



US008642556B2

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

(10) **Patent No.:** **US 8,642,556 B2**
(45) **Date of Patent:** ***Feb. 4, 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.: **13/967,189**

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

(65) **Prior Publication Data**

US 2013/0331341 A1 Dec. 12, 2013

Related U.S. Application Data

(63) Continuation of application No. 13/961,808, 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**
CPC A61K 38/13; A61K 9/0048
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.

(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).

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.

(Continued)

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

20 Claims, No Drawings

(56)

References Cited

U.S. PATENT DOCUMENTS

5,866,159 A 2/1999 Hauer et al.
 5,891,846 A 4/1999 Ishida et al.
 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

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 Ulcerative Colitis, Drugs, 1998, 519-542, 55(4).
 Banic, Marko et al, Effect of Cyclosporine in a Murine Model of Experimental Colitis, Digestive 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 Through 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, Pyodermitis-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).
 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.

(56)

References Cited

OTHER PUBLICATIONS

- Eisen, Dore 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 Mucosal 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/2001030625323/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 Helveticae*, 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 Polyocethylene 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. 13/961,808, filed Aug. 7, 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. 13/967,179, filed Aug. 14, 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.
- U.S. Re-Examination Application: 90/009,944 and its entire prosecution history, filed on Aug. 27, 2011.

* cited by examiner

1

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 entirety 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; "Cyclosporin 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 cyclosporine 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 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

2

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 keratoconjunctivitis, 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

3

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 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

4

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.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.