively inducing and contributing to the infringement of the ’111 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

95. On information and belief, despite having actual notice of the ’111 Patent, Famy Care continues to willfully, wantonly, and deliberately prepare to actively induce and/or contribute to infringement of the ’111 Patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Count IV
(Infringement of the ’162 Patent Under 35 U.S.C. § 271(e)(2) by Famy Care’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

96. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

97. Famy Care submitted ANDA No. 208469 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product throughout the United States. By submitting this application, Famy Care has committed an act of infringement of the ’162 Patent under 35 U.S.C. § 271(e)(2)(A).

98. On information and belief, Famy Care became aware of the ’162 Patent no later than the date on which that patent was listed in the Orange Book.

99. On information and belief, Famy Care knows or should know that the commercial offer for sale and sale of Famy Care’s proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, will constitute an act of induced infringement and will contribute to actual infringement of the ’162 Patent.

100. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will

be especially made for or especially adapted for an infringement of the ’162 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively contribute to the actual infringement of the ’162 Patent.

101. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 in violation of Allergan’s patent rights will cause harm to Allergan for which damages are inadequate.

Count V
(Declaratory Judgment of Infringement of the ’162 Patent Under 35 U.S.C. § 271(b) and (c) by Famy Care’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

102. Allergan incorporates each of the preceding paragraphs as if fully set forth herein

103. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

104. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

105. Famy Care has actual knowledge of the ’162 Patent.

106. On information and belief, Famy Care became aware of the ’162 Patent no later than the date on which that patent was listed in the Orange Book.

107. On information and belief, Famy Care has acted with full knowledge of the ’162 Patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’162 Patent.

108. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will induce the actual infringement of the '162 Patent.

109. On information and belief, Famy Care knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively induce the actual infringement of the '162 Patent.

110. On information and belief, Famy Care will encourage another's infringement of the '162 Patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which is covered by certain claims of the '162 Patent.

111. Famy Care's acts of infringement will be done with knowledge of the '162 Patent and with the intent to encourage infringement.

112. The foregoing actions by Famy Care will constitute active inducement of infringement of the '162 Patent.

113. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made or especially adapted for use in an infringement of the '162 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

114. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the '162 Patent.

115. On information and belief, Famy Care knows or should know that its offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the ’162 Patent.

116. The foregoing actions by Famy Care will constitute contributory infringement of the ’162 Patent.

117. On information and belief, Famy Care intends to, and will, actively induce and contribute to the infringement of the ’162 Patent when ANDA No. 208469 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

118. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will induce and/or contribute to the infringement of the ’162 Patent.

119. The commercial manufacture, use, offer for sale, sale and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which will actively induce and/or contribute to infringement of the ’162 Patent, in violation of Allergan’s patent rights, will cause harm to Allergan for which damages are inadequate.

120. Unless Famy Care is enjoined from actively inducing and contributing to the infringement of the ’162 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

121. On information and belief, despite having actual notice of the ’162 Patent, Famy Care continues to willfully, wantonly, and deliberately prepare to actively induce and/or

contribute to infringement of the ’162 Patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Count VI
(Infringement of the ’556 Patent Under 35 U.S.C. § 271(e)(2) by InnoPharma’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

122. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

123. Famy Care submitted ANDA No. 208469 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product throughout the United States. By submitting this application, Famy Care has committed an act of infringement of the ’556 Patent under 35 U.S.C. § 271(e)(2)(A).

124. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will constitute an act of direct infringement of the ’556 Patent.

125. On information and belief, Famy Care became aware of the ’556 Patent no later than the date on which that patent was listed in the Orange Book.

126. On information and belief, Famy Care knows or should know that the commercial offer for sale and sale of Famy Care’s proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, will constitute an act of induced infringement and will contribute to actual infringement of the ’556 Patent.

127. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made for or especially adapted for an infringement of the ’556 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its

commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively contribute to the actual infringement of the ’556 Patent.

128. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 in violation of Allergan’s patent rights will cause harm to Allergan for which damages are inadequate.

Count VII
(Declaratory Judgment of Infringement of the ’556 Patent Under 35 U.S.C. § 271(a) by Famy Care)

129. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

130. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

131. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

132. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product will constitute an act of direct infringement of one or more claims of the ’556 Patent.

133. On information and belief, Famy Care will engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 immediately and imminently upon approval of ANDA No. 208469.

134. The foregoing actions by Famy Care will constitute infringement of the ’556 Patent.

135. Famy Care will commit those acts of infringement without license or authorization.

136. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will infringe the ’556 Patent.

137. Unless Famy Care is enjoined from infringing the ’556 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

Count VIII
(Declaratory Judgment of Infringement of the ’556 Patent Under 35 U.S.C. § 271(b) and (c) by Famy Care’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

138. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

139. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

140. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

141. Famy Care has actual knowledge of the ’556 Patent.

142. On information and belief, Famy Care became aware of the ’556 Patent no later than the date on which that patent was listed in the Orange Book.

143. On information and belief, Famy Care has acted with full knowledge of the ’556 Patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’556 Patent.

144. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product will induce the actual infringement of the ’556 Patent.

145. On information and belief, Famy Care knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively induce the actual infringement of the ’556 Patent.

146. On information and belief, Famy Care will encourage another’s infringement of the ’556 Patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which is covered by certain claims of the ’556 Patent.

147. Famy Care’s acts of infringement will be done with knowledge of the ’556 Patent and with the intent to encourage infringement.

148. The foregoing actions by Famy Care will constitute active inducement of infringement of the ’556 Patent.

149. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made or especially adapted for use in an infringement of the ’556 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

150. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the '556 Patent.

151. On information and belief, Famy Care knows or should know that its offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the '556 Patent.

152. The foregoing actions by Famy Care will constitute contributory infringement of the '556 Patent.

153. On information and belief, Famy Care intends to, and will, actively induce and contribute to the infringement of the '556 Patent when ANDA No. 208469 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

154. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will induce and/or contribute to the infringement of the '556 Patent.

155. The commercial manufacture, use, offer for sale, sale and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which will actively induce and/or contribute to infringement of the '556 Patent, in violation of Allergan's patent rights, will cause harm to Allergan for which damages are inadequate.

156. Unless Famy Care is enjoined from actively inducing and contributing to the infringement of the ’556 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

157. On information and belief, despite having actual notice of the ’556 Patent, Famy Care continues to willfully, wantonly, and deliberately prepare to actively induce and/or contribute to infringement of the ’556 Patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Count IX
(Infringement of the ’048 Patent Under 35 U.S.C. § 271(e)(2) by Famy Care’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

158. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

159. Famy Care submitted ANDA No. 208469 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product throughout the United States. By submitting this application, Famy Care has committed an act of infringement of the ’048 Patent under 35 U.S.C. § 271(e)(2)(A).

160. On information and belief, Famy Care became aware of the ’048 Patent no later than the date on which that patent was listed in the Orange Book.

161. On information and belief, Famy Care knows or should know that the commercial offer for sale and sale of Famy Care’s proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, will constitute an act of induced infringement and will contribute to actual infringement of the ’048 Patent.

162. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product will be especially made for or

especially adapted for an infringement of the ’048 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively contribute to the actual infringement of the ’048 Patent.

163. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 in violation of Allergan’s patent rights will cause harm to Allergan for which damages are inadequate.

Count X
(Declaratory Judgment of Infringement of the ’048 Patent Under 35 U.S.C. § 271(b) and (c) by Famy Care’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

164. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

165. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

166. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

167. Famy Care has actual knowledge of the ’048 Patent.

168. On information and belief, Famy Care became aware of the ’048 Patent no later than the date on which that patent was listed in the Orange Book.

169. On information and belief, Famy Care has acted with full knowledge of the ’048 Patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’048 Patent.

170. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will induce the actual infringement of the '048 Patent.

171. On information and belief, Famy Care knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively induce the actual infringement of the '048 Patent.

172. On information and belief, Famy Care will encourage another's infringement of the '048 Patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which is covered by certain claims of the '048 Patent.

173. Famy Care's acts of infringement will be done with knowledge of the '048 Patent and with the intent to encourage infringement.

174. The foregoing actions by Famy Care will constitute active inducement of infringement of the '048 Patent.

175. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made or especially adapted for use in an infringement of the '048 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

176. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the '048 Patent.

177. On information and belief, Famy Care knows or should know that its offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the ’048 Patent.

178. The foregoing actions by Famy Care will constitute contributory infringement of the ’048 Patent.

179. On information and belief, Famy Care intends to, and will, actively induce and contribute to the infringement of the ’048 Patent when ANDA No. 208469 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

180. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will induce and/or contribute to the infringement of the ’048 Patent.

181. The commercial manufacture, use, offer for sale, sale and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which will actively induce and/or contribute to infringement of the ’048 Patent, in violation of Allergan’s patent rights, will cause harm to Allergan for which damages are inadequate.

182. Unless Famy Care is enjoined from actively inducing and contributing to the infringement of the ’048 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

183. On information and belief, despite having actual notice of the ’048 Patent, Famy Care continues to willfully, wantonly, and deliberately prepare to actively induce and/or

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contribute to infringement of the ’048 Patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Count XI
(Infringement of the ’930 Patent Under 35 U.S.C. § 271(e)(2) by Famy Care’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

184. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

185. Famy Care submitted ANDA No. 208469 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product throughout the United States. By submitting this application, Famy Care has committed an act of infringement of the ’930 Patent under 35 U.S.C. § 271(e)(2)(A).

186. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will constitute an act of direct infringement of the ’930 Patent.

187. On information and belief, Famy Care became aware of the ’930 Patent no later than the date on which that patent was listed in the Orange Book.

188. On information and belief, Famy Care knows or should know that the commercial offer for sale and sale of Famy Care’s proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, will constitute an act of induced infringement and will contribute to actual infringement of the ’930 Patent.

189. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made for or especially adapted for an infringement of the ’930 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its

commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively contribute to the actual infringement of the '930 Patent.

190. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 in violation of Allergan's patent rights will cause harm to Allergan for which damages are inadequate.

Count XII
(Declaratory Judgment of Infringement of the '930 Patent Under 35 U.S.C. § 271(a) by Famy Care)

191. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

192. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

193. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

194. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will constitute an act of direct infringement of one or more claims of the '930 Patent.

195. On information and belief, Famy Care will engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 immediately and imminently upon approval of ANDA No. 208469.

196. The foregoing actions by Famy Care will constitute infringement of the ’930 Patent.

197. Famy Care will commit those acts of infringement without license or authorization.

198. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will infringe the ’930 Patent.

199. Unless Famy Care is enjoined from infringing the ’930 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

Count XIII
(Declaratory Judgment of Infringement of the ’930 Patent Under 35 U.S.C. § 271(b) and (c) by Famy Care’s Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

200. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

201. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

202. There is an actual case or controversy such that the Court may entertain Allergan’s request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

203. Famy Care has actual knowledge of the ’930 Patent.

204. On information and belief, Famy Care became aware of the ’930 Patent no later than the date on which that patent was listed in the Orange Book.

205. On information and belief, Famy Care has acted with full knowledge of the ’930 Patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’930 Patent.

206. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will induce the actual infringement of the ’930 Patent.

207. On information and belief, Famy Care knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively induce the actual infringement of the ’930 Patent.

208. On information and belief, Famy Care will encourage another’s infringement of the ’930 Patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which is covered by certain claims of the ’930 Patent.

209. Famy Care’s acts of infringement will be done with knowledge of the ’930 Patent and with the intent to encourage infringement.

210. The foregoing actions by Famy Care will constitute active inducement of infringement of the ’930 Patent.

211. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made or especially adapted for use in an infringement of the ’930 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

212. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the '930 Patent.

213. On information and belief, Famy Care knows or should know that its offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the '930 Patent.

214. The foregoing actions by Famy Care will constitute contributory infringement of the '930 Patent.

215. On information and belief, Famy Care intends to, and will, actively induce and contribute to the infringement of the '930 Patent when ANDA No. 208469 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

216. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will induce and/or contribute to the infringement of the '930 Patent.

217. The commercial manufacture, use, offer for sale, sale and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which will actively induce and/or contribute to infringement of the '930 Patent, in violation of Allergan's patent rights, will cause harm to Allergan for which damages are inadequate.

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218. Unless Famy Care is enjoined from actively inducing and contributing to the infringement of the ’930 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

219. On information and belief, despite having actual notice of the ’930 Patent, Famy Care continues to willfully, wantonly, and deliberately prepare to actively induce and/or contribute to infringement of the ’930 Patent in disregard of Allergan’s rights, making this case exceptional and entitling Allergan to reasonable attorneys’ fees pursuant to 35 U.S.C. § 285.

Count XIV
(Infringement of the ’191 Patent Under 35 U.S.C. § 271(e)(2) by Famy Care's Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

220. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

221. Famy Care submitted ANDA No. 208469 to the FDA under section 505(j) of the FDCA to obtain approval to engage in the commercial manufacture, use, offer for sale, sale, or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product throughout the United States. By submitting this application, Famy Care has committed an act of infringement of the ’191 Patent under 35 U.S.C. § 271(e)(2)(A).

222. On information and belief, Famy Care became aware of the ’191 Patent no later than the date on which that patent was listed in the Orange Book.

223. On information and belief, Famy Care knows or should know that the commercial offer for sale and sale of Famy Care’s proposed Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, will constitute an act of induced infringement and will contribute to actual infringement of the ’191 Patent.

224. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will

be especially made for or especially adapted for an infringement of the ’191 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use, and that its commercial manufacture, use, offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively contribute to the actual infringement of the ’191 Patent.

225. The commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 in violation of Allergan's patent rights will cause harm to Allergan for which damages are inadequate.

Count LIV
(Declaratory Judgment of Infringement of the ’191 Patent Under 35 U.S.C. § 271(b) and (c) by Famy Care's Proposed Generic Cyclosporine Ophthalmic Emulsion, 0.05%)

226. Allergan incorporates each of the preceding paragraphs as if fully set forth herein.

227. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

228. There is an actual case or controversy such that the Court may entertain Allergan's request for declaratory relief consistent with Article III of the United States Constitution, and that actual case or controversy requires a declaration of rights by this Court.

229. Famy Care has actual knowledge of the ’191 Patent.

230. On information and belief, Famy Care became aware of the ’191 Patent no later than the date on which that patent was listed in the Orange Book.

231. On information and belief, Famy Care has acted with full knowledge of the ’191 Patent and without a reasonable basis for believing that it would not be liable for actively inducing or contributing to the infringement of the ’191 Patent.

232. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will induce the actual infringement of the ’191 Patent.

233. On information and belief, Famy Care knows or should know that its commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will actively induce the actual infringement of the ’191 Patent.

234. On information and belief, Famy Care will encourage another's infringement of the ’191 Patent by and through the commercial manufacture, use, sale, offer for sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which is covered by certain claims of the ’191 Patent.

235. Famy Care's acts of infringement will be done with knowledge of the ’191 Patent and with the intent to encourage infringement.

236. The foregoing actions by Famy Care will constitute active inducement of infringement of the ’191 Patent.

237. On information and belief, Famy Care knows or should know that its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will be especially made or especially adapted for use in an infringement of the ’191 Patent, and is not a staple article or commodity of commerce suitable for substantial non-infringing use.

238. The commercial manufacture, use, sale, offer for sale, and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the ’191 Patent.

239. On information and belief, Famy Care knows or should know that its offer for sale, sale, and/or importation of its proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 will contribute to the actual infringement of the ’191 Patent.

240. The foregoing actions by Famy Care will constitute contributory infringement of the ’191 Patent.

241. On information and belief, Famy Care intends to, and will, actively induce and contribute to the infringement of the ’191 Patent when ANDA No. 208469 is approved, and plan and intend to, and will, do so immediately and imminently upon approval.

242. Allergan is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469 by Famy Care will induce and/or contribute to the infringement of the ’191 Patent.

243. The commercial manufacture, use, offer for sale, sale and/or importation of Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, which will actively induce and/or contribute to infringement of the ’191 Patent, in violation of Allergan's patent rights, will cause harm to Allergan for which damages are inadequate.

244. Unless Famy Care is enjoined from actively inducing and contributing to the infringement of the ’191 Patent, Allergan will suffer irreparable injury for which damages are an inadequate remedy.

245. On information and belief, despite having actual notice of the ’191 Patent, Famy Care continues to willfully, wantonly, and deliberately prepare to actively induce and/or

contribute to infringement of the ’191 Patent in disregard of Allergan's rights, making this case exceptional and entitling Allergan to reasonable attorneys' fees pursuant to 35 U.S.C. § 285.

Jury Trial Demand

Pursuant to Federal Rule of Civil Procedure 38(b), Allergan hereby demands a trial by jury of all issues so triable.

Prayer for Relief

Allergan respectfully prays for the following relief:

1. A finding that the ’111, ’162, ’556, ’048, ’930, and ’191 Patents are valid and enforceable;

2. That a judgment be entered that Famy Care has infringed the ’111, ’162, ’556, ’048, ’930, and ’191 Patents under 35 U.S.C. § 271(e)(2)(A) by submitting an ANDA under Section 505(j) of the FDCA;

3. That a declaration be issued under 28 U.S.C. § 2201 that if Famy Care, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf engage in the commercial manufacture, use, offer for sale, sale and/or importation of Famy Care’s proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, it will constitute an act of infringement of the ’111, ’556, and ’930 Patents under 35 U.S.C. § 271(a), (b), and (c);

4. That a declaration be issued under 28 U.S.C. § 2201 that if Famy Care, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with them or acting on their behalf engage in the commercial manufacture, use, offer for sale, sale and/or importation of

Famy Care's proposed generic Cyclosporine Ophthalmic Emulsion, 0.05% product described in ANDA No. 208469, it will constitute an act of infringement of the '162, '048, and '191 Patents under 35 U.S.C. § 271(b) and (c);

5. That an order be issued under 35 U.S.C. § 271(e)(4)(A) that the effective date of any FDA approval of Famy Care's ANDA shall be a date which is not earlier than the latest expiration date of the '111, '162, '556, '048, '930, and '191 Patents, including any extensions or periods of exclusivity;

6. That an injunction be issued under 35 U.S.C. § 271(e)(4)(B) permanently enjoining Famy Care, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in active concert or participation with it or acting on its behalf, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product covered by the '111, '162, '556, '048, '930, and '191 Patents;

7. If Famy Care attempts to engage in the commercial manufacture, use, offer to sell, sale, or importation of Famy Care's generic product disclosed in its ANDA prior to the expiration of the '111, '162, '556, '048, '930, and '191 Patents, including any extensions or periods of exclusivity, a preliminary injunction be entered enjoining such conduct;

8. If Famy Care attempts to engage in the commercial manufacture, use, offer to sell, sale, or importation of Famy Care's generic product disclosed in its ANDA prior to the expiration of the '111, '162, '556, '048, '930, and '191 Patents, including any extensions or periods of exclusivity, judgment awarding Allergan damages resulting from such infringement under 35 U.S.C. § 271(e)(4)(C), increased to treble the amount found or assessed together with interest pursuant to 35 U.S.C. § 284;

9. An accounting for any infringing sales not presented at trial and an award by the Court of any additional damages for any such infringing sales;

10. A finding that this action for infringement is an exceptional case under 35 U.S.C. § 285, and that Allergan be awarded reasonable attorneys' fees and costs; and

11. An award of any such other and further relief as the Court may deem just and proper.

Dated: April 12, 2016

Respectfully submitted,

FISH & RICHARDSON P.C.

By: /s/ Jonathan E. Singer by permission Wesley Hill

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COUNSEL FOR PLAINTIFF ALLERGAN, INC.

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS
Allergan, Inc.,

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Jonathan E. Singer, Fish & Richardson P.C., 60 S. 6th Street, Suite 3200, Minneapolis, MN 55402, Tel: (612) 335-5070

DEFENDANTS
Famy Care Limited

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury
- ❒ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ❒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ❒ 370 Other Fraud
- ❒ 371 Truth in Lending
- ❒ 380 Other Personal Property Damage
- ❒ 385 Property Damage Product Liability

CIVIL RIGHTS
- ❒ 440 Other Civil Rights
- ❒ 441 Voting
- ❒ 442 Employment
- ❒ 443 Housing/ Accommodations
- ❒ 445 Amer. w/Disabilities - Employment
- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ❒ 463 Alien Detainee
- ❒ 510 Motions to Vacate Sentence
- ❒ 530 General
- ❒ 535 Death Penalty

Other:
- ❒ 540 Mandamus & Other
- ❒ 550 Civil Rights
- ❒ 555 Prison Condition
- ❒ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ❒ 625 Drug Related Seizure of Property 21 USC 881
- ❒ 690 Other

LABOR
- ❒ 710 Fair Labor Standards Act
- ❒ 720 Labor/Management Relations
- ❒ 740 Railway Labor Act
- ❒ 751 Family and Medical Leave Act
- ❒ 790 Other Labor Litigation
- ❒ 791 Employee Retirement Income Security Act

IMMIGRATION
- ❒ 462 Naturalization Application
- ❒ 465 Other Immigration Actions

BANKRUPTCY
- ❒ 422 Appeal 28 USC 158
- ❒ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ❒ 820 Copyrights
- ☒ 830 Patent
- ❒ 840 Trademark

SOCIAL SECURITY
- ❒ 861 HIA (1395ff)
- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

FEDERAL TAX SUITS
- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ❒ 375 False Claims Act
- ❒ 400 State Reapportionment
- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
- ❒ 490 Cable/Sat TV
- ❒ 850 Securities/Commodities/ Exchange
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
- ❒ 893 Environmental Matters
- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

❒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. Sec. 271

Brief description of cause:
Patent Infringement

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☒ Yes ❒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE Hon. William C. Bryson DOCKET NUMBER 2:15-cv-01455

DATE
04/12/2016

SIGNATURE OF ATTORNEY OF RECORD
/s/ Jonathan E. Singer by permission Wesley Hill

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RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

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Exhibit 1

Business Standard

Mylan completes acquisition of Famy Care's female healthcare biz

Deal will allow Mylan to tap into the female contraceptive and healthcare segment in India

BS Reporter | Mumbai: November 20, 2015 Last Updated at 19:38 IST

Famy Care's Ahmedabad plant

US pharma major has completed its $750 million acquisition of female healthcare business of Famy Care.

The deal will allow Mylan to tap into the female contraceptive and healthcare segment in India. The deal was announced in February and it received a clearance from Cabinet Committee of Economic Affairs (CCEA) earlier this month.

The transaction brings Mylan a broad women's care portfolio, strong technical capabilities and dedicated hormone manufacturing, which, when combined with Mylan's expansive global commercial footprint and supply chain infrastructure, will create a leading women's healthcare franchise, the company announced today.

Mylan CEO Heather Bresch said "We look forward to building upon our existing commercial presence in emerging markets by leveraging our global supply chain and operational excellence to further accelerate our growth. This will include building upon our existing women's care portfolio in India and expanding our reach in support of Family Planning 2020, a global partnership that aims to enable 120 million more women an girls to use contraceptives by 2020.

Mylan, among the top five generic companies globally, has been expanding its presence in India for a while. It entered India in 2007, with a $730-million buyout of Matrix Laboratories. In 2013, it acquired the specialty injectables unit of Bengaluru-based Strides Arcolab for $1.75 billion.

Mylan and Famy Care have an exclusive partnership dating back to 2008, under which Famy Care develops and supplies over-the-counter (OTC) drugs to Mylan for distribution to customers in the US and a few other markets. In the US, Famy Care and Mylan have a portfolio of 12 approved products, with abbreviated new drug applications (ANDA) for 30 drugs pending the approval of the Food and Drug Administration (FDA).

Started in 1990 by Jyotiprasad Taparia, Famy Care is the third-largest maker of over-the-counter contraceptive pills and injectables and the largest producer of copper-Ts globally. Other major products from the company include rings for tubal ligation and condoms. Famy Care recorded a revenue of Rs 400 crore last year.

Exhibit 2

US008629111B2

(12) **United States Patent**
Acheampong et al.

(10) **Patent No.: US 8,629,111 B2**
(45) **Date of Patent: Jan. 14, 2014**

(54) **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS**

(71) Applicant: **Allergan, Inc.**, Irvine, CA (US)

(72) Inventors: **Andrew Acheampong**, Irvine, CA (US); **Diane D. Tang-Liu**, Las Vegas, NV (US); **James N. Chang**, Newport Beach, CA (US); **David F. Power**, Hubert, NC (US)

(73) Assignee: **Allergan, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/967,163**

(22) Filed: **Aug. 14, 2013**

(65) **Prior Publication Data**

US 2013/0331339 A1 Dec. 12, 2013

Related U.S. Application Data

(63) Continuation of application No. 13/961,828, filed on Aug. 7, 2013, which is a continuation of application No. 11/897,177, filed on Aug. 28, 2007, and a continuation of application No. 10/927,857, filed on Aug. 27, 2004, now abandoned.

(60) Provisional application No. 60/503,137, filed on Sep. 15, 2003.

(51) **Int. Cl.**
A61K 38/13 (2006.01)

(52) **U.S. Cl.**
USPC **514/20.5**

(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Marcela M Cordero Garcia
(74) *Attorney, Agent, or Firm* — Laura L. Wine; Joel B. German; Debra D. Condino

(57) **ABSTRACT**

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

27 Claims, No Drawings

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METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

RELATED APPLICATION

This application is a continuation of copending U.S. application Ser. No. 13/961,828 filed Aug. 7, 2013, which is a continuation of copending U.S. application Ser. No. 11/897,177, filed Aug. 28, 2007, which is a continuation of U.S. application Ser. No. 10/927,857, filed Aug. 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed Sep. 15, 2003, which are incorporated in their entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Pat. No. 5,474,979; Garst U.S. Pat. No. 6,254,860; and Garst U.S. Pat. No. 6,350,442, this disclosure of each of which is incorporated in its entirely herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease," Small et al, *J Ocul Pharmacol Ther,* 2002 October, 18(5):411-8; "Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs," Acheampong et al, *Curr Eye Res,* 1999 February, 18(2):91-103b; "Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes," Acheampong et al, *Adv Exp Med Biol,* 1998, 438:1001-4; "Preclinical safety studies of cyclosporine ophthalmic emulsion," Angelov et al, *Adv Exp Med Biol,* 1998, 438:991-5; "Cyclosporin & Emulsion & Eye," Stevenson et al, *Ophthalmology,* 2000 May, 107(5):967-74; and "Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group," Sall et al, *Ophthalmology,* 2000 April, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Pat. No. 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

SUMMARY OF THE INVENTION

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporine

is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can increase tear production in the eye. The treatment can further serve to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratisis, mucopurulent discharge and vascularization of the cornea.

Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of clyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

DETAILED DESCRIPTION

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or

animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

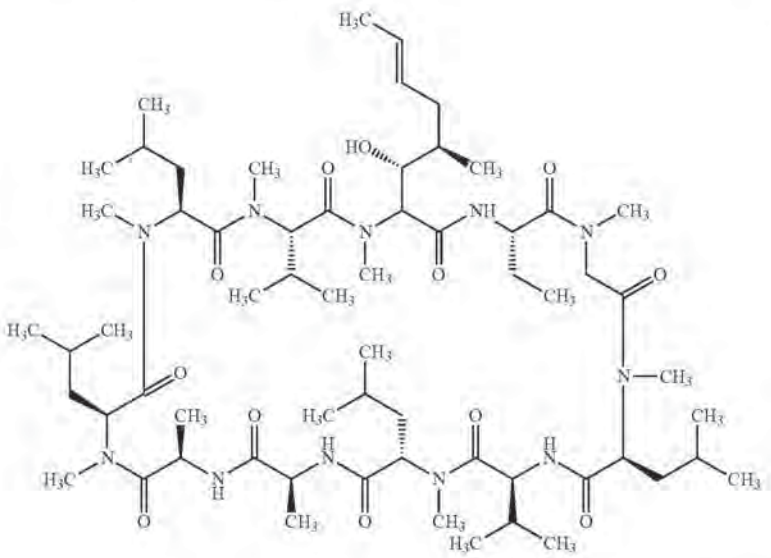
The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1×50 mm, 3 μm pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, Pa.). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

Formula 1



As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)^3-(4'-hydroxy-Me-Leu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)^3-(4'-hy-

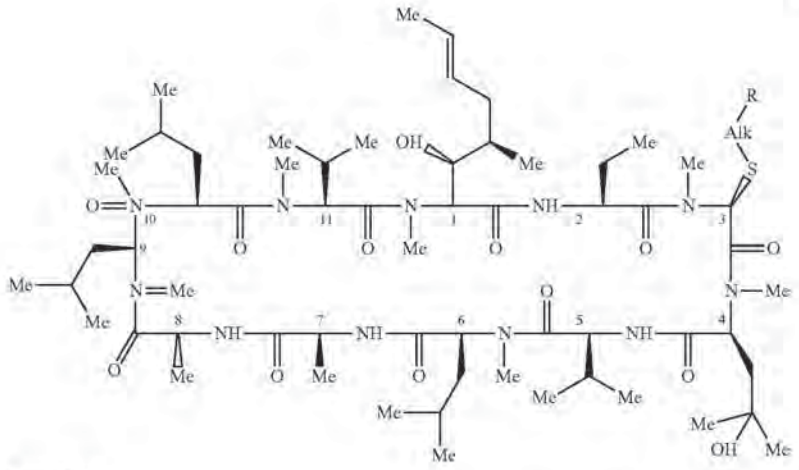
droxy-MeLeu)[4]-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)[3]-cyclosporin A derivatives described below.

These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, $—NR_1R_2$ or $N(R_3)C(CH_2)CNR_1R_2$; wherein R_1, R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy,

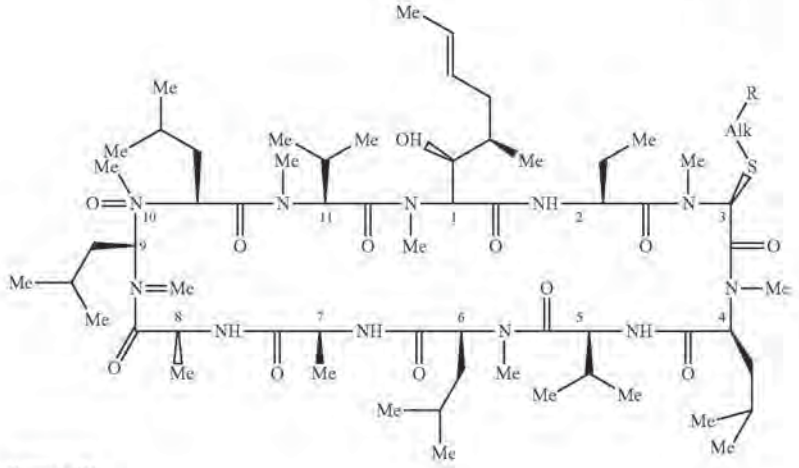
Formula II

(II)



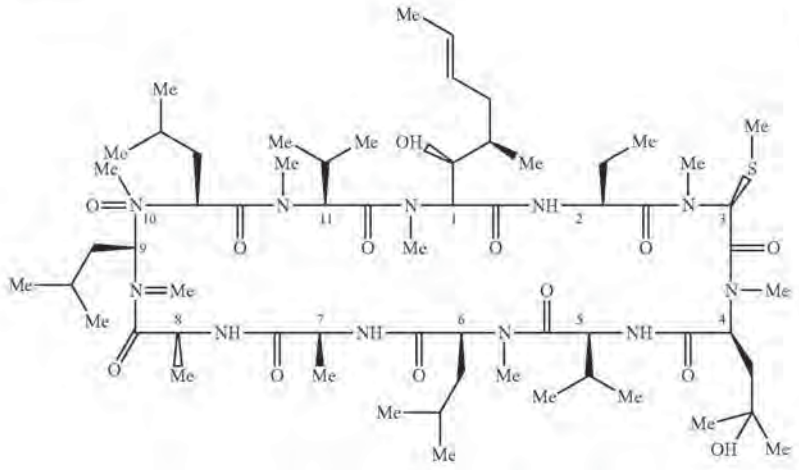
Formula III

(III)



Formula IV

(I)



alkoxycarbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR_1R_2 is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R_3 is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefiting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphoteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

metal carboxy methylcelluloses
metal carboxy methylhydroxyethylcelluloses
metal carboxy methylstarchs

metal carboxy methylhydroxyethylstarchs
hydrolyzed polyacrylamides and polyacrylonitriles
heparin
gucoaminoglycans
hyaluronic acid
chondroitin sulfate
dermatan sulfate
peptides and polypeptides
alginic acid
metal alginates
homopolymers and copolymers of one or more of:
acrylic and methacrylic acids
metal acrylates and methacrylates
vinylsulfonic acid
metal vinylsulfonate
amino acids, such as aspartic acid, glutamic acid and the like
metal salts of amino acids
p-styrenesulfonic acid
metal p-styrenesulfonate
2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magain-

ins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5% w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10° C. above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamicaly stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I wt %	Composition II wt %
Cyclosporin	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen ®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

What is claimed is:

1. A topical ophthalmic emulsion for treating an eye of a human comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight;

wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.

2. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

3. The topical ophthalmic emulsion of claim **2**, wherein the tonicity agent or the demulcent component is glycerine.

4. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion further comprises a buffer.

5. The topical ophthalmic emulsion of claim **4**, wherein the buffer is sodium hydroxide.

6. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

7. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

8. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

9. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight, water, and a buffer.

10. The topical ophthalmic emulsion of claim **9**, wherein the buffer is sodium hydroxide.

11. The topical ophthalmic emulsion of claim **1**, wherein, when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.

12. The topical ophthalmic emulsion of claim **6**, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

13. A topical ophthalmic emulsion for treating an eye of a human, wherein the topical ophthalmic emulsion comprises:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

a tonicity component or a demulcent component in an amount of about 2.2% by weight;

a buffer; and

water;

wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6 and wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.

14. The topical ophthalmic emulsion of claim **13**, wherein the buffer is sodium hydroxide.

15. The topical ophthalmic emulsion of claim **13**, wherein the tonicity component or the demulcent component is glycerine.

16. The topical ophthalmic emulsion of claim **13**, wherein, when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of the cyclosporin A.

17. The topical ophthalmic emulsion of claim **13**, wherein the topical ophthalmic emulsion is effective in treating keratoconjunctivitis sicca.

18. A topical ophthalmic emulsion for treating an eye of a human, the topical ophthalmic emulsion comprising:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water;

wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.

19. The topical ophthalmic emulsion of claim **18**, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

20. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion is therapeutically effective in treating dry eye.

21. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion is therapeutically effective in treating keratoconjunctivitis sicca.

22. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production.

23. The topical ophthalmic emulsion of claim **13**, wherein the topical ophthalmic emulsion is therapeutically effective in treating dry eye.

24. The topical ophthalmic emulsion of claim **13**, wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production.

25. The topical ophthalmic emulsion of claim **18**, wherein the topical ophthalmic emulsion is therapeutically effective in treating dry eye.

26. The topical ophthalmic emulsion of claim **18**, wherein the topical ophthalmic emulsion is therapeutically effective in treating keratoconjunctivitis sicca.

27. The topical ophthalmic emulsion of claim **18**, wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,629,111 B2
APPLICATION NO. : 13/967163
DATED : January 14, 2014
INVENTOR(S) : Andrew Acheampong et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page, item (45), under "Date of Patent", in column 2, line 1,
delete "January 14, 2014" and insert -- *January 14, 2014 --, therefor.
On the Title page, under "(*) Notice:", in column 1, line 4, above "(Item 21)"
insert -- This patent is subject to a terminal disclaimer. --.
On Title page 2, in column 2, under "OTHER PUBLICATIONS", line 25, delete "Pregnanolone" and insert -- Pregnenolone --, therefor.
On Title page 3, in column 1, under "OTHER PUBLICATIONS", line 7, delete "Muscosal" and insert -- Mucosal --, therefor.
On Title page 3, in column 1, under "OTHER PUBLICATIONS", line 22, delete "Pediatr" and insert -- Pediatric --, therefor.
On Title page 3, in column 1, under "OTHER PUBLICATIONS", line 43, delete "Polyocyethylene" and insert -- Polyoxyethylene --, therefor.

In the Specification

In column 1, line 34, delete "cyclosporin a" and insert -- cyclosporin A --, therefor.
In column 1, line 35, delete "cyclosporin a" and insert -- cyclosporin A --, therefor.
In column 2, line 62, delete "kerapoconjunctivitis," and insert -- keratoconjunctivitis, --, therefor.
In column 2, line 67, delete "cyclosporin" and insert -- cyclosporins --, therefor.
In column 3, line 1, delete "is as" and insert -- are as --, therefor.
In column 3, line 10, delete "keratisis" and insert -- keratitis --, therefor.
In column 3, line 23, delete "clyclosporin" and insert -- cyclosporin --, therefor.
In column 5, line 17, delete "kerapoconjunctivitis," and insert -- keratoconjunctivitis, --, therefor.

Signed and Sealed this
Eighth Day of July, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)

U.S. Pat. No. 8,629,111 B2

In column 6, line 10, delete "mobil" and insert -- mobile --, therefor.

In column 10, line 29, delete "amphorteric" and insert -- amphoteric --, therefor.

In column 11, line 4, delete "gucoaminoglycans" and insert -- glycosaminoglycans --, therefor.

In column 11, line 22, delete "methacryloyloxethylsulfonates" and

insert -- methacryloyloxyethylsulfonates --, therefor.

In column 11, line 23, delete "hydroxypropylsulonic" and insert -- hydroxypropylsulfonic --, therefor.

In column 14, lines 4-5, delete "thermodynamicaly" and insert -- thermodynamically --, therefor.

In column 14, line 22, delete "Cyclosporin" and insert -- Cyclosporin A --, therefor.

In column 14, line 25, delete "Premulen ®" and insert -- Pemulen® --, therefor.

Exhibit 3

US008633162B2

(12) United States Patent
Acheampong et al.

(10) Patent No.: US 8,633,162 B2
(45) Date of Patent: *Jan. 21, 2014

(54) **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/967,179**

(22) Filed: **Aug. 14, 2013**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 13/961,818, filed on Aug. 7, 2013, which is a continuation of application No. 11/897,177, filed on Aug. 28, 2007, which is a continuation of application No. 10/927,857, filed on Aug. 27, 2004, now abandoned.

(60) Provisional application No. 60/503,137, filed on Sep. 15, 2003.

(51) **Int. Cl.**
A61K 38/13 (2006.01)

(52) **U.S. Cl.**
USPC **514/20.5**

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1 % by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

24 Claims, No Drawings

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METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

RELATED APPLICATION

This application is a continuation of copending U.S. application Ser. No. 13/961,818 filed Aug. 7, 2013, which is a continuation of copending U.S. application Ser. No. 11/897,177, filed Aug. 28, 2007, which is a continuation of U.S. application Ser. No. 10/927,857, filed Aug. 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed Sep. 15, 2003, which are incorporated in their entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Pat. No. 5,474,979; Garst U.S. Pat. No. 6,254,860; and Garst U.S. Pat. No. 6,350,442, this disclosure of each of which is incorporated in its entirely herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "*Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease*," Small et al, *J Ocul Pharmacol Ther*, 2002 October, 18(5):411-8; "*Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs*," Acheampong et al, *Curr Eye Res*, 1999 February, 18(2):91-103b; "*Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes*," Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "*Preclinical safety studies of cyclosporine ophthalmic emulsion*," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5; "*Cyclosporin & Emulsion & Eye*," Stevenson et al, Ophthalmology, 2000 May, 107(5):967-74; and "*Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group*," Sall et al, *Ophthalmology*, 2000 April, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Pat. No. 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

SUMMARY OF THE INVENTION

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced.

In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective

to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of clyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

DETAILED DESCRIPTION

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art

cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

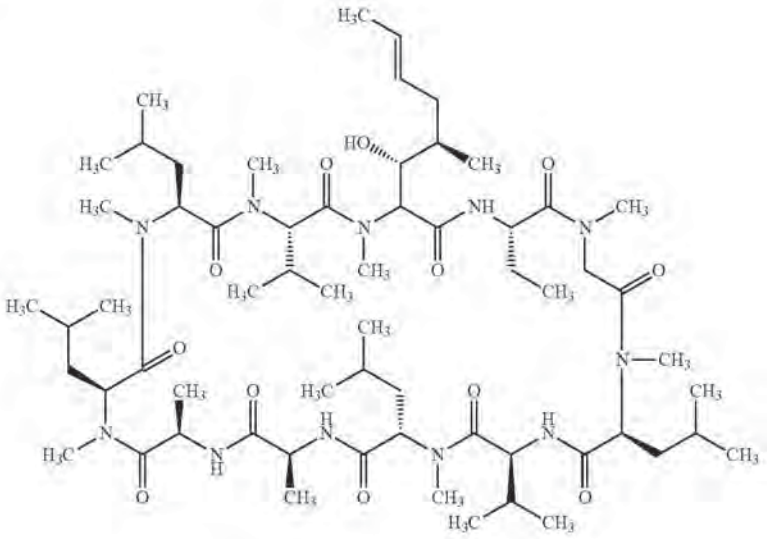
The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1×50 mm, 3 μm pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, Pa.). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

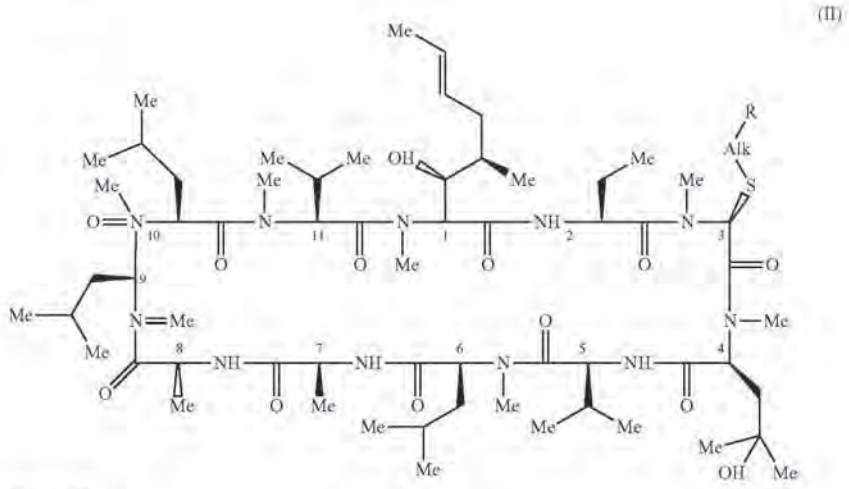
Formula I



As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)^3-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)^3-(4'-hydroxy-MeLeu)^4-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)^3-cyclosporin A derivatives described below.

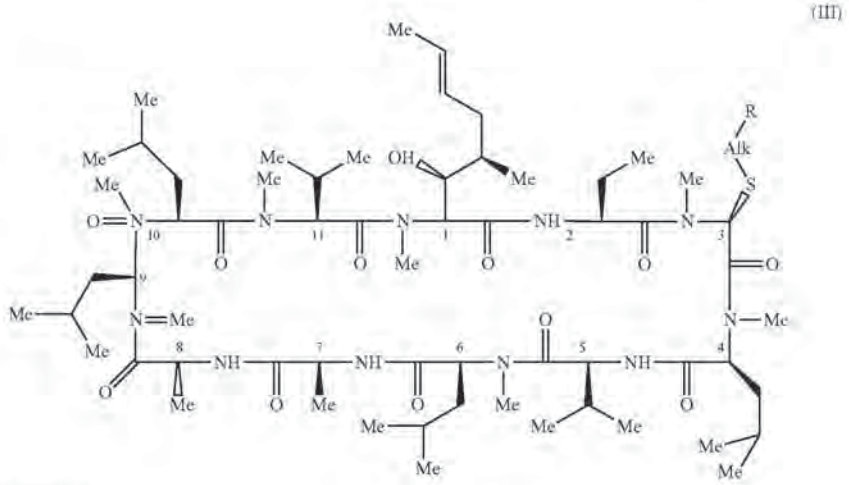
These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

Formula II



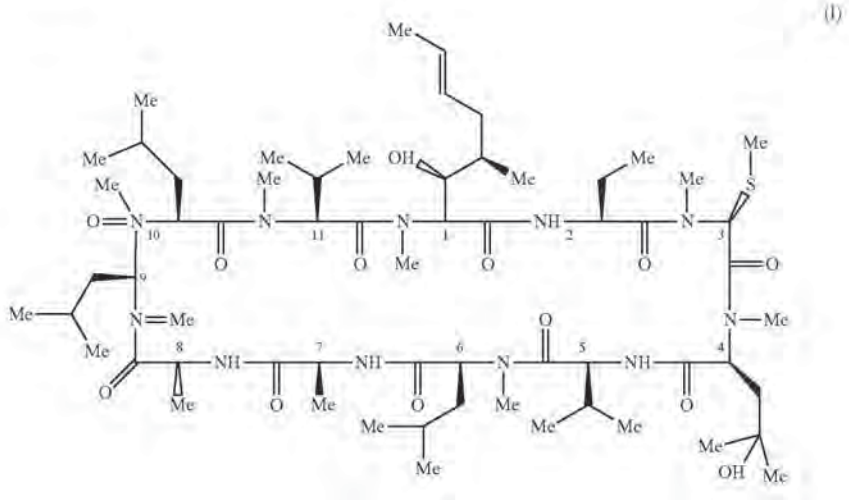
(II)

Formula III



(III)

Formula IV



(I)

wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, $—NR_1R_2$ or $N(R_3)—(CH_2)—NR_1R_2$; wherein R_1, R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxycarbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR_1R_2 is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R_3 is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphorteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

- metal carboxy methylcelluloses
- metal carboxy methylhydroxyethylcelluloses
- metal carboxy methylstarchs
- metal carboxy methylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- gucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- peptides and polypeptides
- alginic acid
- metal alginates
- homopolymers and copolymers of one or more of:
- acrylic and methacrylic acids
- metal acrylates and methacrylates
- vinylsulfonic acid
- metal vinylsulfonate
- amino acids, such as aspartic acid, glutamic acid and the like
- metal salts of amino acids
- p-styrenesulfonic acid
- metal p-styrenesulfonate
- 2-methacryloyloxyethylsulfonic acids
- metal 2-methacryloyloxethylsulfonates
- 3-methacryloyloxy-2-hydroxypropylsulonic acids
- metal 3-methacryloyloxy-2-hydroxypropylsulfonates
- 2-acrylamido-2-methylpropanesulfonic acids
- metal 2-acrylamido-2-methylpropanesulfonates
- allylsulfonic acid
- metal allylsulfonate and the like.

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by

International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5% w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10° C. above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter.

Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamicaly stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I wt %	Composition II wt %
Cyclosporin A	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen ®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for

example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

What is claimed is:

1. A method of treating dry eye disease, the method comprising topically administering to the eye of a human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is effective in treating dry eye disease.

2. The method of claim **1**, wherein the emulsion further comprises a tonicity agent or a demulcent component.

3. The method of claim **2**, wherein the tonicity agent or the demulcent component is glycerine.

4. The method of claim **1**, wherein the emulsion further comprises a buffer.

5. The method of claim **4**, wherein the buffer is sodium hydroxide.

6. The method of claim **1**, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

7. The method of claim **1**, wherein the emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

8. The method of claim **1**, wherein the emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

9. The method of claim **1**, wherein the emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

10. The method of claim **9**, wherein the buffer is sodium hydroxide.

11. The method of claim **1**, wherein, when the emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.

12. The method of claim **6**, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

13. The method of claim **1**, wherein the emulsion is as substantially therapeutically effective as a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

14. The method of claim **1**, wherein the emulsion achieves at least as much therapeutic effectiveness as a second emulsion administered to a human in need thereof a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

15. The method of claim **1**, wherein the emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compared to a second emulsion that contains only 50% as much castor oil.

16. The method of claim **1**, wherein the emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative to a second emulsion administered to a human in need thereof a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

17. The method of claim **16**, wherein the adverse events are side effects.

18. A method of reducing side effects in a human being treated for dry eye syndrome, the method comprising the step of topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

a tonicity component or a demulcent component in an amount of about 2.2% by weight;

a buffer; and

water;

wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

19. The method of claim **18**, wherein the buffer is sodium hydroxide.

20. The method of claim **18**, wherein the tonicity component or the demulcent component is glycerine.

21. The method of claim **18**, wherein, when the emulsion is administered to the eye of a human for treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A.

22. The method of claim **18**, wherein the emulsion is effective in treating dry eye disease.

23. A method of treating dry eye disease, the method comprising the step of topically administering to an eye of a human in need thereof an emulsion at a frequency of twice a day, the emulsion comprising:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water;

wherein the emulsion is effective in treating dry eye disease.

24. The method of claim **23**, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

* * * * *

Exhibit 4

US008642556B2

(12) **United States Patent**
Acheampong et al.

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(45) **Date of Patent: *Feb. 4, 2014**

(54) **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS**

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USPC **514/20.5**

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See application file for complete search history.

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(57) **ABSTRACT**

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

20 Claims, No Drawings

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METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

RELATED APPLICATION

This application is a continuation of copending U.S. application Ser. No. 13/961,808 filed Aug. 7, 2013, which is a continuation of copending U.S. application Ser. No. 11/897,177, filed Aug. 28, 2007, which is a continuation of U.S. application Ser. No. 10/927,857, filed Aug. 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed Sep. 15, 2003, which are incorporated in their entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Pat. No. 5,474,979; Garst U.S. Pat. No. 6,254,860; and Garst U.S. Pat. No. 6,350,442, this disclosure of each of which is incorporated in its entirely herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "*Blood concentrations of: cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease*," Small et al, *J Ocul Pharmacol Ther*, 2002 October, 18(5):421-8; "*Distribution of cyclosporin A in ocular tissues aft topical administration to albino rabbits and beagle dogs*," Acheampong et al, *Curr Eye Res*, 1999 February, 18(2)-103b; "*Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes*," Acheampong et al, *Adv Exp Med Biol*, 1999, 438:1001-4; "*Preclinical safety studies of cyclosporne ophthalmic emulsion*," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991 "*Cyclosporin & Emulsion & Eye*," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74; and "*Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase* 3 *Study Group*," Sall et al, *Ophthalmology*, 2000 April, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug A Ministrati on (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Pat. No. 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

SUMMARY OF THE INVENTION

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such method provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employ the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects, and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment

with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of clyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 15% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

DETAILED DESCRIPTION

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconiunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated, and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography mass spectroscopy mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

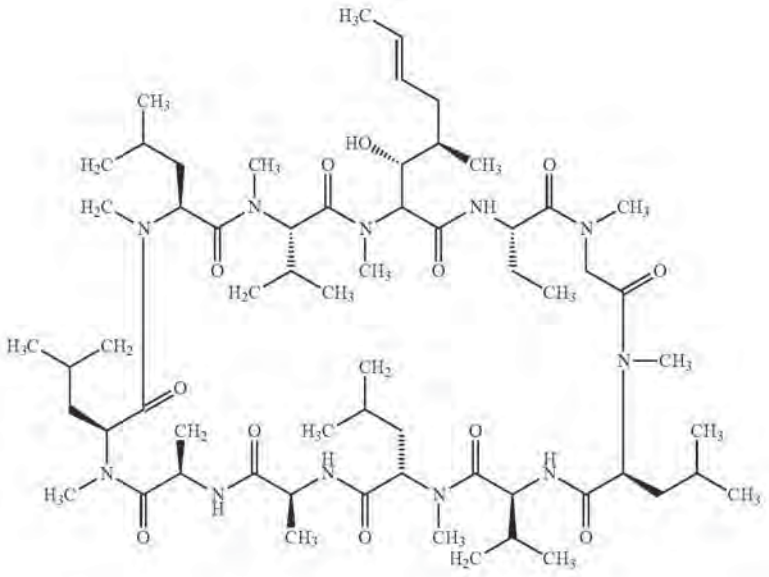
The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1×50 mm, 3 μm pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, Pa.). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula I

Formula I

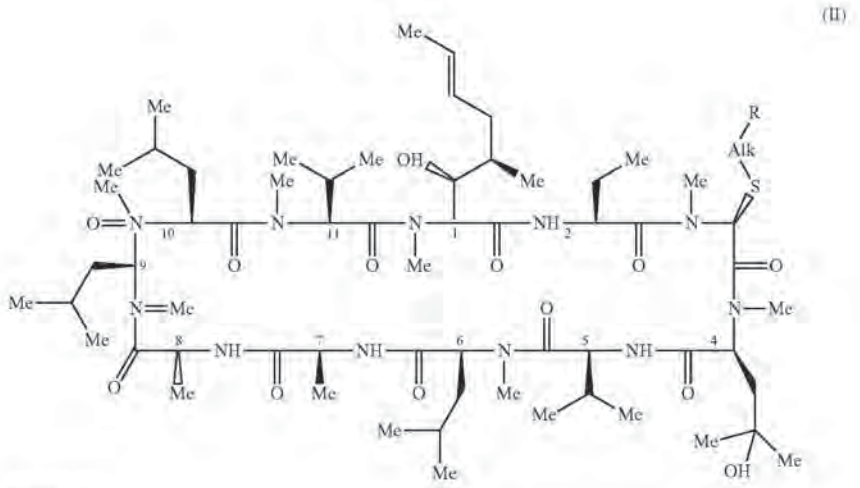


As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are

those selected from ((R)-methylthio-Sar)^3-(4'-hydroxy-Me-Leu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)^3-(4'-hydroxy-MeLeu)^4-cyclosporin A, and ((R)-(Cyclo)alkylthio-Ser)^3-cyclosporin A derivatives described below.

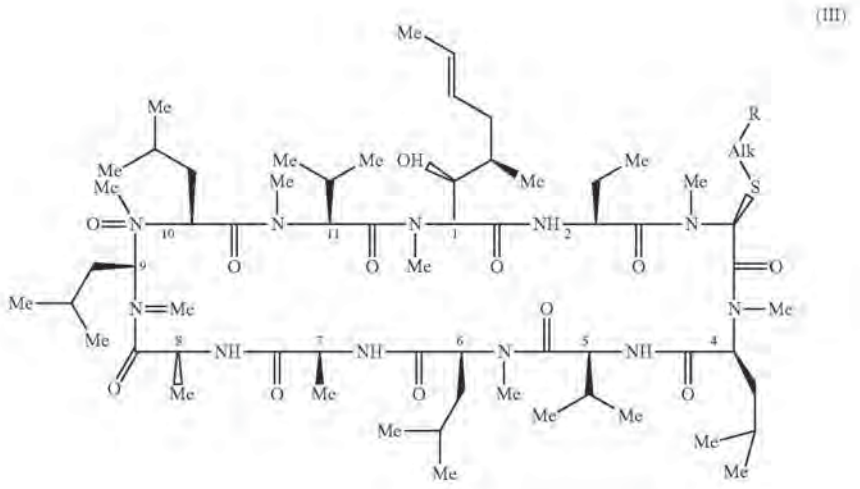
These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

Formula II



(II)

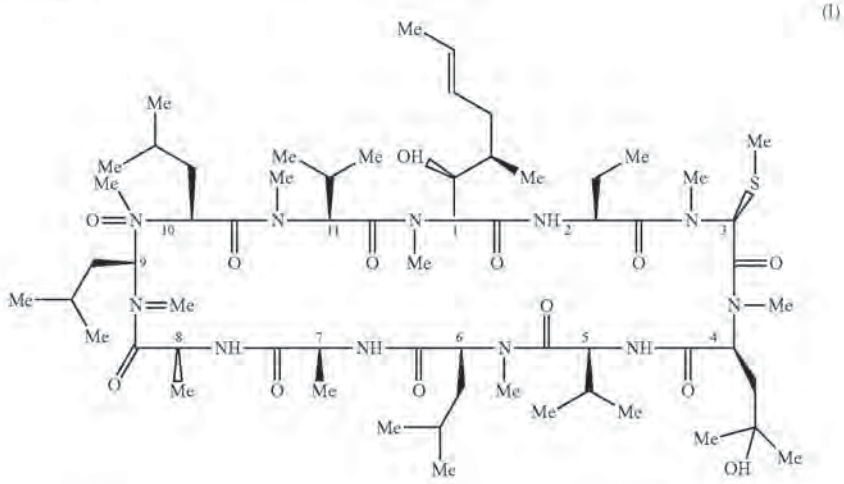
Formula III



(III)

-continued

Formula IV



(I)

wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, $—NR_1R_2$ or $N(R_3)—(CH_2)—NR_1R_2$: wherein R_1,R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxycarbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR_1R is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R_3 is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful composition be sterilized and maintained in a sterile condition prior to use, for example, provided in sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emul-

sifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphorteric in nature. In general, the emulsifier component includes a hydrophobic constituent and hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

metal carboxy methylcelluloses
metal carboxy methylbydroxyethylcelluloses
metal carboxy methylstarchs
metal carboxy methylhydroxyethylstarchs
hydrolyzed polyacrylamides and polyacrylonitriles
heparin
gucoaminoglycans
hyaluronic acid
chondroitin sulfate
dermatan sulfate
peptides and polypeptides
alginic acid
metal alginates
homopolymers and copolymers of one or more of acrylic and methacrylic acids
metal acrylates and methacrylates
vinylsulfonic acid
metal vinylsulfonate
amino acids, such as aspartic acid, giutamic acid and the like
metal salts of amino acids
p-styrenesulfonic acid
metal p-styrenesulfonate
2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxpropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

One particularly useful stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight, co-polymers of acrylic acid and a long chain alkyl methacrylate crosslinked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may iso be effective as demulcent com-

ponents, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5% w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10° C. above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase for the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet si e distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamicaly stable, much like microemulsions, and yet may not be isotropic transparent compositions a are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I wt %	Composition II wt %
Cyclosporin A	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen ®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

What is claimed is:

1. A first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease; and

wherein the first topical ophthalmic emulsion provides overall efficacy substantially equal to a second topical ophthalmic emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight.

2. The first topical ophthalmic emulsion of claim **1**, wherein the first topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

3. The first topical ophthalmic emulsion of claim **2**, wherein the tonicity agent or the demulcent component is glycerine.

4. The first topical ophthalmic emulsion of claim **1**, wherein the first topical ophthalmic emulsion further comprises a buffer.

5. The first topical ophthalmic emulsion of claim **4**, wherein the buffer is sodium hydroxide.

6. The first topical ophthalmic emulsion of claim **1**, wherein the first topical ophthalmic emulsion further comprises glycerine and a buffer.

7. The first topical ophthalmic emulsion of claim **1**, wherein the first topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

8. The first topical ophthalmic emulsion of claim **1**, wherein the first topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

9. The first topical ophthalmic emulsion of claim **1**, wherein the first topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

10. The first topical ophthalmic emulsion of claim **9**, wherein the buffer is sodium hydroxide.

11. The first topical ophthalmic emulsion of claim **1**, wherein, when the first topical ophthalmic emulsion is administered to an eye of a human in an effective amount in treating dry eye disease, the blood of the human has substantially no detectable concentration of cyclosporin A.

12. The first topical ophthalmic emulsion of claim **6**, wherein the first topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

13. A first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease and wherein the first topical ophthalmic emulsion achieves at least as much therapeutic effectiveness as a second topical ophthalmic emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight.

14. A first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the first topical ophthalmic emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distor-

tion in the eye of the human as compared to a second topical ophthalmic emulsion that contains only about 50% as much castor oil as the first topical ophthalmic emulsion.

15. A first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate crosspolymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the first topical ophthalmic emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative to a second topical ophthalmic emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight.

16. The first topical ophthalmic emulsion of claim **15**, wherein the adverse events are side effects.

17. The first topical ophthalmic emulsion of claim **16**, wherein the side effects are selected from the group consisting of visual distortion and eye irritation.

18. The first topical ophthalmic emulsion of claim **13**, wherein, when the first topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.

19. The first topical ophthalmic emulsion of claim **14**, wherein, when the first topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.

20. The first topical ophthalmic emulsion of claim **15**, wherein, when the first topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,642,556 B2
APPLICATION NO. : 13/967189
DATED : February 4, 2014
INVENTOR(S) : Andrew Acheampong et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

In column 1, line 34, delete "of:" and insert -- of --, therefor

In column 1, line 34, delete "cyclosporin a" and insert -- cyclosporin A --, therefor.

In column 1, line 35, delete "cyclosporin a" and insert -- cyclosporin A --, therefor.

In column 1, line 37, delete "421" and insert -- 411 --, therefor.

In column 1, line 38, delete "aft" and insert -- after --, therefor.

In column 1, line 40, delete "18(2)" and insert -- 18(2):91 --, therefor.

In column 1, line 44, delete "1999," and insert -- 1998, --, therefor.

In column 1, line 45, delete "1999," and insert -- 1998, --, therefor.

In column 1, line 46, delete "438:991" and insert --438:991-5; --, therefor.

In column 1, line 56, delete "A Ministrati on" and insert -- Administration --, therefor.

In column 2, line 15, delete "method" and insert -- methods --, therefor.

In column 2, line 17, delete "employ" and insert -- employing --, therefor.

In column 2, line 19, delete "effects," and insert -- effects --, therefor.

In column 3, line 9, delete "clyclosporin" and insert -- cyclosporin --, therefor.

In column 3, line 42, delete "15%" and insert -- 1.5% --, therefor.

In column 5, line 8, delete "kerapoconiunctivitis," and insert -- keratoconjunctivitis, --, therefor.

In column 5, line 25, delete "treated," and insert -- treated --, therefor.

In column 5, line 38, delete "chromatography mass" and insert -- chromatography-mass --, therefor.

In column 5, line 38, delete "spectroscopy mass" and insert -- spectroscopy-mass --, therefor.

In column 6, line 11, delete "mobil" and insert -- mobile --, therefor.

In column 9, line 26, delete "—NR_1R_2:" and insert -- —NR_1R_2; --, therefor.

In column 9, line 30, delete "NR_1R" and insert -- NR_1R_2 --, therefor.

Signed and Sealed this
First Day of July, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)

U.S. Pat. No. 8,642,556 B2

In column 10, line 40, delete "benefitting" and insert -- benefiting --, therefor.

In column 10, line 62, delete "composition" and insert -- compositions may --, therefor.

In column 10, line 63, after "in" insert -- a --.

In column 11, line 14, delete "amphorteric" and insert -- amphoteric --, therefor.

In column 11, line 15, delete "and" and insert -- and a --, therefor.

In column 11, line 51, delete "methylbydroxyethylcelluloses" and insert

-- methylhydroxyethylcelluloses --, therefor.

In column 11, line 56, delete "gucoaminoglycans" and insert -- glycosaminoglycans --, therefor.

In column 11, line 63, delete "of" and insert -- of: --, therefor.

In column 12, line 1, delete "giutamic" and insert -- glutamic --, therefor.

In column 12, line 8, delete "hydroxpropylsulonic" and insert -- hydroxypropylsulfonic --, therefor.

In column 12, line 15, delete "useful" and insert -- useful emulsion --, therefor.

In column 12, line 22, delete "weight," and insert -- weight --, therefor.

In column 12, line 23, delete "crosslinked" and insert -- cross-linked --, therefor.

In column 12, line 67, delete "iso" and insert -- also --, therefor.

In column 12, line 23, delete "for" and insert -- or --, therefor.

In column 14, lines 42-43, delete "or globule" and insert -- (or globule --, therefor.

In column 14, line 51, delete "si e" and insert -- size --, therefor.

In column 14, lines 55-56, delete "thermodynamicaly" and insert -- thermodynamically --, therefor.

In column 14, line 57, delete "a are" and insert -- as are --, therefor.

In column 15, line 8, delete "Premulem ®" and insert -- Pemulem® --, therefor.

Exhibit 5

US008648048B2

(12) **United States Patent**
Acheampong et al.

(10) **Patent No.: US 8,648,048 B2**
(45) **Date of Patent: *Feb. 11, 2014**

(54) **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/967,168**

(22) Filed: **Aug. 14, 2013**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 13/961,835, filed on Aug. 7, 2013, which is a continuation of application No. 11/897,177, filed on Aug. 28, 2007, which is a continuation of application No. 10/927,857, filed on Aug. 27, 2004, now abandoned.

(60) Provisional application No. 60/503,137, filed on Sep. 15, 2003.

(51) **Int. Cl.**
A61K 38/13 (2006.01)

(52) **U.S. Cl.**
USPC **514/20.5**

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

23 Claims, No Drawings

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METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

RELATED APPLICATION

This application is a continuation of copending U.S. application Ser. No. 13/961,835 filed Aug. 7, 2013, which is a continuation of copending U.S. application Ser. No. 11/897,177, filed Aug. 28, 2007, which is a continuation of U.S. application Ser. No. 10/927,857, filed Aug. 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed Sep. 15, 2003, which are incorporated in their entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Pat. No. 5,474,979; Garst U.S. Pat. No. 6,254,860; and Garst U.S. Pat. No. 6,350,442, this disclosure of each of which is incorporated in its entirely herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "*Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease*," Small et al, *J Ocul Pharmacol Ther*, 2002 October, 18(5):411-8; "*Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs*," Acheampong et al, *Curr Eye Res*, 1999 February, 18(2):91-103b; "*Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes*," Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "*Preclinical safety studies of cyclosporine ophthalmic emulsion*," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5; "*Cyclosporin & Emulsion & Eye*," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74; and "*Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group*," Sall et al, *Ophthalmology*, 2000 April, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Pat. No. 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

SUMMARY OF THE INVENTION

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporine

is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can increase tear production in the eye. The treatment can further serve to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratisis, mucopurulent discharge and vascularization of the cornea.

Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of cyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

DETAILED DESCRIPTION

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or

animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.

detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

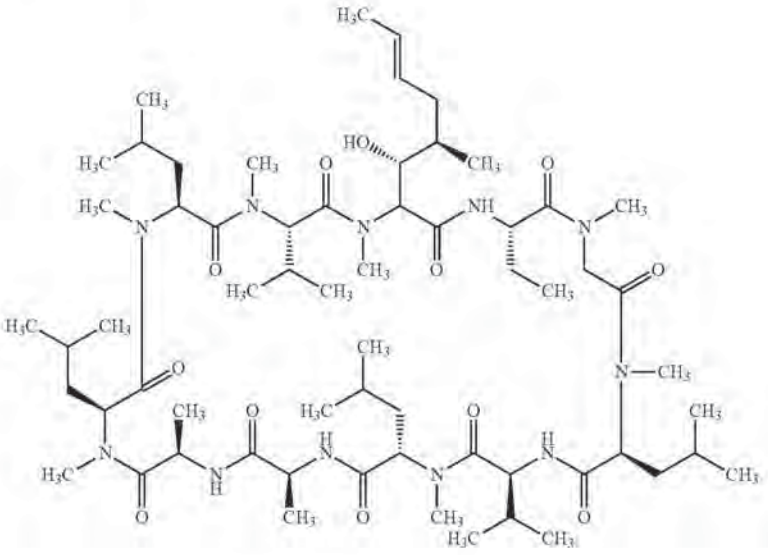
The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1×50 mm, 3 μm pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, Pa.). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

Formula 1

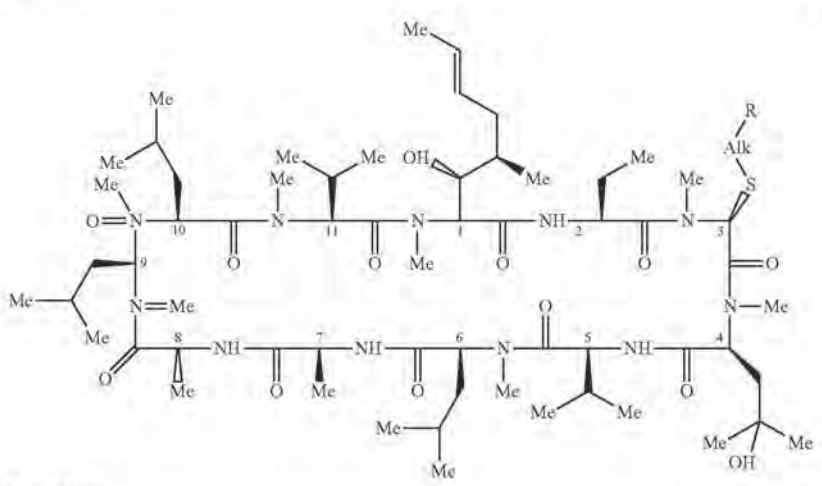


One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component

As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)^3-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)^3-(4'-hydroxy-MeLeu)^4-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)^3-cyclosporin A derivatives described below.

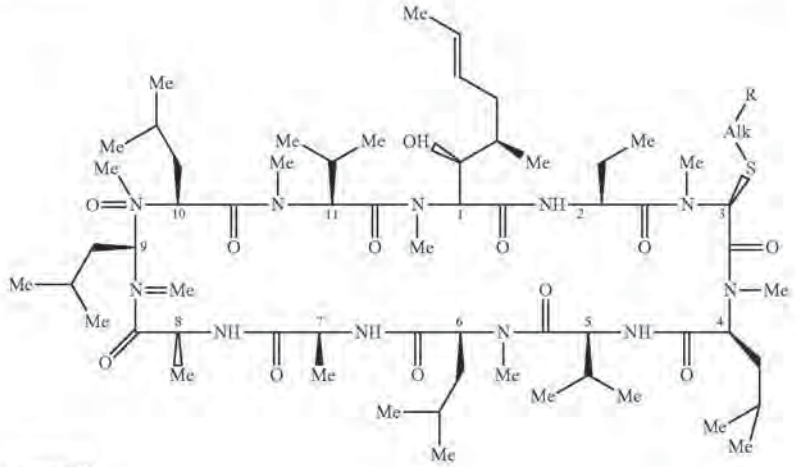
These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

Formula II



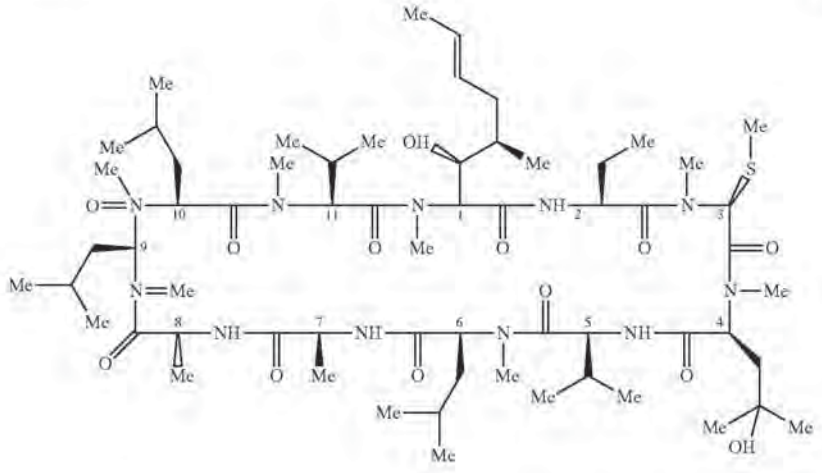
(II)

Formula III



(III)

Formula IV



(I)

wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, $—NR_1R_2$ or $N(R_3)C(CH_2)CNR_1R_2$; wherein R_1,R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxycarbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 mem-

bers and 1-3 heteroatoms; or NR_1R_2 is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R_3 is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefiting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphorteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

metal carboxy methylcelluloses
metal carboxy methylhydroxyethylcelluloses
metal carboxy methylstarchs
metal carboxy methylhydroxyethylstarchs
hydrolyzed polyacrylamides and polyacrylonitriles

heparin
gucoaminoglycans
hyaluronic acid
chondroitin sulfate
dermatan sulfate
peptides and polypeptides
alginic acid
metal alginates
homopolymers and copolymers of one or more of:
acrylic and methacrylic acids
metal acrylates and methacrylates
vinylsulfonic acid
metal vinylsulfonate
amino acids, such as aspartic acid, glutamic acid and the like
metal salts of amino acids
p-styrenesulfonic acid
metal p-styrenesulfonate
2-methacryloyloxyethylsulfonic acids
metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral

activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5% w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10° C. above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I wt %	Composition II wt %
Cyclosporin	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen ®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

What is claimed is:

1. A method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is effective in increasing tear production.

2. The method of claim **1**, wherein the emulsion further comprises a tonicity agent or a demulcent component.

3. The method of claim **2**, wherein the tonicity agent or the demulcent component is glycerine.

4. The method of claim **1**, wherein the emulsion further comprises a buffer.

5. The method of claim **4**, wherein the buffer is sodium hydroxide.

6. The method of claim **1**, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

7. The method of claim **1**, wherein the emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

8. The method of claim **1**, wherein the emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

9. The method of claim **1**, wherein the emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

10. The method of claim **9**, wherein the buffer is sodium hydroxide.

11. The method of claim **1**, wherein, when the emulsion is administered to an eye of a human in an effective amount in increasing tear production, the blood of the human has substantially no detectable concentration of cyclosporin A.

12. The method of claim **6**, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

13. The method of claim **1**, wherein the emulsion is as substantially therapeutically effective as a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

14. The method of claim **1**, wherein the emulsion achieves at least as much therapeutic effectiveness as a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

15. The method of claim **1**, wherein the emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compared to a second emulsion that contains only 50% as much castor oil.

16. The method of claim **1**, wherein the emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative to a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.

17. The method of claim **16**, wherein the adverse events are side effects.

18. A method of treating keratoconjunctivitis sicca, the method comprising the step of topically administering to an eye of a human in need thereof an emulsion at a frequency of twice a day, the emulsion comprising:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

a tonicity component or a demulcent component in an amount of about 2.2% by weight;

a buffer; and

water;

wherein the emulsion is effective in treating keratoconjunctivitis sicca and wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

19. The method of claim **8**, wherein the buffer is sodium hydroxide.

20. The method of claim **8**, wherein the tonicity component or the demulcent component is glycerine.

21. The method of claim **8**, wherein, when the emulsion is administered to the eye of a human in an effective amount in treating keratoconjunctivitis sicca, the blood of the human has substantially no detectable concentration of the cyclosporin A.

22. A method comprising:

administering an emulsion topically to the eye of a human having keratoconjunctivitis sicca at a frequency of twice a day, wherein the emulsion comprises:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of about 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

glycerine in an amount of about 2.2% by weight;

sodium hydroxide; and

water; and

wherein the emulsion is effective in increasing tear production in the human having keratoconjunctivitis sicca.

23. The method of claim **22**, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,648,048 B2
APPLICATION NO.	: 13/967168
DATED	: February 11, 2014
INVENTOR(S)	: Andrew Acheampong et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

In column 16, line 33, delete "claim **8**," and insert -- claim 18, --, therefor.

In column 16, line 35, delete "claim **8**," and insert -- claim 18, --, therefor.

In column 16, line 37, delete "claim **8**," and insert -- claim 18, --, therefor.

Signed and Sealed this
Twenty-seventh Day of May, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,648,048 B2
APPLICATION NO. : 13/967168
DATED : February 11, 2014
INVENTOR(S) : Andrew Acheampong et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On Title page 3, in column 1, under "Other Publications", line 9, delete "Muscosal" and insert -- Mucosal --, therefor.

On Title page 3, in column 1, under "Other Publications", line 45, delete "Polyocyethylene" and insert -- Polyoxyethylene --, therefor.

In the Specification

In column 1, line 34, delete "cyclosporin a" and insert -- cyclosporin A --, therefor.

In column 1, line 35, delete "cyclosporin a" and insert -- cyclosporin A --, therefor.

In column 2, line 62, delete "kerapoconjunctivitis," and insert -- keratoconjunctivitis, --, therefor.

In column 2, line 67 through column 3, line 1, delete "cyclosporine is" and insert -- cyclosporins are --, therefor.

In column 3, line 10, delete "keratisis," and insert -- keratosis, --, therefor.

In column 5, line 15, delete "kerapoconjunctivitis," and insert -- keratoconjunctivitis, --, therefor.

In column 6, line 9, delete "mobil" and insert -- mobile --, therefor.

In column 10, line 27, delete "amphorteric" and insert -- amphoteric --, therefor.

In column 11, line 2, delete "gucoaminoglycans" and insert -- glycosaminoglycans --, therefor.

In column 11, line 20, delete "2-methacryloyloxethylsulfonates" and insert -- 2-methacryloyloxyethylsulfonates --, therefor.

In column 11, line 21, delete "hydroxypropylsulonic" and insert -- hydroxypropylsulfonic --, therefor.

In column 11, lines 63-64, delete "carboxymethylcellulose," and insert -- carboxymethyl cellulose, --, therefor.

In column 14, line 25, delete "Premulen ®" and insert -- Pemulen® --, therefor.

Signed and Sealed this
Seventeenth Day of June, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

Exhibit 6

US008685930B2

(12) **United States Patent**
Acheampong et al.

(10) **Patent No.: US 8,685,930 B2**
(45) **Date of Patent: *Apr. 1, 2014**

(54) **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS**

(71) Applicant: **Allergan, Inc.**, Irvine, CA (US)

(72) Inventors: **Andrew Acheampong**, Irvine, CA (US); **Diane D. Tang-Liu**, Las Vegas, NV (US); **James N. Chang**, Newport Beach, CA (US); **David F. Power**, Hubert, NC (US)

(73) Assignee: **Allergan, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/961,828**

(22) Filed: **Aug. 7, 2013**

(65) **Prior Publication Data**

US 2013/0338082 A1 Dec. 19, 2013

Related U.S. Application Data

(63) Continuation of application No. 11/897,177, filed on Aug. 28, 2007, now Pat. No. 8,618,064, and a continuation of application No. 10/927,857, filed on Aug. 27, 2004, now abandoned.

(60) Provisional application No. 60/503,137, filed on Sep. 15, 2003.

(51) **Int. Cl.**
A61K 38/13 (2006.01)

(52) **U.S. Cl.**
USPC **514/20.5**

(58) **Field of Classification Search**
CPC A61K 38/13
See application file for complete search history.

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Primary Examiner — Marcela M Cordero Garcia

(74) *Attorney, Agent, or Firm* — Laura L. Wine; Joel B. German; Debra D. Condino

(57) **ABSTRACT**

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

36 Claims, No Drawings

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METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

RELATED APPLICATION

This application is a continuation of copending U.S. application Ser. No. 11/897,177, filed Aug. 28, 2007, which is a continuation of U.S. application Ser. No. 10/927,857, filed Aug. 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed Sep. 15, 2003, which are incorporated in their entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Pat. No. 5,474,979; Garst U.S. Pat. No. 6,254,860; and Garst U.S. Pat. No. 6,350,442, this disclosure of each of which is incorporated in its entirely herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "*Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease*," Small et al, *J Ocul Pharmacol Ther*, 2002 October, 18(5):411-8; "*Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs*," Acheampong et al, *Curr Eye Res*, 1999 February, 18(2):91-103b; "*Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes*," Acheampong et al, *Adv Exp Med Biol*, 1998, 438:1001-4; "*Preclinical safety studies of cyclosporine ophthalmic emulsion*," Angelov et al, *Adv Exp Med Biol*, 1998, 438:991-5; "*Cyclosporin & Emulsion & Eye*," Stevenson et al, *Ophthalmology*, 2000 May, 107(5):967-74; and "*Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group*," Sall et al, *Ophthalmology*, 2000 April, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al U.S. Pat. No. 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

SUMMARY OF THE INVENTION

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome. Cyclosporin has been found as effective in treating immune mediated keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom. The activity of cyclosporine is as an immunosuppressant and in the enhancement or restor-

ing of lacrimal gland tearing. Other conditions that can be treated with cyclosporin components include an absolute or partial deficiency in aqueous tear production (keratoconjunctivitis sicca, or KCS). Topical administration to a patient's tear deficient eye can increase tear production in the eye. The treatment can further serve to correct corneal and conjunctival disorders exacerbated by tear deficiency and KCS, such as corneal scarring, corneal ulceration, inflammation of the cornea or conjunctiva, filamentary keratisis, mucopurulent discharge and vascularization of the cornea.

Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of clyclosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through 1, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results are obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

DETAILED DESCRIPTION

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with

cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

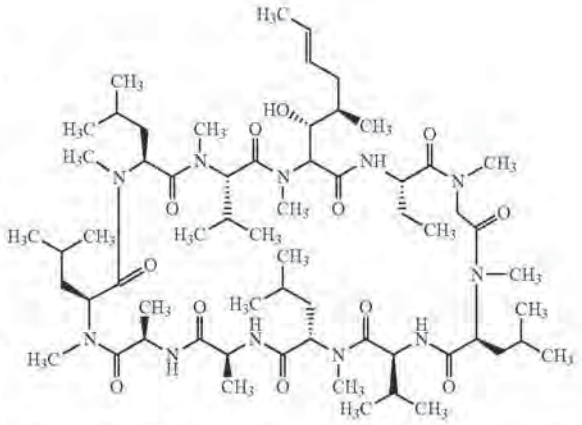
The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetonitrile-based mobil phase, and injected onto a 2.1×50 mm. 3 μm pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, Pa.). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula 1

Formula 1

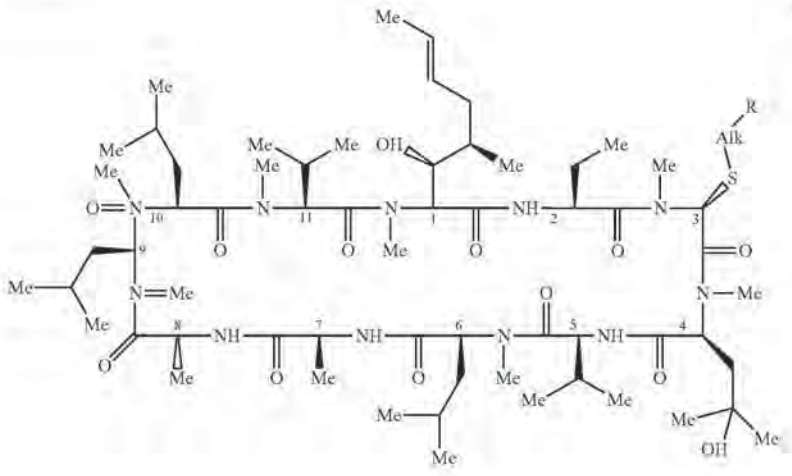


As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)^3-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)^3-(4'-hydroxy-MeLeu)^4-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)^3-cyclosporin A derivatives described below.

These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

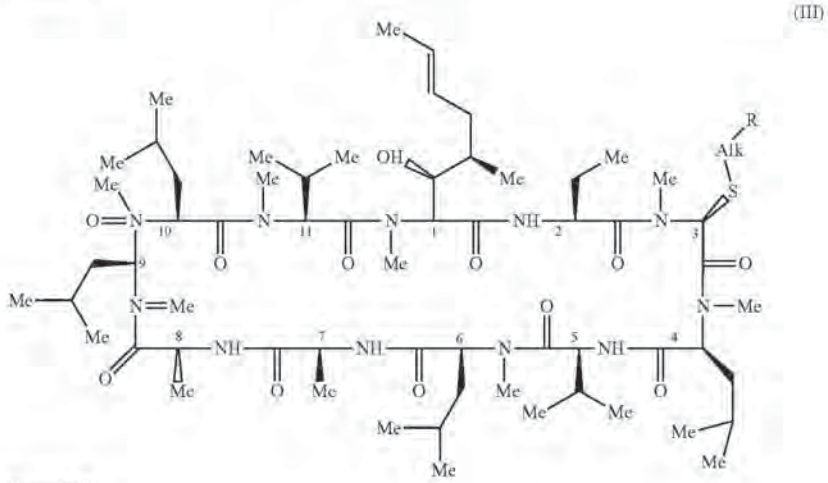
Formula II

(II)



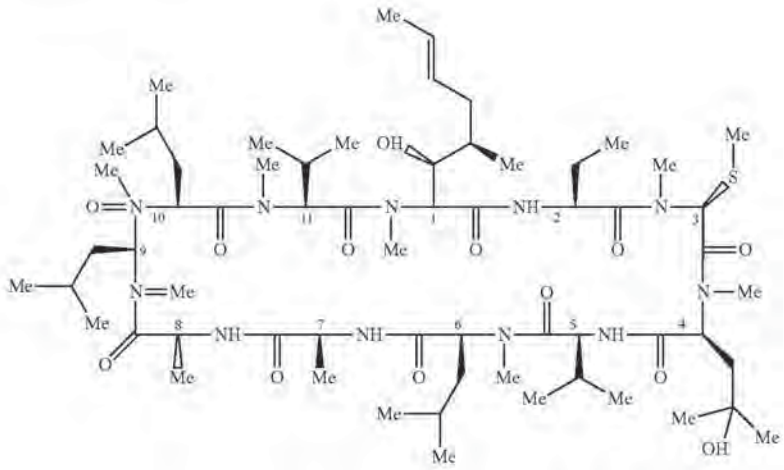
-continued

Formula III



(III)

Formula IV



(I)

wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, $-NR_1R_2$ or $N(R_3)C(CH_2)CNR_1R_2$; wherein R_1,R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxycarbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR_1R_2 is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R_3 is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of such low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which have been processed to alter their chemical structures to some extent or oils which are substantially

entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefitting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective in forming maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphorteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

- metal carboxy methylcelluloses
- metal carboxy methylhydroxyethylcelluloses
- metal carboxy methylstarchs
- metal carboxy methylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- gucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- peptides and polypeptides
- alginic acid
- metal alginates
- homopolymers and copolymers of one or more of:
- acrylic and methacrylic acids
- metal acrylates and methacrylates
- vinylsulfonic acid
- metal vinylsulfonate
- amino acids, such as aspartic acid, glutamic acid and the like
- metal salts of amino acids
- p-styrenesulfonic acid
- metal p-styrenesulfonate
- 2-methacryloyloxyethylsulfonic acids
- metal 2-methacryloyloxethylsulfonates
- 3-methacryloyloxy-2-hydroxypropylsulonic acids
- metal 3-methacryloyloxy-2-hydroxypropylsulfonates
- 2-acrylamido-2-methylpropanesulfonic acids
- metal 2-acrylamido-2-methylpropanesulfonates
- allylsulfonic acid
- metal allylsulfonate and the like.

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be use-

ful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5% w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily material phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10° C. above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dis-

solved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamicaly stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

Example 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I wt %	Composition II wt %
Cyclosporin	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen ®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

What is claimed is:

1. A topical ophthalmic emulsion for treating an eye of a human having keratoconjunctivitis sicca, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is therapeutically effective in treating keratoconjunctivitis sicca.

2. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

3. The topical ophthalmic emulsion of claim **2**, wherein the tonicity agent or the demulcent component is glycerine.

4. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion further comprises a buffer.

5. The topical ophthalmic emulsion of claim **4**, wherein the buffer is sodium hydroxide.

6. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

7. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

8. The topical ophthalmic emulsion of claim **1**, wherein the topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

9. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

10. The topical ophthalmic emulsion of claim 9, wherein the buffer is sodium hydroxide.

11. The topical ophthalmic emulsion of claim 1, wherein, when the topical ophthalmic emulsion is administered to an eye of a human in an effective amount in treating keratoconjunctivitis sicca, the blood of the human has substantially no detectable concentration of cyclosporin A.

12. The topical ophthalmic emulsion of claim 6, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

13. A topical ophthalmic emulsion for treating an eye of a human having dry eye, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is therapeutically effective in treating dry eye.

14. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

15. The topical ophthalmic emulsion of claim 14, wherein the tonicity agent or the demulcent component is glycerine.

16. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion further comprises a buffer.

17. The topical ophthalmic emulsion of claim 16, wherein the buffer is sodium hydroxide.

18. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

19. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

20. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

21. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

22. The topical ophthalmic emulsion of claim 21, wherein the buffer is sodium hydroxide.

23. The topical ophthalmic emulsion of claim 13, wherein, when the topical ophthalmic emulsion is administered to an eye of a human in an effective amount in treating dry eye, the blood of the human has substantially no detectable concentration of cyclosporin A.

24. The topical ophthalmic emulsion of claim 18, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

25. A topical ophthalmic emulsion for increasing tear production in an eye of a human having keratoconjunctivitis sicca, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production in the eye of the human having keratoconjunctivitis sicca.

26. The topical ophthalmic emulsion of claim 25, wherein the topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

27. The topical ophthalmic emulsion of claim 26, wherein the tonicity agent or the demulcent component is glycerine.

28. The topical ophthalmic emulsion of claim 25, wherein the topical ophthalmic emulsion further comprises a buffer.

29. The topical ophthalmic emulsion of claim 28, wherein the buffer is sodium hydroxide.

30. The topical ophthalmic emulsion of claim 25, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.

31. The topical ophthalmic emulsion of claim 25, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

32. The topical ophthalmic emulsion of claim 25, wherein the topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

33. The topical ophthalmic emulsion of claim 25, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

34. The topical ophthalmic emulsion of claim 33, wherein the buffer is sodium hydroxide.

35. The topical ophthalmic emulsion of claim 25, wherein, when the topical ophthalmic emulsion is administered to an eye of a human in an effective amount in increasing tear production in the eye of the human having keratoconjunctivitis sicca, the blood of the human has substantially no detectable concentration of cyclosporin A.

36. The topical ophthalmic emulsion of claim 30, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

* * * * *

Exhibit 7

US009248191B2

(12) **United States Patent**
Acheampong et al.

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(54) **METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS**

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(63) Continuation of application No. 13/961,828, filed on Aug. 7, 2013, now Pat. No. 8,685,930, which is a continuation of application No. 11/897,177, filed on Aug. 28, 2007, now Pat. No. 8,618,064, and a continuation of application No. 10/927,857, filed on Aug. 27, 2004, now abandoned.

(60) Provisional application No. 60/503,137, filed on Sep. 15, 2003.

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Methods of treating an eye of a human or animal include administering to an eye of a human or animal a composition in the form of an emulsion including water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.8.

27 Claims, No Drawings

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Letter from Joseph M. Reisman, Counsel for Mylan Pharmaceuticals Inc., of Knobbe Martens, Cyclosporine Emulsion 0.05%, Route of Administration: Ophthalmic, U.S. Pat. No. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930, Notice of Paragraph IV Certification, dated Jul. 20, 2015, pp. 1-226.

Letter from Joseph Bonaccorsi, General Counsel, Akorn, Inc., Notification of Certification for U.S. Pat. Nos. 8,629,111; 8,633,162; 8,642,556; 8,648,048; and 8,685,930 Pursuant to Section 5050)(2)(13)(iv) of the Federal Food, Drug, and Cosmetic Act—21 USC Section 355(j)(2)(B)(iv) Akorn ANDA 204561, dated Jul. 10, 2015, pp. 1-26.

USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner* v. *Allergan, Inc. Patent Owner*, Case IPR2015-01278, Patent 8,633,162, pp. 1-63, Dated Jun. 4, 2015.

USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner* v. *Allergan, Inc. Patent Owner*, Case IPR2015-01282, Patent 8,629,111, pp. 1-63, Dated Jun. 4, 2015.

USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner* v. *Allergan, Inc. Patent Owner*, Case IPR2015-01283, Patent 8,685,930, pp. 1-63, Dated Jun. 4, 2015.

USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner* v. *Allergan, Inc. Patent Owner*, Case IPR2015-01284, Patent 8,648,048, pp. 1-63, Dated Jun. 4, 2015.

USPTO Before the Patent Trial and Appeal Board, *Apotex, Inc. Petitioner* v. *Allergan, Inc. Patent Owner*, Case IPR2015-01286, Patent 8,642,556, pp. 1-63, Dated Jun. 4, 2015.

* cited by examiner

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

RELATED APPLICATION

This application is a continuation of copending U.S. Application Serial No. 13/961.828 filed Aug. 7, 2013, which is a continuation of U.S. application Ser. No. 11/897,177, filed Aug. 28, 2007, now issued as U.S. Pat. No. 8,618,064, which is a continuation of U.S. application Ser. No. 10/927,857, filed Aug. 27, 2004, now abandoned, which claims the benefit of U.S. Provisional Application No. 60/503,137 filed Sep. 15, 2003, which are incorporated in their entirety herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to methods of providing desired therapeutic effects to humans or animals using compositions including cyclosporin components. More particularly, the invention relates to methods including administering to an eye of a human or animal a therapeutically effective amount of a cyclosporin component to provide a desired therapeutic effect, preferably a desired ophthalmic or ocular therapeutic effect.

The use of cyclosporin-A and cyclosporin A derivatives to treat ophthalmic conditions has been the subject of various patents, for example Ding et al U.S. Pat. No. 5,474,979; Garst U.S. Pat. No. 6,254,860; and Garst U.S. Pat. No. 6,350,442, this disclosure of each of which is incorporated in its entirely herein by reference. In addition, cyclosporin A compositions used in treating ophthalmic conditions is the subject of a number of publications. Such publications include, for example, "*Blood concentrations of cyclosporin a during long-term treatment with cyclosporin a ophthalmic emulsions in patients with moderate to severe dry eye disease*," Small et al, *J Ocul Pharmacol Ther,* 2002, October, 18(5): 411-8; "*Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs*," Acheampong et al, *Curr Eye Res,* 1999 February, 18(2):91-103b; "*Cyclosporine distribution into the conjunctiva, cornea, lacrimal gland, and systemic blood following topical dosing of cyclosporine to rabbit, dog, and human eyes*," Acheampong et al, *Adv Exp Med Biol,* 1998, 438:1001-4; "*Preclinical safety studies of cyclosporine ophthalmic emulsion*," Angelov et al, *Adv Exp Med. Biol,* 1998, 438:991-5; "*Cyclosporin & Emulsion & Eye*," Stevenson et al, *Ophthalmology,* 2000 May, 107(5):967-74; and "*Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group*," Sall et al. *Ophthalmology,* 2000 April, 107(4):631-9. Each of these publications is incorporated in its entirety herein by reference. In addition, cyclosporin A-containing oil-in-water emulsions have been clinically tested, under conditions of confidentiality, since the mid 1990's in order to obtain U.S. Food and Drug Administration (FDA) regulatory approval.

Examples of useful cyclosporin A-containing emulsions are set out in Ding et al. U.S. Pat. No. 5,474,979. Example 1 of this patent shows a series of emulsions in which the ratio of cyclosporin A to castor oil in each of these compositions was 0.08 or greater, except for Composition B, which included 0.2% by weight cyclosporin A and 5% by weight castor oil. The Ding et al patent placed no significance in Composition B relative to Compositions A, C and D of Example 1.

Over time, it has become apparent that cyclosporin A emulsions for ophthalmic use preferably have less than 0.2% by weight of cyclosporin A. With cyclosporin A concentrations less than 0.2%, the amount of castor oil employed has been reduced since one of the functions of the castor oil is to solubilize the cyclosporin A. Thus, if reduced amounts of cyclosporin are employed, reduced amounts of castor oil are needed to provide effective solubilization of cyclosporin A.

There continues to be a need for providing enhanced methods of treating ophthalmic or ocular conditions with cyclosporin-containing emulsions.

SUMMARY OF THE INVENTION

New methods of treating a human or animal using cyclosporin component-containing emulsions have been discovered. Such methods provide substantial overall efficacy in providing desired therapeutic effects. In addition, other important benefits are obtained employing the present methods. For example, patient safety is enhanced. In particular, the present methods provide for reduced risks of side effects and/or drug interactions. Prescribing physicians advantageously have increased flexibility in prescribing such methods and the compositions useful in such methods, for example, because of the reduced risks of harmful side effects and/or drug interactions. The present methods can be easily practiced. In short, the present methods provide substantial and acceptable overall efficacy, together with other advantages, such as increased safety and/or flexibility.

In one aspect of the present invention, the present methods comprise administering to an eye of a human or animal a composition in the form of an emulsion comprising water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the composition. The weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

It has been found that the relatively increased amounts of hydrophobic component together with relatively reduced, yet therapeutically effective, amounts of cyclosporin component provide substantial and advantageous benefits. For example, the overall efficacy of the present compositions, for example in treating dry eye disease, is substantially equal to an identical composition in which the cyclosporin component is present in an amount of 0.1% by weight. Further, a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition. Additionally, and importantly, using reduced amounts of the active cyclosporin component mitigates against undesirable side effects and/or potential drug interactions.

In short, the present invention provides at least one advantageous benefit, and preferably a plurality of advantageous benefits.

The present methods are useful in treating any suitable condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

Employing reduced concentrations of cyclosporin component, as in the present invention, is advantageously effective to provide the blood of the human or animal under treatment with reduced concentrations of cyclosporin component, preferably with substantially no detectable concentration of the cyclosporin component. The cyclosporin component concentration of blood can be advantageously measured using a validated liquid chromatography/mass spectrometry-mass spectrometry (VLC/MS-MS) analytical method, such as described elsewhere herein.

In one embodiment, in the present methods the blood of the human or animal has concentrations of clyclcosporin component of 0.1 ng/ml or less.

Any suitable cyclosporin component effective in the present methods may be used.

Cyclosporins are a group of nonpolar cyclic oligopeptides with known immunosuppressant activity. Cyclosporin A, along with several other minor metabolites, cyclosporin B through I, have been identified. In addition, a number of synthetic analogs have been prepared.

In general, commercially available cyclosporins may contain a mixture of several individual cyclosporins which all share a cyclic peptide structure consisting of eleven amino acid residues with a total molecular weight of about 1,200, but with different substituents or configurations of some of the amino acids.

The term "cyclosporin component" as used herein is intended to include any individual member of the cyclosporin group and derivatives thereof, as well as mixtures of two or more individual cyclosporins and derivatives thereof.

Particularly preferred cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof. Cyclosporin A is an especially useful cyclosporin component.

Any suitable hydrophobic component may be employed in the present invention. Advantageously, the cyclosporin component is solubilized in the hydrophobic component. The hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions.

The hydrophobic component preferably is present in the emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount of up to about 1.0% by weight or about 1.5% by weight or more of the composition.

Preferably, the hydrophobic component comprises one or more oily materials. Examples of useful oil materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils and the like and mixtures thereof. In a very useful embodiment, the hydrophobic component comprises one or more higher fatty acid glycerides. Excellent results were obtained when the hydrophobic component comprises castor oil.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the compositions. Examples of such other components include, without limitation, emulsifier components, tonicity components, polyelectrolyte components, surfactant components, viscosity inducing components, acids and/or bases to adjust the pH of the composition, buffer components, preservative components and the like. Components may be employed which are effective to perform two or more functions in the presently useful compositions. For example, components which are effective as both emulsifiers and surfactants may be employed, and/or components which are effective as both polyelectrolyte components and viscosity inducing components may be employed. The specific composition chosen for use in the present invention advantageously is selected taking into account various factors present in the specific application at hand, for example, the desired therapeutic effect to be achieved, the desired properties of the compositions to be employed, the sensitivities of the human or animal to whom the composition is to be administered, and the like factors.

The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

Such compositions have pH's within the physiological range of about 6 to about 10, preferably in a range of about 7.0 to about 8.0 and more preferably in a range of about 7.2 to about 7.6.

The present methods preferably provide for an administering step comprising topically administering the presently useful compositions to the eye or eyes of a human or animal.

Each and every feature described herein, and each and every combination of two or more such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent.

These and other aspects and advantages of the present invention are apparent in the following detailed description, example and claims.

DETAILED DESCRIPTION

The present methods are effective for treating an eye of a human or animal. Such methods, in general, comprise administering, preferably topically administering, to an eye of a human or animal a cyclosporin component-containing emulsion. The emulsion contains water, for example U.S. pure water, a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight of the emulsion. In addition, beneficial results have been found when the weight ratio of the cyclosporin component to the hydrophobic component is less than 0.08.

As noted above, the present administering step preferably includes topically administering the emulsion to the eye of a patient of a human or animal. Such administering may involve a single use of the presently useful compositions, or repeated or periodic use of such compositions, for example, as required or desired to achieve the therapeutic effect to be obtained. The topical administration of the presently useful composition may involve providing the composition in the form of eye drops or similar form or other form so as to facilitate such topical administration.

The present methods have been found to be very effective in providing the desired therapeutic effect or effects while, at the same time, substantially reducing, or even substantially eliminating, side effects which may result from the presence of the cyclosporin component in the blood of the human or animal being treated, and eye irritation which, in the past, has been caused by the presence of certain components in prior art cyclosporin-containing emulsions. Also, the use of the present compositions which include reduced amounts of the cyclosporin components allow for more frequent administration of the present compositions to achieve the desired therapeutic effect or effects without substantially increasing the risk of side effects and/or eye irritation.

The present methods are useful in treating any condition which is therapeutically sensitive to or treatable with cyclosporin components. Such conditions preferably are ophthalmic or ocular conditions, that is relating to or having to do with one or more parts of an eye of a human or animal. Included among such conditions are, without limitation, dry eye syndrome, phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic kerapoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

The frequency of administration and the amount of the presently useful composition to use during each administration varies depending upon the therapeutic effect to be obtained, the severity of the condition being treated and the like factors. The presently useful compositions are designed to allow the prescribing physician substantial flexibility in treating various ocular conditions to achieve the desired therapeutic effect or effects with reduced risk of side effects and/or eye irritation. Such administration may occur on an as needed basis, for example, in treating or managing dry eye syndrome, on a one time basis or on a repeated or periodic basis once, twice, thrice or more times daily depending on the needs of the human or animal being treated and other factors involved in the application at hand.

One of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal as a result of administering the present composition as described herein. One very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood of the human or animal. Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.

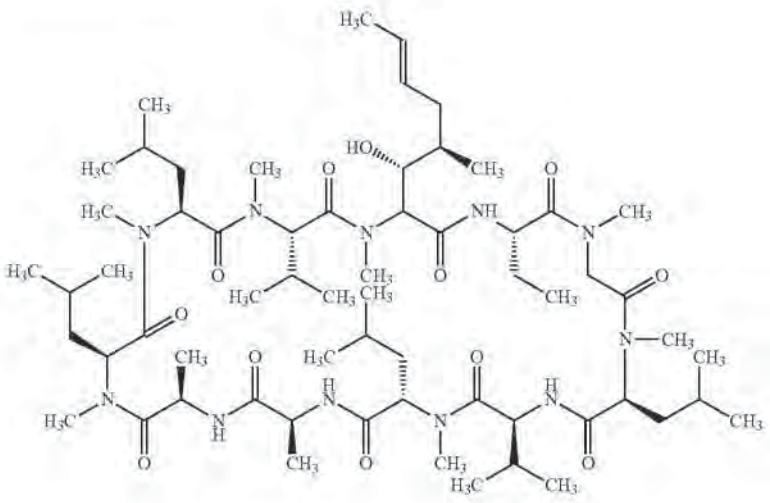
The LC-MS/MS test is advantageously run as follows.

One ml of blood is acidified with 0.2 ml of 0.1 N HCl solution, then extracted with a 5 ml of methyl t-butyl ether. After separation from the acidified aqueous layer, the organic phase is neutralized with 2 ml of 0.1 N NaOH, evaporated, reconstituted in a water/acetronitrile-based mobile phase, and injected onto a 2.1×50 mm, 3 μm pore size C-8 reverse phase high pressure liquid chromatography (HPLC) column (Keystone Scientific, Bellefonte, Pa.). Compounds are gradient-eluted at 0.2 mL/min and detected using an API III triple quadrupole mass spectrometer with a turbo-ionspray source (PE-Sciex, Concord, Ontario, Canada). Molecular reaction monitoring enhances the sensitivity and selectivity of this assay. Protonated molecules for the analyte and an internal standard are collisionally dissociated and product ions at m/z 425 are monitored for the analyte and the internal standard. Under these conditions, cyclosporin A and the internal standard cyclosporin G elute with retention times of about 3.8 minutes. The lower limit of quantitation is 0.1 ng/mL, at which concentration the coefficient of variation and deviation from nominal concentration is <15%.

As noted previously, any suitable cyclosporin component effective in the present methods may be employed. Very useful cyclosporin components include, without limitation, cyclosporin A, derivatives of cyclosporin A and the like and mixtures thereof.

The chemical structure for cyclosporin A is represented by Formula I

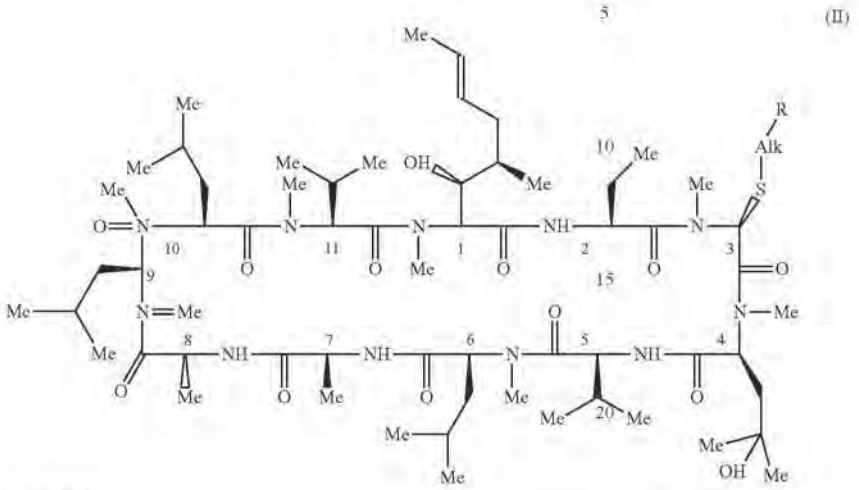
Formula I



As used herein the term "derivatives" of a cyclosporin refer to compounds having structures sufficiently similar to the cyclosporin so as to function in a manner substantially similar to or substantially identical to the cyclosporin, for example, cyclosporin A, in the present methods. Included, without limitation, within the useful cyclosporin A derivatives are those selected from ((R)-methylthio-Sar)^3-(4'-hydroxy-MeLeu) cyclosporin A, ((R)-(Cyclo)alkylthio-Sar)^3-(4'-hydroxy-MeLeu)^4-cyclosporin A, and ((R)-(Cyclo)alkylthio-Sar)^3-cyclosporin A derivatives described below.

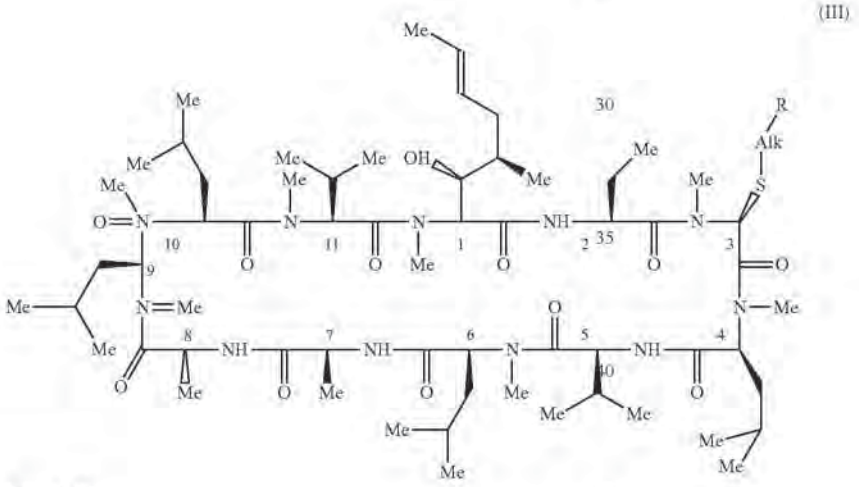
These cyclosporin derivatives are represented by the following general formulas (II), (III), and (IV) respectively:

Formula II



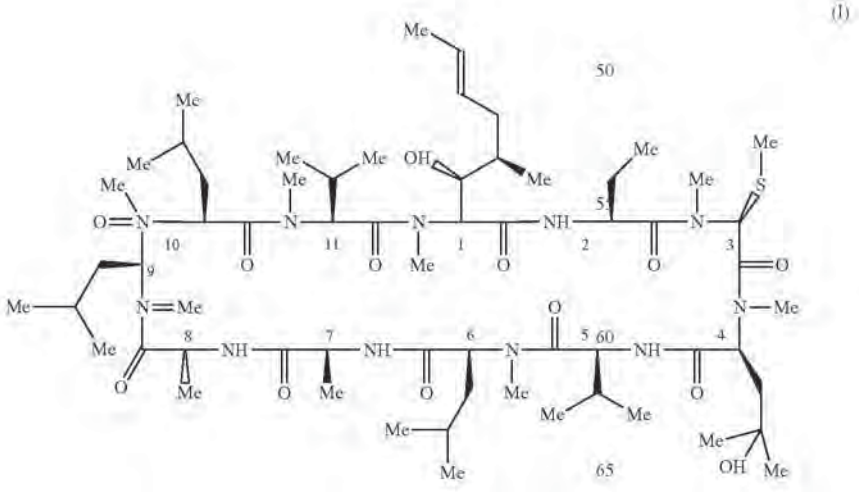
(II)

Formula III



(III)

Formula IV



(I)

wherein Me is methyl; Alk is 2-6C alkylene or 3-6C cycloalkylene; R is OH, COOH, alkoxycarbonyl, $—NR_1R_2$ or $N(R_3)—(CH_2)—NR_1R_2$; wherein R_1,R_2 is H, alkyl, 3-6C cycloalkyl, phenyl (optionally substituted by halo, alkoxy, alkoxycarbonyl, amino, alkylamino or dialkylamino), benzyl or saturated or unsaturated heterocyclyl having 5 or 6 members and 1-3 heteroatoms; or NR_1R_2 is a 5 or 6 membered heterocycle which may contain a further N, O or S heteroatom and may be alkylated; R_3 is H or alkyl and n is 2-4; and the alkyl moieties contain 1-4C.

In one embodiment, the cyclosporin component is effective as an immunosuppressant. Without wishing to be limited to any particular theory of operation, it is believed that, in certain embodiments of the present invention, the cyclosporin component acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.

One important feature of the present invention is that the presently useful compositions contain less than 0.1% by weight of the cyclosporin component. The advantages of each low-concentrations of cyclosporin components have been discussed in some detail elsewhere herein. Low concentrations of cyclosporin component, together with concentrations of the hydrophobic component such that the weight ratio of cyclosporin component to hydrophobic component is greater than 0.08, provides one or more substantial advantages in the present methods.

Any suitable hydrophobic component may be employed in the present invention. Such hydrophobic component may be considered as comprising a discontinuous phase in the presently useful cyclosporin component-containing emulsions, with the water or aqueous phase being considered the continuous phase in such emulsion. The hydrophobic component is preferably selected so as to solubilize the cyclosporin component, which is often substantially insoluble in the aqueous phase. Thus, with a suitable hydrophobic component included in the presently useful emulsions, the cyclosporin component is preferably solubilized in the emulsions.

In one very useful embodiment, the hydrophobic component comprises an oily material, in particular, a material which is substantially not miscible in water. Examples of useful oily materials include, without limitation, vegetable oils, animal oils, mineral oils, synthetic oils, and the like and mixtures thereof. Thus, the present hydrophilic components may comprise naturally occurring oils, including, without limitation refined naturally occurring oils, or naturally occurring oils which have been processed to alter their chemical structures to some extant or oils which are substantially entirely synthetic. One very useful hydrophobic component includes higher fatty acid glycerides.

Examples of useful hydrophobic components include, without limitation, olive oil, arachis oil, castor oil, mineral oil, silicone fluid and the like and mixtures thereof. Higher fatty acid glycerides such as olive oil, peanut oil, castor oil and the like and mixtures thereof are particularly useful in the present invention. Excellent results are obtained using a hydrophobic component comprising castor oil. Without wishing to limit the invention to any particular theory of operation, it is believed that castor oil includes a relatively high concentration of ricinoleic acid which itself may be useful in benefiting ocular tissue and/or in providing one or more therapeutic effects when administered to an eye.

The hydrophobic component is preferably present in the presently useful cyclosporin component-containing emulsion compositions in an amount greater than about 0.625% by weight. For example, the hydrophobic component may be present in an amount up to about 0.75% by weight or about 1.0% by weight or about 1.5% by weight or more of the presently useful emulsion compositions.

The presently useful compositions may include one or more other components in amounts effective to facilitate the usefulness and effectiveness of the present methods and/or the presently useful compositions. Examples of such other components include, without limitation, emulsifier components, surfactant components, tonicity components, poly electrolyte components, emulsion stability components, viscosity inducing components, demulcent components, acid and/or bases to adjust the pH of the composition, buffer components, preservative components and the like.

In one very useful embodiment, the presently useful compositions are substantially free of preservatives. Thus, the presently useful compositions may be sterilized and maintained in a sterile condition prior to use, for example, provided in a sealed package or otherwise maintained in a substantially sterile condition.

Any suitable emulsifier component may be employed in the presently useful compositions, provided, that such emulsifier component is effective informing maintaining the emulsion and/or in the hydrophobic component in emulsion, while having no significant or undue detrimental effect or effects on the compositions during storage or use.

In addition, the presently useful compositions, as well as each of the components of the present compositions in the concentration present in the composition advantageously are ophthalmically acceptable.

Useful emulsifier components may be selected from such component which are conventionally used and well known in the art. Examples of such emulsifier components include, without limitation, surface active components or surfactant components which may be anionic, cationic, nonionic or amphorteric in nature. In general, the emulsifier component includes a hydrophobic constituent and a hydrophilic constituent. Advantageously, the emulsifier component is water soluble in the presently useful compositions. Preferably, the emulsifier component is nonionic. Specific examples of suitable emulsifier components include, without limitation, polysorbate 80, polyoxyalkylene alkylene ethers, polyalkylene oxide ethers of alkyl alcohols, polyalkylene oxide ethers of alkylphenols, other emulsifiers/surfactants, preferably nonionic emulsifiers/surfactants, useful in ophthalmic compositions, and the like and mixtures thereof.

The emulsifier component is present in an amount effective in forming the present emulsion and/or in maintaining the hydrophobic component in emulsion with the water or aqueous component. In one preferred embodiment, the emulsifier component is present in an amount in a range of about 0.1% to about 5%, more preferably about 0.2% to about 2% and still more preferably about 0.5% to about 1.5% by weight of the presently useful compositions.

Polyelectrolyte or emulsion stabilizing components may be included in the presently useful compositions. Such components are believed to be effective in maintaining the electrolyte balance in the presently useful emulsions, thereby stabilizing the emulsions and preventing the emulsions from breaking down prior to use. In one embodiment, the presently useful compositions include a polyanionic component effective as an emulsion stabilizing component. Examples of suitable polyanionic components useful in the presently useful compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing polymers, anionic methacrylic acid-containing polymers, anionic amino acid-containing polymers and the like and mixtures thereof.

A particularly useful class of polyanionic components include one or more polymeric materials having multiple anionic charges. Examples include, but are not limited to:

- metal carboxy methylcelluloses
- metal carboxy methylhydroxyethylcelluloses
- metal carboxy methylstarches
- metal carboxy methylhydroxyethlystarches
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- glucoaminoglycans
- hyaluronic acid
- chondroitin sulfate
- dermatan sulfate
- peptides and polypeptides
- alginic acid
- metal alginates
- homopolymers and copolymers of one or more of:
- acrylic and methacrylic acids
- metal acrylates and methacrylates
- vinylsulfonic acid
- metal vinylsulfonate
- amino acids, such as aspartic acid, glutamic acid and the like
- metal salts of amino acids
- p-styrenesulfonic acid
- metal p-styrenesulfonate
- 2-methacrylolyoxyethlysulfonic acids
- metal 2-methacryloyloxethylsulfonates
- 3-methacryloyloxy-2-hydroxyproplysulfonic acids
- metal 3-methacryloyloxy-2-hydroxypropylsulfonates
- 2-acrylamido-2-methylpropanesulfonic acids
- metal 2-acrylamido-2-methylpropanesulfonates
- allylsulfonic acid
- metal allylsulfonate and the like.

One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate crosslinked with allyl ethers of pentaerythritol.

The presently useful polyanionic components may also be used to provide a suitable viscosity to the presently useful compositions. Thus, the polyanionic components may be useful in stabilizing the presently useful emulsions and in providing a suitable degree of viscosity to the presently useful compositions.

The polyelectrolyte or emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion. For example, the polyelectrolyte/emulsion stabilizing component may be present in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition.

Any suitable tonicity component may be employed in accordance with the present invention. Preferably, such tonicity component is non-ionic, for example, in order to avoid interfering with the other components in the presently useful emulsions and to facilitate maintaining the stability of the emulsion prior to use. Useful tonicity agents include, without limitation, glycerine, mannitol, sorbitol and the like and mixtures thereof. The presently useful emulsions are preferably within the range of plus or minus about 20% or about 10% from being isotonic.

Ophthalmic demulcent components may be included in effective amounts in the presently useful compositions. For example, ophthalmic demulcent components such as carboxymethylcellulose, other cellulose polymers, dextran 70, gelatin, glycerine, polyethylene glycols (e.g., PEG 300 and PEG 400), polysorbate 80, propylene glycol, polyvinyl, alcohol, povidone and the like and mixtures thereof, may be used in the present ophthalmic compositions, for example, compositions useful for treating dry eye.

The demulcent components are preferably present in the compositions, for example, in the form of eye drops, in an amount effective in enhancing the lubricity of the presently useful compositions. The amount of demulcent component in the present compositions may be in a range of at least about 0.01% or about 0.02% to about 0.5% or about 1.0% by weight of the composition.

Many of the presently useful polyelectrolyte/emulsion stabilizing components may also be effective as demulcent components, and vice versa. The emulsifier/surfactant components may also be effective as demulcent components and vice versa.

The pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide and/or hydrochloric acid to a physiological pH level. The pH of the presently useful emulsions preferably is in the range of about 6 to about 10, more preferably about 7.0 to about 8.0 and still more preferably about 7.2 to about 7.6.

Although buffer components are not required in the presently useful compositions, suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH in the presently useful compositions.

The presently useful compositions may include an effective amount of a preservative component. Any suitable preservative or combination of preservatives may be employed. Examples of suitable preservatives include, without limitation, benzalkonium chloride, methyl and ethyl parabens, hexetidine, phenyl mercuric salts and the like and mixtures thereof. The amounts of preservative components included in the present compositions are such to be effective in preserving the compositions and can vary based on the specific preservative component employed, the specific composition involved, the specific application involved, and the like factors. Preservative concentrations often are in the range of about 0.00001% to about 0.05% or about 0.1% (w/v) of the composition, although other concentrations of certain preservatives may be employed.

Very useful examples of preservative components in the present invention include, but are not limited to, chlorite components. Specific examples of chlorite components useful as preservatives in accordance with the present invention include stabilized chlorine dioxide (SCD), metal chlorites such as alkali metal and alkaline earth metal chlorites, and the like and mixtures thereof. Technical grade (or USP grade) sodium chlorite is a very useful preservative component. The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Pat. No. 3,278,447, which is incorporated in its entirety by reference herein. Specific examples of useful SCD products include that sold under the trademark Dura Klor by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by

International Disoxide, Inc. An especially useful SCD is a product sold under the trademark Bio-Cide® by Bio-Cide International, Inc., as well as a product identified by Allergan, Inc. by the trademark Purite®.

Other useful preservatives include antimicrobial peptides. Among the antimicrobial peptides which may be employed include, without limitation, defensins, peptides related to defensins, cecropins, peptides related to cecropins, magainins and peptides related to magainins and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Mixtures of antimicrobial peptides or mixtures of antimicrobial peptides with other preservatives are also included within the scope of the present invention.

The compositions of the present invention may include viscosity modifying agents or components, such as cellulose polymers, including hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and carboxymethyl cellulose; carbomers (e.g. carbopol, and the like); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. Such viscosity modifying components are employed, if at all, in an amount effective to provide a desired viscosity to the present compositions. The concentration of such viscosity modifiers will typically vary between about 0.01 to about 5% w/v of the total composition, although other concentrations of certain viscosity modifying components may be employed.

The presently useful compositions may be produced using conventional and well known methods useful in producing ophthalmic products including oil-in-water emulsions.

In one example, the oily phase of the emulsion can be combined with the cyclosporin component to solubilize the cyclosporin component in the oily materiel phase. The oily phase and the water may be separately heated to an appropriate temperature. This temperature may be the same in both cases, generally a few degrees to about 10° C. above the melting temperature of the ingredient(s) having the highest melting point in the case of a solid or semi-solid oily phase for emulsifier components in the oily phase. Where the oily phase is a liquid at room temperature, a suitable temperature for preparation of a composition may be determined by routine experimentation in which the melting point of the ingredients aside from the oily phase is determined. In cases where all components of either the oily phase or the water phase are soluble at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble are dissolved in the water and oil soluble components including the surfactant components are dissolved in the oily phase.

To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water, phase or into the final water phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case where the final oil phase is first gently mixed into an intermediate water phase, the resulting emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase may not be at the same temperature or heated above room temperature, as the emulsion may be already formed at this point.

The oil-in-water emulsions of the present invention can be sterilized after preparation using heat, for example, autoclave steam sterilization or can be sterile filtered using, for example, a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet sized material may be acceptable.

The present oil-in-water emulsions preferably are thermodynamically stable, much like microemulsions, and yet may not be isotropic transparent compositions as are microemulsions. The emulsions of the present invention advantageously have a shelf life exceeding one year at room temperature.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Two compositions are selected for testing. These compositions are produced in accordance with well known techniques and have the following make-ups:

	Composition I wt %	Composition II wt %
Cyclosporin A	0.1	0.05
Castor Oil	1.25	1.25
Polysorbate 80	1.00	1.00
Premulen ®	0.05	0.05
Glycerine	2.20	2.20
Sodium hydroxide	qs	qs
Purified Water	qs	qs
pH	7.2-7.6	7.2-7.6
Weight Ratio of Cyclosporin A to Castor Oil	0.08	0.04

These compositions are employed in a Phase 3, double-masked, randomized, parallel group study for the treatment of dry eye disease.

The results of this study indicate that Composition II, in accordance with the present invention, which has a reduced concentration of cyclosporin A and a cyclosporin A to castor oil ratio of less than 0.08, provides overall efficacy in treating dry eye disease substantially equal to that of Composition I. This is surprising for a number of reasons. For example, the reduced concentration of cyclosporin A in Composition II would have been expected to result in reduced overall efficacy in treating dry eye disease. Also, the large amount of castor oil relative to the amount of cyclosporin A in Composition II might have been expected to cause increased eye irritation relative to Composition I. However, both Composition I and Composition II are found to be substantially non-irritating in use.

Using relatively increased amounts of castor oil, with reduced amounts of cyclosporin component, as in Composition II, is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome in combination with cyclosporin A.

In addition, it is found that the high concentration of castor oil relative to cyclosporin component, as in Composition II, provides the advantage of more quickly or rapidly (for example, relative to a composition which includes only 50% as much castor oil) breaking down or resolving the emulsion

in the eye, for example, as measured by split-lamp techniques to monitor the composition in the eye for phase separation. Such rapid break down of the emulsion in the eye reduces vision distortion as the result of the presence of the emulsion in the eye, as well as facilitating the therapeutic effectiveness of the composition in treating dry eye disease.

Using reduced amounts of cyclosporin A, as in Composition II, to achieve therapeutic effectiveness mitigates even further against undesirable side effects and potential drug interactions. Prescribing physicians can provide (prescribe) Composition II to more patients and/or with fewer restrictions and/or with reduced risk of the occurrence of adverse events, e.g., side effects, drug interactions and the like, relative to providing Composition I.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

What is claimed is:

1. A method of treating dry eye disease, the method comprising topically administering to a human eye in need thereof a first topical ophthalmic emulsion at a frequency of twice a day, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 005% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight;

wherein the method is therapeutically effective in treating dry eye disease;

wherein the method provides overall efficacy substantially equal to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight; and

wherein the method results in substantially no detectable concentration of cyclosporin A in the blood of the human.

2. The method of claim **1**, wherein the first topical ophthalmic emulsion further comprises a tonicity agent or a demulcent component.

3. The method of claim **2**, wherein the tonicity agent or the demulcent component is glycerine.

4. The method of claim **1**, wherein the first topical ophthalmic emulsion further comprises a buffer.

5. The method of claim **4**, wherein the buffer is sodium hydroxide.

6. The method of claim **1**, wherein the first topical ophthalmic emulsion further comprises glycerine and a buffer.

7. The method of claim **1**, wherein the first topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.

8. The method of claim **1**, wherein the first topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.

9. The method of claim **1**, wherein the first topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

10. The method of claim **9**, wherein the buffer is sodium hydroxide.

11. The method of claim **2**, wherein the first topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

12. The method of claim **1**, wherein substantially no detectable concentration of cyclosporin A in the blood of the human means that the concentration of cyclosporin A in the blood of the human is less than about 0.1 ng/ml.

13. A method of enhancing tearing in a human eye, the method comprising topically administering to a human eye in need thereof a first topical ophthalmic emulsion at a frequency of twice a day, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight;

wherein the method is therapeutically effective in treating dry eye disease and wherein the method achieves at least as much therapeutic efficacy as administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight; and

wherein the method results in a concentration of cyclosporin A in the blood of the human of less than about 0.1 ng/ml.

14. The method of claim **13**, wherein the first topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight, polysorbate 80 in an amount of about 1.0% by weight, and wherein the first topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

15. The method of claim **14**, wherein the first topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

16. The method of claim **13**, wherein the method is effective in enhancing lacrimal gland tearing.

17. A method of treating dry eye disease, the method comprising topically administering to a human eye in need thereof a first topical ophthalmic emulsion at a frequency of twice a day, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and

wherein the first topical ophthalmic emulsion breaks down more quickly in the human eye, once administered to the human eye, thereby reducing vision distortion in the human eye as compared to a second topical ophthalmic emulsion that contains only about 50% as much castor oil as the first topical ophthalmic emulsion.

18. The method of claim **17**, wherein the first topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight, polysorbate 80 in an amount of about 1.0% by weight, and wherein the first topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

19. The method of claim **18**, wherein the first topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

20. The method of claim **19**, wherein the method results in a concentration of cyclosporin A in the blood of the human of less than about 0.1 ng/ml.

21. A method of restoring tearing, the method comprising topically administering to a human eye in need thereof a first topical ophthalmic emulsion at a frequency of twice a day, wherein the first topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight;

wherein the method demonstrates a reduction in adverse events in the human, compared to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second topical ophthalmic emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight; and

wherein the method achieves at least as much therapeutic efficacy as administration of the second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day.

22. The method of claim **21**, wherein the method results in a concentration of cyclosporin A in the blood of the human of less than about 0.1 ng/ml.

23. The method of claim **21**, wherein the adverse events are selected from the group consisting of visual distortion and eye irritation.

24. The method of claim **21**, wherein the first topical ophthalmic emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight, polysorbate 80 in an amount of about 1.0% by weight, and wherein the first topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight and a buffer.

25. The method of claim **24**, wherein the first topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

26. The method of claim **21**, wherein the method is effective in restoring lacrimal gland tearing.

27. The method of claim **21**, wherein the adverse events are selected from the group consisting of visual distortion and eye irritation and wherein the method results in a concentration of cyclosporin A in the blood of the human of less than about 0.1 ng/ml.

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