

(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**
- (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.: **13/967,179**
- (22) Filed: **Aug. 14, 2013**
- (65) **Prior Publication Data**  
US 2013/0338083 A1 Dec. 19, 2013

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.

**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.
- (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.

(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.	

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 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- $\beta$ -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- $\beta$ -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

(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, Drorre 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](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 Helvetica*, 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 Polyocetylhlene 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](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.
- U.S. Re-Examination Application: 90/009,944 Filed on Aug. 27, 2011.

\* 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 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):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 emul-

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 keratoconjunctivitis, corneal graft rejection and the like conditions. The present invention is particularly effective in treating dry eye syndrome.

Employing reduced concentrations of cyclosporin compo-

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

positions. 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

# 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.