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(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)

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

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 3,278,447 | A | 10/1966 | McNicholas |
| 4,388,229 | A | 6/1983 | Fu |
| 4,388,307 | A | 6/1983 | Cavanak |
| 4,614,736 | A | 9/1986 | Delevallee et al. |
| 4,649,047 | A | 3/1987 | Kaswan |
| 4,764,503 | A | 8/1988 | Wenger |
| 4,814,323 | A | 3/1989 | Andrieu et al. |
| 4,839,342 | A | 6/1989 | Kaswan |
| 4,970,076 | A | 11/1990 | Horrobin |
| 4,990,337 | A | 2/1991 | Kurihara et al. |
| 4,996,193 | A | 2/1991 | Hewitt et al. |
| 5,047,396 | A | 9/1991 | Orban et al. |
| 5,051,402 | A | 9/1991 | Kurihara et al. |
| 5,053,000 | A | 10/1991 | Booth et al. |
| 5,286,730 | A | 2/1994 | Caufield et al. |
| 5,286,731 | A | 2/1994 | Caufield et al. |
| 5,294,604 | A | 3/1994 | Nussenblatt et al. |
| 5,296,158 | A | 3/1994 | MacGilp et al. |
| 5,342,625 | A | 8/1994 | Hauer et al. |
| 5,368,854 | A | 11/1994 | Rennick |
| 5,411,952 | A | 5/1995 | Kaswan |
| 5,424,078 | A | 6/1995 | Dziabo |
| 5,474,919 | A | 12/1995 | Chartrain et al. |
| 5,474,979 | A | 12/1995 | Ding et al. |
| 5,504,068 | A | 4/1996 | Komiya et al. |
| 5,540,931 | A | 7/1996 | Hewitt et al. |
| 5,543,393 | A | 8/1996 | Kim et al. |
| 5,589,455 | A | 12/1996 | Woo |
| 5,591,971 | A | 1/1997 | Shahar et al. |
| 5,614,491 | A | 3/1997 | Walch et al. |
| 5,639,724 | A | 6/1997 | Cavanak |
| 5,652,212 | A | 7/1997 | Cavanak et al. |
| 5,719,123 | A | 2/1998 | Morley et al. |
| 5,739,105 | A | 4/1998 | Kim et al. |
| 5,753,166 | A | 5/1998 | Dalton et al. |
| 5,766,629 | A | 6/1998 | Cho et al. |
| 5,798,333 | A | 8/1998 | Sherman |
| 5,807,820 | A | 9/1998 | Elias et al. |
| 5,827,822 | A | 10/1998 | Floch'h et al. |
| 5,827,862 | A | 10/1998 | Yamamura |
| 5,834,017 | A | 11/1998 | Cho et al. |
| 5,843,452 | A | 12/1998 | Wiedmann et al. |
| 5,843,891 | A | 12/1998 | Sherman |
| 5,858,401 | A | 1/1999 | Bhalani et al. |
| 5,866,159 | A | 2/1999 | Hauer et al. |
| 5,891,846 | A | 4/1999 | Ishida et al. |

(Continued)

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| DE | 19810655 | 9/1999 |
| EP | 0471293 | 2/1992 |

(Continued)

OTHER PUBLICATIONS

Abdulrazik, M. et al, Ocular Delivery of Cyclosporin A II. Effect of Submicron Emulsion's Surface Charge on Ocular Distribution of Topical Cyclosporin A, S.T.P. Pharma Sciences, Dec. 2001, 427-432, 11(6).

Acheampong, Andrew et al, Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog and Human eyes, 1996, 179.

Acheampong, Andrew et al, Cyclosporine Distribution Into the Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes, Adv. Exp. Med. Biol., 1998, 1001-1004, 438.

Acheampong, Andrew et al, Distribution of Cyclosporin A in Ocular Tissues After Topical Administration to Albino Rabbits and Beagle Dogs, Current Eye Research, 1999, 91-103, 18(2).

(Continued)

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

(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**

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | | |
|---|---|---|---|---|
| 5,916,589 | A | 6/1999 | Hauer et al. | |
| 5,929,030 | A | 7/1999 | Hamied et al. | |
| 5,951,971 | A | 9/1999 | Kawashima et al. | |
| 5,962,014 | A | 10/1999 | Hauer et al. | |
| 5,962,017 | A | 10/1999 | Hauer et al. | |
| 5,962,019 | A | 10/1999 | Cho et al. | |
| 5,977,066 | A | 11/1999 | Cavanak | |
| 5,981,479 | A | 11/1999 | Ko et al. | |
| 5,981,607 | A | 11/1999 | Ding et al. | |
| 5,998,365 | A | 12/1999 | Sherman | |
| 6,004,566 | A | 12/1999 | Friedman et al. | |
| 6,007,840 | A | 12/1999 | Hauer et al. | |
| 6,008,191 | A | 12/1999 | Singh | |
| 6,008,192 | A | 12/1999 | Al-Razzak et al. | |
| 6,022,852 | A | 2/2000 | Klokkers et al. | |
| 6,024,978 | A | 2/2000 | Hauer et al. | |
| 6,046,163 | A | 4/2000 | Stuchlik et al. | |
| 6,057,289 | A | 5/2000 | Mulye | |
| 6,159,933 | A | 12/2000 | Sherman | |
| 6,197,335 | B1 | 3/2001 | Sherman | |
| 6,254,860 | B1 | 7/2001 | Garst | |
| 6,254,885 | B1 | 7/2001 | Cho et al. | |
| 6,267,985 | B1 | 7/2001 | Chen et al. | |
| 6,284,268 | B1 | 9/2001 | Mishra et al. | |
| 6,294,192 | B1 | 9/2001 | Patel et al. | |
| 6,306,825 | B1 | 10/2001 | Cavanak | |
| 6,323,204 | B1 | 11/2001 | Burke | |
| 6,346,511 | B1 | 2/2002 | Singh et al. | |
| 6,350,442 | B2 | 2/2002 | Garst | |
| 6,413,547 | B1 | 7/2002 | Bennett et al. | |
| 6,420,355 | B2 | 7/2002 | Richter et al. | |
| 6,468,968 | B2 | 10/2002 | Cavanak et al. | |
| 6,475,519 | B1 | 11/2002 | Meinzer et al. | |
| 6,486,124 | B2 | 11/2002 | Olbrich et al. | |
| 6,544,953 | B2 | 4/2003 | Tsuzuki et al. | |
| 6,555,526 | B2 | 4/2003 | Matsuo | |
| 6,562,873 | B2 | 5/2003 | Olejnik et al. | |
| 6,569,463 | B2 | 5/2003 | Patel et al. | |
| 6,582,718 | B2 | 6/2003 | Kawashima | |
| 6,656,460 | B2 | 12/2003 | Benita et al. | |
| 6,872,705 | B2 | 3/2005 | Lyons | |
| 6,984,628 | B2 * | 1/2006 | Bakhit et al. | 514/20.8 |
| 7,202,209 | B2 | 4/2007 | Chang | |
| 7,276,476 | B2 | 10/2007 | Chang et al. | |
| 7,288,520 | B2 | 10/2007 | Chang et al. | |
| 7,297,679 | B2 | 11/2007 | Chang | |
| 7,501,393 | B2 | 3/2009 | Tien et al. | |
| 8,211,855 | B2 | 7/2012 | Chang et al. | |
| 8,288,348 | B2 | 10/2012 | Chang et al. | |
| 2001/0003589 | A1 | 6/2001 | Neuer et al. | |
| 2001/0014665 | A1 | 8/2001 | Fischer et al. | |
| 2001/0036449 | A1 | 11/2001 | Garst | |
| 2002/0012680 | A1 | 1/2002 | Patel et al. | |
| 2002/0013272 | A1 | 1/2002 | Cavanak et al. | |
| 2002/0016290 | A1 | 2/2002 | Floc'h et al. | |
| 2002/0016292 | A1 | 2/2002 | Richter et al. | |
| 2002/0025927 | A1 | 2/2002 | Olbrich et al. | |
| 2002/0045601 | A1 | 4/2002 | Kawashima | |
| 2002/0107183 | A1 | 8/2002 | Petszulat et al. | |
| 2002/0119190 | A1 | 8/2002 | Meinzer et al. | |
| 2002/0165134 | A1 | 11/2002 | Richter et al. | |
| 2003/0021816 | A1 | 1/2003 | Kang et al. | |
| 2003/0044452 | A1 | 3/2003 | Ueno | |
| 2003/0055028 | A1 | 3/2003 | Stergiopoulos et al. | |
| 2003/0059470 | A1 | 3/2003 | Muller | |
| 2003/0060402 | A1 | 3/2003 | Cavanak et al. | |
| 2003/0087813 | A1 | 5/2003 | Or et al. | |
| 2003/0104992 | A1 | 6/2003 | Or et al. | |
| 2003/0108626 | A1 | 6/2003 | Benita et al. | |
| 2003/0109425 | A1 | 6/2003 | Or et al. | |
| 2003/0109426 | A1 | 6/2003 | Or et al. | |
| 2003/0133984 | A1 | 7/2003 | Ambuhl et al. | |
| 2003/0143250 | A1 | 7/2003 | Hauer et al. | |
| 2003/0147954 | A1 | 8/2003 | Yang et al. | |
| 2003/0166517 | A1 | 9/2003 | Fricker et al. | |
| 2005/0014691 | A1 | 1/2005 | Bakhit et al. | |
| 2005/0059583 | A1 | 3/2005 | Acheampong | |
| 2007/0015691 | A1 | 1/2007 | Chang | |
| 2007/0027072 | A1 | 2/2007 | Tien et al. | |
| 2007/0087962 | A1 | 4/2007 | Tien et al. | |
| 2007/0149447 | A1 | 6/2007 | Chang et al. | |
| 2007/0299004 | A1 | 12/2007 | Acheampong et al. | |
| 2008/0039378 | A1 | 2/2008 | Graham et al. | |
| 2008/0070834 | A1 | 3/2008 | Chang et al. | |
| 2008/0146497 | A1 | 6/2008 | Graham et al. | |
| 2008/0207495 | A1 | 8/2008 | Graham et al. | |
| 2009/0131307 | A1 | 5/2009 | Tien et al. | |
| 2010/0279951 | A1 | 11/2010 | Morgan et al. | |
| 2011/0009339 | A1 | 1/2011 | Schiffman | |
| 2011/0294744 | A1 | 12/2011 | Morgan et al. | |
| 2012/0270805 | A1 | 10/2012 | Chang et al. | |
| 2013/0059796 | A1 | 3/2013 | Chang et al. | |

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| EP | 0547229 | 1/1993 |
| EP | 0760237 | 3/1997 |
| WO | 95-31211 | 11/1995 |
| WO | 00-00179 | 1/2000 |
| WO | 01-32142 | 5/2001 |
| WO | 01-41671 | 6/2001 |
| WO | 02-09667 | 2/2002 |
| WO | 02-49603 | 6/2002 |
| WO | 03-030834 | 4/2003 |
| WO | 03-053405 | 7/2003 |

OTHER PUBLICATIONS

Akpek, Esen Karamursel et al, A Randomized Trial of Topical Cyclosporin 0.05% in Topical Steroid-Resistant Atopic Keratoconjunctivitis, Ophthalmology, 2004, 476-482, 111.

Angelov, O. et al, Preclinical Safety Studies of Cyclosporine Ophthalmic Emulsion, Adv Exp Med Biol, 1998, 991-995, 438.

Angelov, O. et al, Safety Assessment of Cyclosporine Ophthalmic Emulsion in Rabbits and Dogs, XIth Congress of the European Society of Ophthalmology, 1997, 25-28, 1-5, Soc. Ophthalmol Eur., Hu.

Ardizzone Sandro et al, A Practical Guide to the Management of Distal Ulceratve Colitis, Drugs, 1998, 519-542, 55(4).

Banic, Marko et al, Effect of Cyclosporine in a Murine Model of Experimental Colitis, Digestve Diseases and Sciences, Jun. 2002, 1362-1368, 47(6).

Bonini, S. et al, Vernal Keratoconjunctivitis, Eye, 2004, 345-351, 18.

Brewster, Marcus et al, Enhanced Delivery of Ganciclovir to the Brain Though the Use of Redox Targeting, Antimicrobial Agents and Chemotherapy, Apr. 1994, 817-823, 38(4).

Brewster, Marcus et al, Intravenous and Oral Pharmacokinetic Evaluation of a 2-Hydroxypropyl-β-cyclodextrin-Based Formulation of Carbamazepine in the Dog: Comparison with Commercially Available Tablets and Suspensions, Journal of Pharmaceutical Sciences, Mar. 1997, 335-339, 86(3).

Brewster, Marcus et al, Preparation, Characterization, and Anesthetic Properties of 2-Hydroxypropyl-β-cyclodextrin Complexes of Pregnanolone and Pregnenolone in Rat and Mouse, Journal of Pharmaceutical Sciences, Oct. 1995, 1154-1159, 84(10).

Brinkmeier, Thomas et al, Pyodermatitis-Pyostomatitis Vegetans: A Clinical Course of Two Decades with Response to Cyclosporine and Low-Dose Prednisolone, Acta Derm Venereol, 2001, 134-136, 81.

Castillo, Jose M. Benitez Del et al, Influence of Topical Cyclosporine A and Dissolvent on Corneal Epithelium Permeability of Fluorescein, Documenta Ophthalmologica, 1995, 49-55, 91.

Cheeks, Lisa et al, Influence of Vehicle and Anterior Chamber Protein Concentration on Cyclosporine Penetration Through the Isolated Rabbit Cornea, Current Eye Research, 1992, 641-649, 11(7).

Database WPI Week 200044, Derwent Pub. Ltd., London, GB; An 2000-492678 & JP2000/143542, 2000, 2 Pages.

Ding, Shulin et al, Cyclosporine Ophthalmic O/W emulsion: Formulation and Emulsion Characterization, Pharm Res, 1997, 1 page, 14 (11).

Donnenfeld, Eric D., The Economics of Using Restasis, Ophthalmology Management, Oct. 2003, 3 pages, US.

Drosos, A. A. et al, Efficacy and Safety of Cyclosporine-A Therapy for Primary Sjogren's Syndrome, Ter. Arkh., 1998, 77-80, 60(4).

(56) **References Cited**

OTHER PUBLICATIONS

Drosos, A.A. et al, Cyclosporin A Therapy in Patients with Primary Sjogren's Syndrome: Results at One Year, Scand J Rheumatology, 1986, 246-249, 61.

Eisen, Drore et al, Topical Cyclosporine for Oral Mucosal Disorders, J Am Acad Dermatol, Dec. 1990, 1259-1264, 23.

Epstein, Joel et al, Topical Cyclosporine in a Bioadhesive for Treatment of Oral Lichenoid Muscosal Reactions, Oral Surg Oral Med Oral Pathol Oral, 1996, 532-536, 82.

Erdmann, S. et al, Pemphigus Vulgaris Der Mund- Und Kehlkopfschleimhaut Pemphigus Vulgaris of the Oral Mucosa and the Larynx, H+G Zeitschrift Fuer Hautkrankheiten, 1997, 283-286, 72(4).

FDA Concludes Restasis (Cyclosporine) Not Effective for Dry Eye (Jun. 18, 1999). Accessed online at http://www.dryeyeinfo.org/Restasis_Cyclosporine.htm on Aug. 14, 2009. 1 Page.

Gaeta, G.M. et al, Cyclosporin Bioadhesive Gel in the Topical Treatment of Erosive Oral Lichen Planus, International Journal of Immunopathology and Pharmacology, 1994, 125-132, 7(2).

Gipson, Ilene et al, Character of Ocular Surface Mucins and Their Alteration in Dry Eye Disease, The Ocular Surface, Apr. 2004, 131-148, 2(2).

Gremse, David et al, Ulcerative Colitis in Children, Pediatr Drugs, 2002, 807-815, 4(12).

Gunduz, Kaan et al, Topical Cyclosporin Treatment of Keratoconjunctivitis Sicca in Secondary Sjogren's Syndrome, Acta Ophthalmologica, 1994, 438-442, 72.

http://web.archive.org/web/20010306253231/http://www.surfactant.co.kr/surfactants/pegester.html, 2001, 6 Pages, retrieved on Jul. 5, 2008.

Hunter, P.A. et al, Cyclosporin A Applied Topically to the Recipient Eye Inhibits Corneal Graft Rejection, Clin Exp Immunol, 1981, 173-177, 45.

Jumaa, Muhannad et al, Physicochemical Properties and Hemolytic Effect of Different Lipid Emulsion Formulations Using a Mixture of Emulsifiers, Pharmaceutica Acta Helvetiae, 1999, 293-301, 73.

Kanai, A. et al, The Effect on the Cornea of Alpha Cyclodextrin Vehicle for Eye Drops, Transplantation Proceedings, Feb. 1989, 3150-3152, vol. 21.

Kanpolat, Ayfer et al, Penetration of Cyclosporin A into the Rabbit Cornea and Aqueous Humor after Topical Drop and Collagen Shield Administration, Cornea/External Disease, Apr. 1994, 119-122, 20(2).

Kaur, Rabinder et al, Solid Dispersions of Drugs in Polyocyethylene 40 Stearate: Dissolution Rates and Physico-Chemical Interactions, Journal of Pharmacy and Pharmacology, Dec. 1979, 48P.

Kuwano, Mitsuaki et al, Cyclosporine A Formulation Affects Its Ocular Distribution in Rabbits, Pharmaceutical Research, Jan. 2002, 108-111, 19(1).

Lambert Technologies Corp. Material Safety Data Sheet for LUMULSE™ POE-40 MS KP, last revision Aug. 22, 2003. 3 pages.

Leibovitz, Z. et al., Our Experience In Processing Maize (Corn) Germ Oil, Journal of the American Oil Chemists Society, Feb. 1983, 395-399, 80 (2), US.

Lixin, Xie et al, Effect of Cyclosporine A Delivery System in Corneal Transplantation, Chinese Medical Journal, 2002, 110-113, 115 (1), US.

Lopatin, D.E., Chemical Compositions and Functions of Saliva, Aug. 24, 2001, 31 Pages.

Lyons, R.T. et al, Influence of Three Emulsion Formulation Parameters on the Ocular Bioavailability of Cyclosporine A in Albino Rabbits, Am Assoc Pharm Sci, 2000, 1 Page, 2(4).

Pedersen, Anne Marie et al, Primary Sjogren's Syndrome: Oral Aspects on Pathogenesis, Diagnostic Criteria, Clinical Features and Approaches for Therapy, Expert Opin Pharma, 2001, 1415-1436, 2(9).

Phillips, Thomas et al, Cyclosporine Has a Direct Effect on the Differentiation of a Mucin-Secreting Cell Line, Journal of Cellular Physiology, 2000, 400-408, 184.

Present, D.H. et al, Cyclosporine and Other Immunosuppressive Agents: Current and Future Role in the Treatment of Inflammatory Bowel Disease, American Journal of Gastroenterology, 1993, 627-630, 88(5).

Restasis® Product Information Sheet, Allergan, Inc., 2009, 5 Pages.

Restasis® Increasing Tear Production, Retrieved on Aug. 14, 2009, http://www.restasisprofessional.com/_clinical/clinical_increasing.htm 3 pages.

Robinson, N.A. et al, Desquamative Gingivitis: A Sign of Mucocutaneous Disorders—a Review, Australian Dental Journal, 2003, 205-211, 48(4).

Rudinger, J., Characteristics of the Amino Acids as Components of a Peptide Hormone Sequence, Peptide Hormones, 1976, 1-7.

Sall, Kenneth et al, Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease, Ophthalmology, 2000, 631-639, 107.

Sandborn, William et al, A Placebo-Controlled Trial of Cyclosporine Enemas for Mildly to Moderately Active Left-Sided Ulcerative Colitis, Gastroenterology, 1994, 1429-1435, 106.

Sandborn, William et al, Cyclosporine Enemas for Treatment-Resistant, Mildly to Moderately Active, Left-Sided Ulcerative Colitis, American Journal of Gastroenterology, 1993, 640-645, 88(5).

Schwab, Matthias et al, Pharmacokinetic Considerations in the Treatment of Inflammatory Bowel Disease, Clin Pharm, 2001, 723-751, 60(10).

Secchi, Antonio et al, Topical Use of Cyclosporine in the Treatment of Vernal Keratoconjunctivitis, American Journal of Ophthalmology, Dec. 1990, 641-645, 110.

Small, Dave et al, The Ocular Pharmacokinetics of Cyclosporine in Albino Rabbits and Beagle Dogs, Ocular Drug Delivery and Metabolism, 1999, 54.

Small, David et al, Blood Concentrations of Cyclosporin A During Long-Term Treatment With Cyclosporin A ophthalmic Emulsions in Patients with Moderate to Severe Dry Eye Disease, Journal of Ocular Pharmacology and Therapeutics, 2002, 411-418, 18(5).

Smilek, Dawn et al, A Single Amino Acid Change in a Myelin Basic Protein Peptide Confers the Capacity to Prevent Rather Than Induce Experimental Autoimmune Encephalomyelitis, Proc. Natl. Acad. Sci., Nov. 1991, 9633-9637, 88.

Stephenson, Michelle, The Latest Uses of Restasis, Review of Ophthalmology, Dec. 30, 2005, 7 Pages, US.

Stevenson, Dara et al, Efficacy and Safety of Cyclosporin A ophthalmic Emulsion in the Treatment of Moderate-to-Severe Dry Eye Disease, Ophthalmology, 2000, 967-974, 107.

Tesavibul, N. et al, Topical Cyclosporine A (CsA) for Ocular Surface Abnormalities in Graft Versus Host Disease Patients, Invest Ophthalmol Vis Sci, Feb. 1996, S1026, 37(3).

The Online Medical Dictionary, Derivative, Analog, Analogue, Xerostomia, accessed Jul. 7, 2005 and Jul. 13, 2005, 6 Pages.

Tibell, A. et al., Cyclosporin A In Fat Emulsion Carriers: Experimental Studies on Pharmacokinetics and Tissue Distribution, Pharmacology & Toxicology, 1995, 115-121, 76, US.

Tsubota, Kazuo et al, Use of Topical Cyclosporin A in a Primary Sjogren's Syndrome Mouse Model, Invest Ophthalmol Vis Sci, Aug. 1998, 1551-1559, 39(9).

Van Der Reijden, Willy et al, Treatment of Oral Dryness Related Complaints (Xerostomia) in Sjogren's Syndrome, Ann Rheum Dis, 1999, 465-473, 58.

Winter, T.A. et al, Cyclosporin A Retention Enemas in Refractory Distal Ulcerative Colitis and 'Pouchitis', Scand J Gastroenterol, 1993, 701-704, 28.

Pending U.S. Appl. No. 13/967,189, filed Aug. 14, 2013.

Pending U.S. Appl. No. 13/961,818, filed Aug. 7, 2013.

Pending U.S. Appl. No. 13/961,828, filed Aug. 7, 2013.

Pending U.S. Appl. No. 13/961,835, filed Aug. 7, 2013.

Pending U.S. Appl. No. 13/961,808, filed Aug. 7, 2013.

Pending U.S. Appl. No. 13/967,163, filed Aug. 14, 2013.

Pending U.S. Appl. No. 13/967,168, filed Aug. 14, 2013.

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* cited by examiner

# 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

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