IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

NOVARTIS AG, Lichtstrasse 35, CH-4056, Basel, Switzerland; and NOVARTIS PHARMACEUTICALS CORPORATION, 59 Route 10, East Hanover, New Jersey 07936 Plaintiffs, v. ACCORD HEALTHCARE, INC. USA, 1009 Slater Road, Suite 210-B, Durham, North Carolina 27703; and INTAS PHARMACEUTICAL LTD., Chinubhai Centre, off Nehru Bridge, Ashram Road, Ahmedabad 38009, Gujarat, India Defendants.	Case No.: _____

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Novartis AG and Novartis Pharmaceuticals Corporation (hereinafter "Plaintiffs"), for their Complaint herein against Defendants Accord Healthcare, Inc. USA and Intas Pharmaceutical Ltd. (hereinafter "Defendants") allege as follows:

NATURE OF ACTION

1. This is an action for patent infringement.

PARTIES

2. Plaintiff Novartis AG is a corporation organized and existing under the laws of Switzerland, having an office and place of business at Lichtstrasse 35, CH-4056, Basel,

Switzerland.

3. Plaintiff Novartis Pharmaceuticals Corporation ("NPC") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 59 Route 10, East Hanover, New Jersey 07936.

4. On information and belief, Defendant Accord Healthcare, Inc. USA ("Accord") is a corporation organized under the laws of North Carolina, having a place of business at 1009 Slater Road, Suite 210-B, Durham, North Carolina 27703.

5. On information and belief, Defendant Intas Pharmaceutical Ltd. ("Intas") is a company organized under the laws of India, having a place of business at Chinubhai Centre, off Nehru Bridge, Ashram Road, Ahmedabad 380009, Gujarat, India.

6. On information and belief, Defendant Accord is a wholly owned subsidiary of Defendant Intas, and the acts of Defendant Accord complained of herein were and are aided and abetted by, and done with the cooperation, participation, and assistance of, Defendant Intas.

7. Defendant Accord has designated Chidambaram S. Iyer, Esq., of Sughrue Mion, PLLC, 2100 Pennsylvania Avenue, NW, Washington, D.C. 20037-3213 to accept service of process on Defendant Accord's behalf pursuant to 21 C.F.R. § 314.95(c)(7).

JURISDICTION AND VENUE

8. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

9. Because Defendant Accord has designated Chidambaram S. Iyer, Esq., of Sughrue Mion, PLLC, 2100 Pennsylvania Avenue, NW, Washington, D.C. 20037-3213, as

Defendant Accord's agent authorized to accept service of process for Defendant Accord in this action, it has hereby consented to personal jurisdiction in this district.

10. On information and belief, Defendant Intas is in the business of manufacturing, marketing, importing and selling pharmaceutical drug products, including generic drug products. On information and belief, Defendant Intas directly, or through its affiliates and agents, including Defendant Accord, markets and sells drug products throughout the United States and in this judicial district.

11. This Court has personal jurisdiction over Defendant Intas by virtue of *inter alia*, the abovementioned facts.

12. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and (c) and 28 U.S.C. § 1400(b).

CLAIM FOR RELIEF – PATENT INFRINGEMENT

13. Plaintiff NPC holds an approved new drug application ("NDA"), NDA No. 50-791, for Myfortic® delayed-release tablets (180 mg and 360 mg), which tablets contain the active ingredient mycophenolic acid, in its sodium salt form, mycophenolate sodium. Myfortic® tablets were approved by the United States Food and Drug Administration ("FDA") in 2004 for the prophylaxis (or prevention) of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids. NPC markets Myfortic® delayed-release tablets (180 mg and 360 mg) in the United States.

14. Myfortic® delayed-release tablets are an enteric formulation of mycophenolate sodium that delivers the active moiety mycophenolic acid. Mycophenolic acid is an immunosuppressant agent. As the sodium salt, mycophenolic acid can be chemically

designated as (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt.

15. Novartis AG is the owner of United States Letters Patent No. 6,025,391 ("the '391 patent"). The '391 patent was duly and legally issued on February 15, 2000. A true copy of the '391 patent is attached hereto as Exhibit A.

16. The '391 patent claims, *inter alia*, pharmaceutical compositions, containing a mycophenolate salt, adapted to prevent release of the mycophenolic salt in the stomach and to release the mycophenolate salt in the upper part of the intestinal tract. It also claims, *inter alia*, pharmaceutical compositions containing an enteric coated pharmaceutically acceptable mycophenolate salt. The '391 patent also claims, *inter alia,* methods of immunosuppressing a subject in need of immunosuppression, by administering a therapeutically effective amount of enteric coated pharmaceutically acceptable mycophenolate salt.

17. The '391 patent was assigned by the inventors to Novartis AG.

18. Novartis AG is the owner of United States Letters Patent No. 6,172,107 ("the '107 patent"). The '107 patent was duly and legally issued on January 9, 2001. A true copy of the '107 patent is attached hereto as Exhibit B.

19. The '107 patent claims, *inter alia*, pharmaceutical compositions, containing a mycophenolate salt, formulated to disintegrate selectively in the intestinal tract to release mycophenolate there. It also claims, *inter* alia, pharmaceutical compositions containing an enteric coating that are suitable as an immunosuppressant medicament. The '107 patent also claims, *inter alia,* methods of immunosuppressing a subject in need of immunosuppression, by administering a therapeutically effective amount of a composition formulated to disintegrate selectively in the intestinal tract to release mycophenolate there.

20. The '107 patent was assigned by the inventors to Novartis AG.

21. Novartis AG is the owner of United States Letters Patent No. 6,306,900 ("the '900 patent"). The '900 patent was duly and legally issued on October 23, 2001. A true copy of the '900 patent is attached hereto as Exhibit C.

22. The '900 patent claims, *inter alia*, pharmaceutical compositions, containing a mycophenolate salt, adapted to prevent release of mycophenolate in the stomach.

23. The '900 patent was assigned by the inventors to Novartis AG.

24. On information and belief, Defendant Accord submitted to the FDA an abbreviated new drug application ("ANDA") under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of generic Myfortic® delayed-release tablets 180 mg and 360 mg (hereinafter "Defendants' Products").

25. On information and belief, Defendants submitted their ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' Products before the expiration of the '391, '107 and '900 patents.

26. By filing the ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' Products before the expiration of the '391, '107 and '900 patents, Defendants have committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, the commercial manufacture, use, offer for sale, sale and/or importation of Defendants' Products for which Defendants seek approval will also infringe one or more claims of the '391, '107 and '900 patents.

27. Defendants' Products, if approved, will be administered to human patients in an amount effective to immunosuppress those patients, which administration constitutes direct infringement of the '391 and '107 patents. This will occur at Defendants' active behest, and with its specific intent, knowledge and encouragement. On information and belief, Defendants will actively induce, encourage, aid and abet this administration with the knowledge that it is in contravention of Plaintiffs' rights under the '391 and '107 patents.

28. Defendants made, and included in their ANDA, a certification under 21 U.S.C. § 355(j)(2)(vii)(IV) ("Paragraph IV certification") that, in their opinion and to the best of their knowledge, the '391, '107 and '900 patents are invalid. Defendants did not allege non-infringement of any of the '391, '107 and '900 patents in their Paragraph IV certification. Defendants did not allege unenforceability of any of the '391, '107 and '900 patents in their Paragraph IV certification.

29. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of any approval of the aforementioned ANDA relating to Defendants' Products be a date which is not earlier than the later of the April 10, 2017 expiration dates of the '391, '107 and '900 patents or any later date of exclusivity to which Plaintiffs are or become entitled. Further, Plaintiffs are entitled to an award of damages for any commercial sale or use of Defendants' Products, and any act committed by Defendants with respect to the subject matter claimed in the '391, '107 and '900 patents, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

30. On information and belief, when Defendants filed their ANDA, they were aware of the '391, '107 and '900 patents, and that the filing of their ANDA with the request for its approval prior to the expiration of that patent was an act of infringement.

31. This is an exceptional case, and Plaintiffs are entitled to an award of reasonable attorneys fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. Judgment that Defendants have infringed one or more claims of the '391, '107 and '900 patents by filing the aforesaid ANDA relating to Defendants' Products;

B. A permanent injunction restraining and enjoining Defendants and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Defendants' Products;

C. An Order that the effective date of any approval of the aforementioned ANDA relating to Defendants' Products be a date which is not earlier than the later of the expiration of the right of exclusivity under the '391, '107 and '900 patents, or any later right of exclusivity to which Plaintiffs are or become entitled;

D. Damages from Defendants for any commercial activity constituting infringement of the '391, '107 and '900 patents;

E. A finding that this is an exceptional case under 35 U.S.C. § 285, and that Plaintiffs are entitled to the costs and reasonable attorney fees in this action; and

F. Such other and further relief as the Court may deem just and proper.

Respectfully submitted,

Dated: September 9, 2011

Edmund J. Haughey (DC Bar No. 462773)
FITZPATRICK, CELLA, HARPER & SCINTO
975 F Street, NW
Washington, DC 20004-1462
Tel: (202) 530-1010
Fax: (202) 530-1055
E-mail: ehaughey@fchs.com

Attorney for Plaintiffs Novartis AG and Novartis Pharmaceuticals Corporation

Of Counsel:

Nicholas N. Kallas
Lisa Pensabene
FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104-3800
Tel: (212) 218-2100
Fax: (212) 218-2200
E-mail: nkallas@fchs.com, lpensabene@fchs.com

EXHIBIT A

US006025391A

United States Patent [19]

Haeberlin et al.

[11] Patent Number: 6,025,391

[45] Date of Patent: Feb. 15, 2000

[54] **ENTERIC-COATED PHARMACEUTICAL COMPOSITIONS OF MYCOPHENOLATE**

[75] Inventors: **Barbara Haeberlin**, Riehen; **Ching-Pong Mak**, Therwil, both of Switzerland; **Armin Meinzer**, Buggingen, Germany; **Jacky Vonderscher**, Riedisheim, France

[73] Assignee: **Novartis AG**, Basel, Switzerland

[21] Appl. No.: **09/077,398**

[22] PCT Filed: **Apr. 10, 1997**

[86] PCT No.: **PCT/EP97/01800**

§ 371 Date: **May 28, 1998**

§ 102(e) Date: **May 28, 1998**

[87] PCT Pub. No.: **WO97/38689**

PCT Pub. Date: **Oct. 23, 1997**

[30] **Foreign Application Priority Data**

Apr. 12, 1996 [GB] United Kingdom 9607564
Oct. 24, 1996 [GB] United Kingdom 9622028

[51] **Int. Cl.**[7] **A01N 43/08**; A61G 31/34

[52] **U.S. Cl.** **514/470**; 514/8; 514/11; 514/570; 514/576; 514/960; 514/962; 424/457; 424/458; 424/459; 424/461; 424/462; 424/463; 424/468; 424/474; 424/475; 424/479; 424/480; 424/482; 424/490; 424/493; 424/494; 424/495; 424/497

[58] **Field of Search** 424/457, 458, 424/459, 461, 462, 463, 468, 478, 475, 479, 480, 482, 490, 493, 494, 495, 497; 514/8, 11, 470, 570, 571, 960, 962

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,705,894	12/1972	Gerzon et al.	260/240
3,705,946	12/1972	Dyke et al	424/279
3,777,020	12/1973	Johnson	424/180
3,825,571	7/1974	Mori et al.	260/343.3
3,853,919	12/1974	Mori et al.	260/343.3
3,868,454	2/1975	Johnson	424/248
3,880,995	4/1975	Jones	424/180
3,903,071	9/1975	Holmes	260/210
4,005,108	1/1977	Kupchan et al. .	
4,017,647	5/1972	Ohno	427/3
4,234,684	11/1980	Abbott et al.	435/75
4,680,299	7/1987	Hesson	514/311
4,686,234	8/1987	Nelson et al.	514/469
4,725,622	2/1988	Nelson et al.	514/469
4,727,069	2/1988	Nelson et al.	514/211
4,753,935	6/1988	Nelson et al.	514/233.5
4,786,637	11/1988	Allison et al.	514/233.5
4,808,592	2/1989	Nelson et al.	514/233.5
4,847,381	7/1989	Sutherland et al.	546/156
4,868,153	9/1989	Allison et al.	514/470
4,959,387	9/1990	Nelson et al.	524/469
4,992,467	2/1991	Allison et al.	514/464

FOREIGN PATENT DOCUMENTS

704 326	3/1968	Belgium .
815330	5/1973	Belgium .
0 281 713	9/1988	European Pat. Off. .
0281713	9/1988	European Pat. Off. .
551182	7/1993	European Pat. Off. .
0691130	1/1996	European Pat. Off. .
31237	11/1967	South Africa .
1157099	7/1969	United Kingdom .
1157100	7/1969	United Kingdom .
1158387	7/1969	United Kingdom .
1 203 328	8/1970	United Kingdom .
1203328	8/1970	United Kingdom .
1261060	1/1972	United Kingdom .
2 117 238	10/1983	United Kingdom .
2117238	10/1983	United Kingdom .
94/01105	1/1994	WIPO .
94/26265	11/1994	WIPO .
94/26266	11/1994	WIPO .
95/04627	4/1995	WIPO .
95/09626	4/1995	WIPO .
95/13082	5/1995	WIPO .

OTHER PUBLICATIONS

Sweeney et al., Cancer Research 32, pp. 1803–1809, Sep. 1972.

JF Bach et al. The mode of action of immunosuppressive agents, Elsevier Publisher, Amsterdam, 1985, pp. 105–174.

Allison et al., Springer Semin Immunopathol (1993) 14:353–380.

Chemical Abstract 122:197032, "Enteric Immunosuppressant Compositions for the Treatment of Chron's Disease and Ulcerative Colitis", Mar. 1995.

Epinette et al. Journal of the American Academy of Dermatology, pp. 962–971, 1981.

Ohsugi et al. Cancer Research 36, pp. 2923–2927, Aug. 1976.

Franklin et al., Biochem. J. (1969), vol. 113, pp. 515–524.

Mitsui et al., CA 75:150091, Progr. Antimicrob. Anticancer Chemother., Proc. Int. Congr. Chemother., 6th (1970) vol. 2, pp. 130–135.

Schiantarelli et al. Agents and Actions, vol. 14, No. 2 (1984) pp. 247–256.

Suzuki et al. The Journal of Antibiotics, vol. XXIX, No. 3, pp. 275–285, 1991.

Harrison et al. J.C.S. Perkin II, pp. 1542–1544, 1982.

Seki et al. Antimicrobial Agents and Chemotherapy, vol. 33, No. 5, May 1989, pp. 773–775.

Allison et al. In: Immunosuppressive Drugs—Development in anti–rejection therapy, pp. 141–159, 1995.

Mitsui et al., The Journal of Antibiotics, Aug. 1969, pp. 358–363.

James J. Lipsky, The Lancet 1996; vol. 348, Nov. 16, 1996, pp. 1357–1359.

(List continued on next page.)

Primary Examiner—Frederick Krass
Attorney, Agent, or Firm—Stephen G. Kalinchak

[57] **ABSTRACT**

Disclosed are pharmaceutical compositions which have been modified to release pharmaceutically acceptable mycophenolate salts in the upper part of the intestinal tract and methods of treatment using the pharmaceutical compositions.

11 Claims, No Drawings

OTHER PUBLICATIONS

H. Boxenbaum, Journal of Pharmacokinetics and Biopharmaceutics, vol. 10, No. 2, 1982, pp. 201–227.
Eugui et al. Scand. J. Immunol. 33, pp. 175–183, 1991.
Morris et al. Transplant. Proc. vol. 22, pp. 1659–1662 (1990).
Lee et al., Pharmaceutical Research, vol. 7, No. 2, 1990, pp. 161–165, 1991.
Boit, Beilsteins Handbuch der Organischen Chemi, vol. 18, Part 7, p. 6513, 1987.
Luckenbach, Beilstein Handbook of Organic Chemistry, vol. 18, Part 9, p. 239, 1993.
Makara et al., CA 124:139508 (abstract of Journal Med. Chem. 1996, 39, pp. 1236–1242.
Suzuki et al., CA BA62:38453, The Journal of Antibiotics, Mar. 1976, vol. 29, No. 3, pp. 286–291.
Potel, Aus der Bakteriologischen Forschungsabteilung der Asta–Werke AG., pp. 527–532, 1996.
XP 002043101 Fester orale and perorate Arzneiformen, pp. 356–361, 1992.
Nature, vol. 223, Aug. 23, 1969, pp. 848–850.
Aisenberg, The New England Journal of Medicine, May 27, 1965, pp. 1114–1116.
Marinari et al., XP 002043018, Arch Dermatol, vol. 113, Jul. 1977, pp. 930–931.
XP002043019, European Mycophenolate Mofetil Cooperative Study Group, vol. 345, May 27, 1995, pp. 1321–1322.
80538 Chemical Abstracts vol. 73, 1970, p. 230, No. 80540w.
Chemical Abstracts, vol. 80, 1974, p. 338, No. 59722s.
Chemical Abstract, vol. 80, 1974, p. 420, No. 120748y.
Chemical Abstract, vol. 96, 1982, p. 646, No. 199422x.
Chemical Abstract 7–Enzymes, vol. 124, Nov. 11, 1996, p. 559, No. 139508w.
26–Biomolecules, vol. 96, 1982, p. 647.
Chemical Abstract, vol. 98, 1983, p. 564, No. 143262w.
Chemical Abstract, vol. 98, 1983, p. 632, No. 198004w.
27 Heterocytes, vol. 98, 1983, p. 565.
Schnitzer, Academic Press, vol. 10, 1972, pp. 14–19, 24, 25, 70 and 71.
The Lancet, vol. 345, May 27, 1995, pp. 1323–1325.
Sollinger, H. W., Chem. Abstr. 1996, 95370774, Kidney Int'l, Supplement, 1995, vol. 52, pp. 514–517.
Platz et al., "A new and potent immunosuppressive agent," Transplantation, vol. 51, No. 1, 1991, pp. 27–31.
Ohsugi, et al., "Antitumor and immunosuppressive effects of mycophenolic acid derivatives", Cancer Rres. vol. 36, No. 1976, pp. 2923–2927.
Chemical Abstract 108174f, Gerzon et al., "Mycophenolic acid and its derivatives, inhibitors of malignant tumor cell growth in warm–blooded mammals", 1995.
Ito et al., Pharmacokinetics of Mycophenolic Acid in Healthy Human Volunteers, J. Med. Soc. Toho, Japan, vol. 29, No. 3, 1982, pp. 412–418.
Kajiwara et al., General Pharmacology of Mycophenolic Acid, J. Med. Soc. Toho, Japan, vol. 29, No. 3, 1982, pp. 419–425.
Kajiwara et al., Species Differences of Mycophenolic Acid, a New Drug for Psoriasis in Acute, Sub–acute and Chronic Toxicity, Journal of the Medical Society of Toho University, Sep. 1, 1982.
Ohsugi et al., CA 84:103774, Arerugi, (1975) 24 (12) pp. 820–825.
Hasunuma, et al., CA 112:191604 Abstract of Adv. Exp. Med. Biol. (1989) 253A (Purine Pyrimidine Metab. Man 6, Pt. A), pp. 455–460.
Derwent Abstract 93–329920/41 corresponding to JP 06256182–A (1994).
Derwent Abstract 94–313614/39 corresponding to JP 06239740–A (1994).
Derwent Abstract 93–220931/28 corresponding to EP 551182–A1 (1993).
Derwent Abstract 84509V/49 corresponding to BE 815–330 (1974).
Derwent Abstract 37140T–B corresponding to BE 775785 (1972).
Derwent Abstract 88322 C/49 corresponding to US 4234–684 (1980).

ENTERIC-COATED PHARMACEUTICAL COMPOSITIONS OF MYCOPHENOLATE

This application is a 371 of PCT/EP97/01800, filed Apr. 10, 1997.

This invention relates to mycophenolic acid.

Mycophenolic acid, also referred to herein as MPA, was first isolated in 1896, and has been extensively investigated as a pharmaceutical of potential commercial interest. It is known to have anti-tumor, anti-viral, immunosuppressive, anti-psoriatic, and anti-inflammatory activity [see e.g. W. A. Lee et al, Pharmaceutical Research (1990), 7, p. 161–166 and references cited therein]. Publications have appeared on MPA as an anti-cancer agent by Lilly scientists, see e.g. M. J. Sweeney et al., Cancer Research (1972), 32, 1795–1802, and by ICI scientists, see e.g. GB 1,157,099 and 1,203,328 and as an immunosuppressant agent see e.g. A. Mitsui et al. J. Antibiotics (1969) 22, p. 358–363. In the above-mentioned article by W. A. Lee et al it is stated that attempts have been made to increase the bio-availability or specificity of MPA by making derivatives. The poor bioavailability of the acid was thought to be caused by undetermined factors such as drug complexation in the gastro-intestinal lumen, a narrow absorption window, metabolism before absorption etc. The preparation of the morpholinoethyl ester, also known as mycophenolate mofetil (sometimes referred to herein as MMF), was described which had considerably higher bioavailability than MPA (100% for MMF and 43% for MPA). This derivative has been recently introduced commercially as an immunosuppressant for the treatment or prevention of organ or tissue transplant rejection, at daily dosages of from about 200 mg to about 3 grams p.o., e.g. about 2 g p.o. Patient compliance with MMF is not ideal, inter alia, because of side-effects e.g. gastro-intestinal side effects, the origin of which is not known.

We have now found, after exhaustive testing, that mycophenolate salts when enteric coated or adapted to be released in the upper part of the intestines, e.g. in the duodenum, jejeunum and/or ileum, are effective, well-tolerated, pharmaceuticals particularly for immunosuppressive indications especially for the treatment or prevention of organ, tissue or cellular allograft or xenograft rejection, e.g. after transplant, or the treatment or prevention of immune-mediated diseases (autoimmune diseases) and have interesting bioavailability and stability characteristics. Moreover fewer unit dosage forms are required to be administered than for MMF, leading to easier administration.

The present invention provides in one aspect a pharmaceutical composition comprising a myophenolate salt, the composition being adapted to release mycophenolate in the upper part of the intestinal tract (hereinafter referred to as a composition of the invention). The composition may be adapted in any conventional manner, preferably with means adapted to prevent release of the myocophenolate in the stomach and to ensure release in the upper part of the intestinal tract. In a further aspect the invention provides a pharmaceutical composition comprising a coated pharmaceutically acceptable mycophenolate salt.

Such salts are cationic salts, e.g. of alkali metals, especially the sodium salts. Sodium mycophenolate salts are known, e.g. in South African Patent 68/4959. We prefer to use the mono-sodium salt. This may be obtained in crystalline form by recrystallization from acetone/ethanol if necessary with water; Mpt. 189–191° C.

The invention provides, more specifically, a solid enteric-coated composition in unit dose form for oral application, the core of the composition containing sodium mycophenolate in solid or liquid form.

The term "core" comprises sodium mycophenolate (or other cationic salt) if desired in admixture with further physiologically acceptable material, that can be surrounded by an enteric-coating. The term "core" comprises, in a wide sense, not only tablets, pellets or granules but also capsules, e.g. soft or hard capsules of gelatine or starch. Such cores may be produced in conventional manner. We have found that the mycophenolate salts, particularly the sodium salt, are particularly interesting for the production of tablets. When tablet cores are used they have preferably a hardness of from ca. 10 to 70 N.

The pellets or granules may, after application of the enteric-coating as described hereinafter may be used as such or to fill capsules, e.g. hard gelatine capsules. If desired the capsules may be alternatively enteric-coated, e.g. in conventional manner.

Other pharmaceutically acceptable ingredients may be present in the cores, e.g. those conventionally used in the preparation of pharmaceutically compositions, e.g. fillers, e.g. lactose, glidants, e.g. silica, and lubricants, e.g. magnesium stearate.

The term "enteric coating" comprises any pharmaceutically acceptable coating preventing the release of the active agent in the stomach and sufficiently disintegrating in the intestine tract (by contact with approximately neutral or alkaline intestine juices) to allow the resorption of the active agent through the walls of the intestinal tract. Various in vitro tests for determining whether or not a coating is classified as an enteric coating have been published in the pharmacopoeia of various countries.

More specifically, the term "enteric coating" as used herein refers to a coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38° C. and preferably thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH_2PO_4 buffered solution of pH 6.8.

The thickness of the coating may vary and depends inter alia on its permeability in water and acids. A typical coating may be about 16–30, e.g. 16–20 or to 25, mg on a size 1 gelatine capsule. Similar thicknesses may be applied in other formulations.

In general satisfactory results are obtained with a coating of 5–100 μm, preferably 20–80 μm thickness. The coating is suitably selected from macromolecular polymers. Suitable polymers are listed in e.g. L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 3rd Ed, 1986, p. 365–373, H. Sucker et al, Pharmazeutische Technologie, Thieme, 1991, p. 355–359, Hagers Handbuch der pharmazeutischen Praxis, 4th Ed. Vol. 7, pages 739 to 742 and 766 to 778, (Springer Verlag, 1971) and Remington's Pharmaceutical Sciences, 13th Ed., pages 1689 to 1691 (Mack Publ., Co., 1970) and comprise e.g. cellulose ester derivatives, cellulose ethers, acrylic resins, such as methylacrylate copolymers and copolymers of maleic acid and phthalic acid derivatives.

The preferred films are made from cellulose acetate phthalate and trimellitate; methacrylic acid copolymers, e.g. copolymers derived from methylacrylic acid and esters thereof, containing at least 40% methylacrylic acid; and especially hydroxypropyl methylcellulose phthalate.

Methylacrylates include those of molecular weight above 100,000 daltons based on, e.g. methylacrylate and methyl or ethyl methylacrylate in a ratio of about 1:1. Typical products include Endragit L, e.g. L 100-55, marketed by Rohm GmbH, Darmstadt, Germany.

Typical cellulose acetate phthalates have an acetyl content of 17–26% and a phthalate content of from 30–40% with a viscosity of ca. 45–90 cP.

Typical cellulose acetate trimellitates have an acetyl content of 17–26%, a trimellityl content from 25–35% with a viscosity of ca. 15–20 cS. An example of an appropriate cellulose acetate trimellitate is the marketed product CAT (Eastman Kodak Company, USA).

Hydroxypropyl methylcellulose phthalates, typically have a molecular weight of from 20,000 to 100,000 daltons e.g. 80,000 to 130,000 daltons, e.g. a hydroxypropyl content of from 5 to 10%, a methoxy content of from 18 to 24% and a phthalyl content from 21 to 35%.

An example of an appropriate cellulose acetate phthalate is the marketed product CAP (Eastman Kodak, Rochester N.Y., USA).

Examples of suitable hydroxypropyl methylcellulose phthalates are the marketed products having a hydroxypropyl content of from 6–10%, a methoxy content of from 20–24%, a phthalyl content of from 21–27%, a molecular weight of about 84,000 daltons known under the trade mark HP50 and available from Shin-Etsu Chemical Co. Ltd., Tokyo, Japan, and having a hydroxypropyl content, a methoxy content, and a phthalyl content of 5–9%, 18–22% and 27–35% respectively, and a molecular weight of 78,000 daltons, known under the trademark HP55 and available from the same supplier.

A preferred coating is HP 50.

The enteric coating may be carried out in conventional manner, e.g. so that the cores are sprayed with a solution of the enteric-coating.

Suitable solvents for the enteric-coating are for example organic solvents, e.g. an alcohol such as ethanol, a ketone such as acetone, halogenated hydrocarbons such as CH_2Cl_2 or mixtures of such solvents, e.g. ethanol/acetone, e.g. 1:1 to 10:1.

Conveniently a softener such as di-n-butylphthalate or triacetin is added to such a solution, e.g. in a ratio of coating material to softener of from 1:1 about 0.05 to about 0.3.

If desired for cellulose phthalates and other acidic coating materials an ammonium salt may be found and an aqueous solution may be used.

A fluidized bed coater may be used for coating.

Conveniently the cores are treated at room temperature or warmed up to 40° C. e.g. by means of warm air of 40° up to 70° C., before spraying. To avoid a sticking of the cores the spray procedure is preferably interrupted at certain time intervals and the cores then warmed up again. It is, however, also possible to proceed without interruption of the spray procedure, e.g. by automatic regulation of the spray amount taking into account the temperature of exhaust air and/or cores.

The spray pressure may vary within wide ranges, in general satisfactory results are obtained with a spray pressure of from about 1 to about 1.5 bar.

The compositions of the invention are useful as immunosuppressants as indicated by standard tests.

The activity and characteristics of the compositions of the invention may be indicated in standard

a) clinical trials, e.g. observing the first acute rejection episodes or treatment failure six months after transplant of kidneys or maintaining a rejection—free state within 6 months after initiation of treatment with the invention. The compositions of the invention are administered at a dose in the range of 0.5 to 2.0 g/day e.g. about 1.5 g/day and decrease the acute rejection rates when administered during the period around transplant surgery, and maintain a rejection-free state in patients who are 3 months or more after transplantation. Thus the compositions of the invention may be administered during the initial 72 hours after transplantation at dose of about 0.5 g administered twice a day in combination with a conventional steroid and cyclosporin, e.g. as NEORAL for which the cyclosporin dose is the conventional dose e.g. ca. 8±3 mg/kg for renal transplants. The steroid dose is to be administered at about 2.5 mg/kg for 4 days after transplant, 1 mg/kg thereafter for 1 week, 0.6 mg/kg thereafter for 2 weeks thereafter 0.3 mg/kg for 1 month for prednisone.

and in

b) animal trials e.g. observing the kidney allograft reaction in rat. In this test one kidney from a female fisher 344 rat is transplanted onto the renal vessel of a unilaterally (left side) nephrectomized WF recipient rat using an end-to-end anastomosis. Ureteric anastomosis is also end-to-end. Treatment commences on the day of transplantation and is continued for 14 days. A contralateral nephrectomy is done seven days after transplantation, leaving the recipient relying on the performance of the donor kidney. Survival of the graft recipient is taken as the parameter for a functional graft. Typical doses of the compositions of the invention are from about 1 to 30 mg/kg p.o.

The compositions of the invention are particularly useful for the following conditions:

a) Treatment and prevention of native or transgenic organ, tissue or cellular allograft or xenograft transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, pancreatic islet cell, neural cell or corneal transplant; including treatment and prevention of acute rejection; treatment and prevention of hyperacute rejection, e.g. as associated with xenograft rejection; and treatment and prevention of chronic rejection, e.g. as associated with graft-vessel disease. The compositions of the invention are also indicated for the treatment and prevention of graft-versus-host disease, such as following bone marrow transplantation.

b) Treatment and prevention of autoimmune diseases, e.g. immune-mediated diseases and inflammatory conditions, in particular inflammatory conditions with an etiology including an immunological component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific immune-mediated diseases for which the compositions of the invention may be employed include, autoimmune hematological disorders, including, but not limited to hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scierodoma, Wegener granulosis, dermatomyositis, polymyositis, chronic active hepatitis, primary bilary cirrhosis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, pemphigus, idiophatic sprue, inflammatory bowel diseases (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmophathy, Graves disease, sarcoidosis, multiple sclerosis, juvenile diabetes (diabetes mellitus type I), non-infectious uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, vasculitis, glomerulonephritides (with and without nephrotic syndrome, e.g. including idiophatic nephrotic syndrome or minimal change nephropathy) and juvenile dermatomyositis.

Appropriate dosages of the compositions of the invention will of course vary, e.g. depending on the condition to be treated (for example the disease type or the nature of resistance), the MPA salt used, the effect desired and the mode of administration.

In general however satisfactory results are obtained on administration e.g. orally at dosages on the order of from

about 1 to about 30 mg salt per kg animal body weight per day, administered once or in divided doses up to 4 times per day. Suitable daily dosages for patients are thus in the order of 200 mg to 3 g p.o. salt e.g. from about 50 to 100% that of mycophenolate mofetil. For the preferred mono sodium salt the dosage of the salt is about two thirds that of mycophenolate mofetil.

Representative unit dosage forms contain from about 50 mg, e.g. 100 mg, to about 1.5 g of the pharmaceutically acceptable mycophenolate salt.

The bioavailability characteristics of compositions of the invention may be determined in conventional manner, e.g. by oral administration to beagle dogs. Dosages are typically 50 mg salt animal e.g. ca 3–5 mg salt/kg animal body weight. Dogs are adult (ca. 10 kg e.g. 6–14 kg) and fasted. Three hours after administration ca. 200 g food is administered. Blood samples are taken from the cephalic vein, before administration and 10, 30, and 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours, after administration. Plasma levels of free MPA are determined by HPLC analysis (with UV detection).

In a relative bioavailability trial as described above in male beagle dogs dosages of 3.8 mg salt/kg animal body weight p.o. were administered with the Example 1 composition as described hereinafter and with a MPA or MMF formulation corresponding to the Example 1 composition but containing an identical amount of MPA or commercially available MMF.

Results are as follows:

	Ex 1	MPA	MMF
MPA (AUC Relative Bioavailability, Frel [ng · hr · ml^{-1}]			
Mean	4612 (218)	3579 (174)	2709 (100)
Median	4204 (168)	2911 (182)	2513 (100)
SD	939	1889	1363
CV	20	53	50
Cmax [ng/ml] (Relative Cmax)			
Mean	5391 (313)	3683 (227)	2052 (100)
Median	5359 (367)	2719 (172)	1462 (100)
SD	1847	2504	945
CV (%)	34 (46)	68 (87)	46 (0)

The coefficients of variation (CV) of AUC (20%) and Cmax (34%) of the Example 1 composition are significantly less than those of the reference compositions, indicating less inter-subject and intra-subject variability with the Example 1 composition.

The area under the curve (AUC) and Cmax with the Example 1 composition are higher than those of the reference compositions.

Naturally the advantageous bioavailability characteristics of the present compositions may be ascertained in standard clinical bioavailability trials. For example, doses from 200 mg to 1.5 g of the Example 1 composition and MPA, and MMF may be administered to 12 healthy volunteers in single doses in a cross-over trial. Increased AUC and C_{max} may be observed for the Example 1 composition.

The compositions of the present invention are surprisingly tolerated better than MMF, inducing less gastro-intestinal side effects such as diarrhoea and burning. They show less long term side effects e.g. in the colon.

The compositions of the invention may be administered as the sole active ingredient or with another immunosuppressant e.g. together with simultaneous or separate administration of other immunosuppressants, for example, in immunosuppressive applications such as prevention and treatment of graft vs. host disease, transplant rejection, or immune-mediated disease, the compositions of the invention may be used in combination with cyclosporins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, FK-506 (tacrolimus), etc., rapamycin; corticosteroids; cyclophosphamide; azathioprine; methotrexate; brequinar; leflunomide; mizoribine; deoxyspergualin; analogues thereof, and immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD25, CD28, CTLA4, B7, CD45, or CS58 or their ligands; or other immunomodulatory compounds.

When the compositions of the invention are co-administered with such other immunosuppressants the dosages of the other immunosuppressants may be reduced e.g. to one-half to one-third their dosages when used alone.

Representative doses for ciclosporin to be used are e.g. 1 to 10, e.g. 1 to 2 mg/kg/day.

The present invention provides in another aspect the use, method and compositions as defined hereinafter in the claims.

Insofar as details of excipients are not described herein, these are known, or available e.g. in the Handbook of Pharmaceutical Excipients, Second Edition, edited by Ainley Wade and Paul J. Weller, American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik and angrenzende Gebiete edited by H. P. Fiedler, 4th Edition, Edito Cantor, Aulendorf and earlier editions.

Following is a description by way of example only of compositions of this invention:

EXAMPLE 1

COMPOSITION	
Capsule contents	
MPA mono sodium salt	53.43 mg (= 50 mg MPA)
Lactose (1:1 mixture of 100/200 mesh)	256.57 mg
Silica (Aerosil)	3.1 mg
Magnesium stearate	1.55 mg
	314.65 mg
Capsule is size 1	
Enteric coating (ca 17 mg)	
Hydroxypropyl methyl cellulose phthalate (HP50)	9 parts
Triacetin	1 part

Procedure

The capsule ingredients are mixed and filled into size 1 capsules. The capsules are coated in a fluidized bed coater with a solution of the enteric coating ingredients in ethanol (containing 10% acetone). The coating on each capsule is about 17 mg. The capsules meet the enteric coating test described herein and do not disintegrate within 2 hours in artificial gastric juices (pH 1, HCl). The compositions are stable, e.g for 2 years at room temperature.

If desired larger capsules containing 534.3 mg MPA mono sodium salt may be made in analogous manner, reducing the amount of lactose. These are well tolerated in clinical trials.

EXAMPLE 2

Capsules of size 1 are made up as in Example 1. A solution for enteric coating is made up as follows:

Hydroxypropyl methyl cellulose phthalate (HP50)	270 g
Triacetin	30 g
Acetone	900 g
Ethanol	1800 g

600 g of this enteric coating solution are used for 1 kg of capsules (ca. 2400). The amount of coating applied to each capsule is about 25 mg giving a film thickness of 5–6 mg/cm^2.

We claim:

1. A pharmaceutical composition comprising a mycophenolate salt, the composition being adapted to prevent release of the mycophenolate salt in the stomach and to release the mycophenolate salt in the upper part of the intestinal tract.

2. A pharmaceutical composition comprising an enteric coated pharmaceutically acceptable mycophenolate salt.

3. A method of immunosuppressing a subject which comprises administering a therapeutically effective amount of enteric coated pharmaceutically acceptable mycophenolate salt or a composition of claim **1** to a subject in need of such immunosuppression, optionally with the simultaneous or separate administration of another immunosuppressant.

4. A composition containing an enteric coated pharmaceutically acceptable mycophenolate salt or a composition of claim **1** and another immunosuppressant for simultaneous, sequential or separate administration.

5. A pharmaceutical composition according to claim **1** wherein the mycophenolate salt is a mono-sodium salt.

6. A pharmaceutical composition according to claim **2** wherein the mycophenolate salt is a mono-sodium salt.

7. A method according to claim **3** wherein the mycophenolate salt is a mono-sodium salt.

8. A method according to claim **3** wherein said another immunosuppressant is cyclosporin.

9. A pharmaceutical composition according to claim **4** wherein the mycophenolate salt is a mono-sodium salt.

10. A pharmaceutical composition according to claim **9** wherein said another immunosuppressant is cyclosporin.

11. A pharmaceutical composition according to claim **4** wherein said another immunosuppressant is cyclosporin.

* * * * *

EXHIBIT B

US006172107B1

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

(10) **Patent No.: US 6,172,107 B1**
(45) **Date of Patent: *Jan. 9, 2001**

(54) **ENTRIC-COATED PHARMACEUTICAL COMPOSITIONS**

(75) Inventors: **Barbara Haeberlin**, Riehen; **Ching-Pong Mak**, Therwil, both of (CH); **Armin Meinzer**, Buggingen (DE); **Jacky Vonderscher**, Riedisheim (FR)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/469,536**

(22) Filed: **Dec. 22, 1999**

Related U.S. Application Data

(63) Continuation of application No. 09/077,398, filed as application No. PCT/EP97/01800 on Apr. 10, 1997, now Pat. No. 6,025,391.

(30) **Foreign Application Priority Data**

Apr. 12, 1996 (GB) 9607564
Oct. 24, 1996 (GB) 9622028

(51) **Int. Cl.**[7] **A61K 31/34**; A01N 43/08

(52) **U.S. Cl.** **514/470**; 514/8; 514/11; 514/570; 514/576; 514/960; 514/962; 514/885; 424/457; 424/458; 424/459; 424/461; 424/462; 424/463; 424/468; 424/474; 424/475; 424/479; 424/480; 424/482; 424/490; 424/493; 424/494; 424/495; 424/497

(58) **Field of Search** 514/8, 11, 470, 514/570, 576, 885, 960, 962; 424/457, 458, 459, 461, 462, 463, 468, 474, 475, 479, 480, 482, 490, 493, 494, 495, 497

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,705,894	12/1972	Gerzon et al.	260/240
3,705,946	12/1972	Dyke et al.	424/279
3,777,020	12/1973	Johnson	424/180
3,825,571	7/1974	Mori et al.	260/343.3
3,853,919	12/1974	Mori et al.	260/343.3
3,868,454	2/1975	Johnson	424/248
3,880,995	4/1975	Jones	424/180
3,903,071	9/1975	Holmes	260/210
4,005,108	1/1977	Kupchan et al.	260/343 R
4,017,647	4/1977	Ohno et al.	427/3
4,234,684	11/1980	Abbott et al.	435/75
4,680,299	7/1987	Hesson	514/311
4,686,234	8/1987	Nelson et al.	514/469
4,725,622	2/1988	Nelson et al.	514/469
4,727,069	2/1988	Nelson et al.	514/211
4,753,935	6/1988	Nelson et al.	514/233.5
4,786,637	11/1988	Allison et al.	514/233.5
4,808,592	2/1989	Nelson et al.	514/233.5
4,847,381	7/1989	Sutherland et al.	546/156
4,868,153	9/1989	Allison et al.	514/470
4,959,387	9/1990	Nelson et al.	524/469
4,992,467	2/1991	Allison et al.	514/464

FOREIGN PATENT DOCUMENTS

704 326	3/1968	(BE) .
815330	5/1973	(BE) .
0 281 713	9/1988	(EP) .
0281713	9/1988	(EP) .
551182	7/1993	(EP) .
0691130	1/1996	(EP) .
1157099	7/1969	(GB) .
1157100	7/1969	(GB) .
1158387	7/1969	(GB) .
1203328	8/1970	(GB) .
1261060	1/1972	(GB) .
2 117 238	10/1983	(GB) .
2117238	10/1983	(GB) .
94/01105	1/1994	(WO) .
94/26265	11/1994	(WO) .
94/26266	11/1994	(WO) .
95/04627	4/1995	(WO) .
95/09626	4/1995	(WO) .
95/13082	5/1995	(WO) .
31237	11/1967	(ZA) .

OTHER PUBLICATIONS

Chemical Abstracts 71:94783, "Antitumor and Immunosuppressive Active Mycophenolic Acid" , Jun. 1966.*

Sweeney et al., Cancer Research 32, pp. 1803–1809, Sep. 1972.

JF Bach et al. The mode of action of immunosuppressive agents, Elsevier Publisher, Amsterdam, 1985, pp. 105–174.

Allison et al., Springer Semin Immunopathol (1993) 14:353–380.

Epinette et al. Journal of the American Academy of Dermatology, pp. 962–971, 1975.

Ohsugi et al. Cancer Research 36, pp. 2923–2927, Aug. 1976.

Franklin et al., Biochem. J. (1969), vol 113, pp. 515–524.

Mitsui et al., CA 75:150091, Progr. Antimicrob. Anticancer Chemother., Proc. Int. Congr. Chemother., 6th (1970) vol. 2, pp. 130–5.

Schiantarelli et al. Agents and Actions, vol. 14, No. 2 (1984) pp. 247–256.

Suzuki et al. The Journal of Antibiotics, vo. XXIX, No. 3, pp. 275–285, 1984.

Harrison et al. J.C.S. Perkin II, pp. 1542–1544, 1984.

Seki et al. Antimicrobial Agents and Chemotherapy, vol. 33, No. 5, May 1989, pp. 773–775.

Allison et al. In: Immunosuppressive Drugs—Development in anti–rejection therapy, pp. 141–159, 1989.

(List continued on next page.)

Primary Examiner—Frederick Krass
(74) *Attorney, Agent, or Firm*—Michael U. Lee; Stephen G. Kalinchak

(57) **ABSTRACT**

This invention provides a pharmaceutical composition comprising a mycophenolate salt, the composition being adapted to release mycophenolate in the upper part of the intestinal tract.

8 Claims, No Drawings

OTHER PUBLICATIONS

Mitsui et al., The Journal of Antibiotics, Aug. 1969, pp. 358–363.
James J. Lipsky, The Lancet 1996; vol. 348, Nov. 16, 1996, pp. 1357–1359.
H. Boxenbaum, Journal of Pharmacokinetics, and Biopharmaceuties, vol. 10, No. 2, 1982, pp. 201–227.
Eugui et al. Scand. J. Immunol. 33, pp. 175–183, 1991.
Morris et al. Transplant. Proc. vol. 22, pp. 1659–1662 (1990).
Lee et al., Pharmaceutical Research, vol. 7, No. 2, 1990, pp. 161–165.
Boit, Beilsteins Handbuch der Organischen Chemi, vol. 18, Part 7, p. 6513, 1990.
Luckenbach, Beilstein Handbook of Organic Chemistry, vol. 18, Part 9, p. 239, 1990.
Makara et al., CA 124:139508 (abstract of Journal Med. Chem. 1996, 39, pp. 1236–1242.
Suzuki et al., CA BA62:38453, The Journal of Antibiotics, Mar. 1976, vol. 29, No. 3, pp. 286–291.
Potel, Aus der Bakteriologischen Forschungsabteilung der Asta–Werke AG., pp. 527–532, 1977.
XP 002043101 Fester orale and perorate Arzneiformen, pp. 356–361, 1978.
Nature, vol. 223, Aug. 23, 1969, pp. 848–850.
Aisenberg, The New England Journal of Medicine, May 27, 1965, pp. 1114–1116.
Marinari et al., XP 002043018, Arch Dermatol, vol. 113, Jul. 1977, pp. 930–931.
XP002043019, European Mycophenolate Mofetil Cooperative Study Group, vol. 345, May 27, 1995, pp. 1321–1322.
80538 Chemical Abstracts vol. 73, 1970, p. 230, No. 80540w.
Chemical Abstracts, vol. 80, 1974, p. 338, No. 59722s.
Chemical Abstract, vol. 80, 1974, p. 420, No. 120748y.
Chemical Abstract, vol. 96, 1982, p. 646, No. 199422x.
Chemical Abstract 7–Enzymes, vol. 124, Nov. 11, 1996, p. 559, No. 139508w.
26–Biomolecules, vol. 96, 1982, p. 647.
Chemical Abstract, vol. 98, 1983, p. 564, No. 143262w.
Chemical Abstract, vol. 98, 1983, p. 632, No. 198004w.
27 Heterocytes, vol. 98, 1983, p. 565.
Schnitzer, Academic Press, vol. 10, 1972, pp. 14–19, 24, 25, 70 and 71.
The Lancet, vol. 345, May 27, 1995, pp. 1323–1325.
Sollinger, H. W., Chem. Abstr. 1996, 95370774, Kidney Int'l, Supplement, 1995, vol. 52, pp. 514–517.
Platz et al., "A new and potent immunosuppressive agent," Transplantation, vol. 51, No. 1, 1991, pp. 27–31.
Ohsugi, et al., "Antitumor and immunosuppressive effects of mycophenolic acid derivatives", Cancer Rres. vol. 36, No. 1976, pp. 2923–7.
Chemical Abstract 108174f, Gerzon et al., "Mycophenolic acid and its derivatives, inhibitors of malignant tumor cell growth in warm–blooded mammals", 1976.
Ito et al., Pharmacokinetics of Mycophenolic Acid in Healthy Human Volunteers, J. Med. Soc. Toho, Japan, vol. 29, No. 3, 1982, pp. 412–418.
Kajiwara et al., General Pharmacology of Mycophenolic Acid, J. Med. Soc. Toho, Japan, vol. 29, No. 3, 1982, pp. 419–425.
Kajiwara et al., Species Differences of Mycophenolic Acid, a New Drug for Psoriasis in Acute, Sub–acute and Chronic Toxicity, Journal of the Medical Society of Toho University, Sep. 1, 1982.
Ohsugi et al., CA 84:103774, Arerugi, (1975) 24 (12) pp. 820–5.
Hasunuma, et al., CA 112:191604 Abstract of Adv. Exp. Med. Biol. (1989) 253A (Purine Pyrimidine Metab. Man 6, Pt. A), pp. 455–60.
Derwent Abstract 93–329920/41 corresponding to JP 06256182–A (1994).
Derwent Abstract 94–313614/39 corresponding to JP 06239740–A (1994).
Derwent Abstract 93–220931/28 corresponding to EP 551182–A1 (1993).
Derwent Abstract 84509V/49 corresponding to BE 815–330 (1974).
Derwent Abstract 37140T–B corresponding to BE 775785 (1972).
Derwent Abstract 88322 C/49 corresponding to US 4234–684 (1980).
Osugi, Y. et al., "Immunosuppressive Effect of Mycophenolic Acid—Prolongation of the Survival Time of Homologous Skin Grafts in Mice," vol. 7, No. 4, Xpl. 28, 1985.
Chemical Abstract 80:120748y of JP 48086861 (1973).
Chemical Abstract 80:59722 of JP 48086860 (1973).
Chemical Abstract 96:199422 of JP 57024380 (1982).
Chemical Abstract 98:143262 of JP 57183776 (1982).
Chemical Abstract 98:198004 of JP 57183777 (1982).

* cited by examiner

ENTRIC-COATED PHARMACEUTICAL COMPOSITIONS

This application is a continuation of U.S. application Ser. No. 09/077,398, filed May 28, 1998 and now U.S. Pat. No. 6,025,391, which is a 371 of PCT/EP97/01800, filed Apr. 10, 1997. The entire contents of application Ser. No. 09/077,398 are incorporated herein by reference.

This invention relates to mycophenolic acid.

Mycophenolic acid, also referred to herein as MPA, was first isolated in 1896, and has been extensively investigated as a pharmaceutical of potential commercial interest. It is known to have anti-tumor, anti-viral, immunosuppressive, anti-psoriatic, and anti-inflammatory activity [see e.g. W. A. Lee et al, Pharmaceutical Research (1990), 7, p. 161–166 and references cited therein]. Publications have appeared on MPA as an anti-cancer agent by Lilly scientists, see e.g. M. J. Sweeney et al., Cancer Research (1972), 32, 1795–1802, and by ICI scientists, see e.g. GB 1,157,099 and 1,203,328 and as an immunosuppressant agent see e.g. A. Mitsui et al. J. Antibiotics (1969) 22, p. 358–363. In the above-mentioned article by W. A. Lee et al it is stated that attempts have been made to increase the bio-availability or specificity of MPA by making derivatives. The poor bioavailability of the acid was thought to be caused by undetermined factors such as drug complexation in the gastrointestinal lumen, a narrow absorption window, metabolism before absorption etc.. The preparation of the morpholinoethyl ester, also known as mycophenolate mofetil (sometimes referred to herein as MMF), was described which had considerably higher bioavailability than MPA (100% for MMF and 43% for MPA). This derivative has been recently introduced commercially as an immunosuppressant for the treatment or prevention of organ or tissue transplant rejection, at daily dosages of from about 200 mg to about 3 grams p.o., e.g. about 2 g-p.o. Patient compliance with MMF is not ideal, inter alia, because of side-effects e.g. gastro-intestinal side effects, the origin of which is not known.

We have now found, after exhaustive testing, that mycophenolate salts when enteric coated or adapted to be released in the upper part of the intestines, e.g. in the duodenum, jejeunum and/or ileum, are effective, well-tolerated, pharmaceuticals particularly for immunosuppressive indications especially for the treatment or prevention of organ, tissue or cellular allograft or xenograft rejection, e.g. after transplant, or the treatment or prevention of immune-mediated diseases (autoimmune diseases) and have interesting bioavailability and stability characteristics. Moreover fewer unit dosage forms are required to be administered than for MMF, leading to easier administration.

The present invention provides in one aspect a pharmaceutical composition comprising a myophenolate salt, the composition being adapted to release mycophenolate in the upper part of the intestinal tract (hereinafter referred to as a composition of the invention). The composition may be adapted in any conventional manner, preferably with means adapted to prevent release of the myocophenolate in the stomach and to ensure release in the upper part of the intestinal tract. In a further aspect the invention provides a pharmaceutical composition comprising a coated pharmaceutically acceptable mycophenolate salt.

Such salts are cationic salts, e.g. of alkali metals, especially the sodium salts. Sodium mycophenolate salts are known, e.g. in South African Patent 6814959. We prefer to use the mono-sodium salt. This may be obtained in crystalline form by recrystallization from acetone/ethanol if necessary with water; Mpt. 189–191° C.

The invention provides, more specifically, a solid enteric-coated composition in unit dose form for oral application, the core of the composition containing sodium mycophenolate in solid or liquid form.

The term "core" comprises sodium mycophenolate (or other cationic salt) if desired in admixture with further physiologically acceptable material, that can be surrounded by an enteric-coating. The term "core" comprises, in a wide sense, not only tablets, pellets or granules but also capsules, e.g. soft or hard capsules of gelatine or starch. Such cores may be produced in conventional manner. We have found that the mycophenolate salts, particularly the sodium salt, are particularly interesting for the production of tablets. When tablet cores are used they have preferably a hardness of from ca. 10 to 70 N.

The pellets or granules may, after application of the enteric-coating as described hereinafter may be used as such or to fill capsules, e.g. hard gelatine capsules. If desired the capsules may be alternatively enteric-coated, e.g. in conventional manner.

Other pharmaceutically acceptable ingredients may be present in the cores, e.g. those conventionally used in the preparation of pharmaceutically compositions, e.g. fillers, e.g. lactose, glidants, e.g. silica, and lubricants, e.g. magnesium stearate.

The term "enteric coating" comprises any pharmaceutically acceptable coating preventing the release of the active agent in the stomach and sufficiently disintegrating in the intestine tract (by contact with approximately neutral or alkaline intestine juices) to allow the resorption of the active agent through the walls of the intestinal tract. Various in vitro tests for determining whether or not a coating is classified as an enteric coating have been published in the pharmacopoeia of various countries.

More specifically, the term "enteric coating" as used herein refers to a coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38° C. and preferably thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH_2PO_4 buffered solution of pH 6.8.

The thickness of the coating may vary and depends inter alia on its permeability in water and acids. A typical coating may be about 16–30, e.g. 16–20 or to 25, mg on a size 1 gelatine capsule. Similar thicknesses may be applied in other formulations.

In general satisfactory results are obtained with a coating of 5–100 μm, preferably 20–80 μm thickness. The coating is suitably selected from macromolecular polymers. Suitable polymers are listed in e.g. L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 3rd Ed, 1986, p. 365–373, H. Sucker et al, Pharmazeutische Technologie, Thieme, 1991, p. 355–359, Hagers Handbuch der pharmazeutischen Praxis, 4th Ed. Vol. 7, pages 739 to 742 and 766 to 778, (Springer Verlag, 1971) and Remington's Pharmaceutical Sciences, 13th Ed., pages 1689 to 1691 (Mack Publ., Co., 1970) and comprise e.g. cellulose ester derivatives, cellulose ethers, acrylic resins, such as methylacrylate copolymers and copolymers of maleic acid and phthalic acid derivatives.

The preferred films are made from cellulose acetate phthalate and trimellitate; methacrylic acid copolymers, e.g. copolymers derived from methylacrylic acid and esters thereof, containing at least 40% methylacrylic acid; and especially hydroxypropyl methylcellulose phthalate.

Methylacrylates include those of molecular weight above 100,000 daltons based on, e.g. methylacrylate and methyl or ethyl methylacrylate in a ratio of about 1:1. Typical products include Endragit L, e.g. L 100-55, marketed by Rohm GmbH, Darmstadt, Germany.

Typical cellulose acetate phthalates have an acetyl content of 17–26% and a phthalate content of from 30–40% with a viscosity of ca. 45–90 cP.

Typical cellulose acetate trimellitates have an acetyl content of 17–26%, a trimellityl content from 25–35% with a viscosity of ca. 15–20 cS. An example of an appropriate cellulose acetate trimellitate is the marketed product CAT (Eastman Kodak Company, USA).

Hydroxypropyl methylcellulose phthalates, typically have a molecular weight of from 20,000 to 100,000 daltons e.g. 80,000 to 130,000 daltons, e.g. a hydroxypropyl content of from 5 to 10%. a methoxy content of from 18 to 24% and a phthalyl content from 21 to 35%.

An example of an appropriate cellulose acetate phthalate is the marketed product CAP (Eastman Kodak, Rochester N.Y., USA).

Examples of suitable hydroxypropyl methylcellulose phthalates are the marketed products having a hydroxypropyl content of from 6–10%, a methoxy content of from 20–24%, a phthalyl content of from 21–27%, a molecular weight of about 84,000 daltons known under the trade mark HP50 and available from Shin-Etsu Chemical Co. Ltd., Tokyo, Japan, and having a hydroxypropyl content, a methoxyl content, and a phthalyl content of 5–9%, 18–22% and 27–35% respectively, and a molecular weight of 78,000 daltons, known under the trademark HP55 and available from the same supplier.

A preferred coating is HP 50.

The enteric coating may be carried out in conventional manner, e.g. so that the cores are sprayed with a solution of the enteric-coating.

Suitable solvents for the enteric-coating are for example organic solvents, e.g. an alcohol such as ethanol, a ketone such as acetone, halogenated hydrocarbons such as CH_2Cl_2 or mixtures of such solvents, e.g. ethanol/acetone, e.g. 1:1 to 10:1.

Conveniently a softener such as di-n-butylphthalate or triacetin is added to such a solution, e.g. in a ratio of coating material to softener of from 1: about 0.05 to about 0.3.

If desired for cellulose phthalates and other acidic coating materials an ammonium salt may be found and an aqueous solution may be used.

A fluidized bed coater may be used for coating.

Conveniently the cores are treated at room temperature or warmed up to 40° C. e.g. by means of warm air of 40° up to 70° C., before spraying. To avoid a sticking of the cores the spray procedure is preferably interrupted at certain time intervals and the cores then warmed up again. It is, however, also possible to proceed without interruption of the spray procedure, e.g. by automatic regulation of the spray amount taking into account the temperature of exhaust air and/or cores.

The spray pressure may vary within wide ranges, in general satisfactory results are obtained with a spray pressure of from about 1 to about 1.5 bar.

The compositions of the invention are useful as immunosuppressants as indicated by standard tests.

The activity and characteristics of the compositions of the invention may be indicated in standard

a) clinical trials, e.g. observing the first acute rejection episodes or treatment failure six months after transplant of kidneys or maintaining a rejection—free state within 6 months after imitation of treatment with the invention. The compositions of the invention are administered at a dose in the range of 0.5 to 2.0 g/day e.g. about 1.5 g day and decrease the acute rejection rates when administered during the period around transplant surgery, and maintain a rejection-free state in patients who are 3 months or more after transplantation. Thus the compositions of the invention may be administered during the initial 72 hours after transplantation at dose of about 0.5 g administered twice a day in combination with a conventional steroid and cyclosporin, e.g. as NEORAL for which the cyclosporin dose is the conventional dose e.g. ca. 8±3 mg/kg for renal transplants. The steroid dose is to be administered at about 2.5 mg/kg for 4 days after transplant, 1 mg/kg thereafter for 1 week, 0.6 mg/kg thereafter for 2 weeks thereafter 0.3 mg/kg for 1 month for prednisone.

and in

b) animal trials e.g. observing the kidney allograft reaction in rat. In this test one kidney from a female fisher 344 rat is transplanted onto the renal vessel of a unilaterally (left side) nephrectomized WF recipient rat using an end-to-end anastomosis. Ureteric anastomosis is also end-to-end. Treatment commences on the day of transplantation and is continued for 14 days. A contralateral nephrectomy is done seven days after transplantation, leaving the recipient relying on the performance of the donor kidney. Survival of the graft recipient is taken as the parameter for a functional graft. Typical doses of the compositions of the invention are from about 1 to 30 mg/kg p.o.

The compositions of the invention are particularly useful for the following conditions:

a) Treatment and prevention of native or transgenic organ, tissue or cellular allograft or xenograft transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, pancreatic islet cell, neural cell or corneal transplant; including treatment and prevention of acute rejection; treatment and prevention of hyperacute rejection, e.g. as associated with xenograft rejection; and treatment and prevention of chronic rejection, e.g. as associated with graft-vessel disease. The compositions of the invention are also indicated for the treatment and prevention of graft-versus-host disease, such as following bone marrow transplantation.

b) Treatment and prevention of autoimmune diseases, e.g. immune-mediated diseases and inflammatory conditions, in particular inflammatory conditions with an etiology including an immunological component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific immune-mediated diseases for which the compositions of the invention may be employed include, autoimmune hematological disorders, including, but not limited to hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulosis, dermatomyositis, polymyositis, chronic active hepatitis, primary bilary cirrhosis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, pemphigus, idiophatic sprue, inflammatory bowel diseases (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmophathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), non-infectious uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, vasculitides, glomerulonephritides (with and without nephrotic syndrome, e.g. including idiophatic nephrotic syn-

drome or minimal change nephropathy) and juvenile dermatomyositis.

Appropriate dosages of the compositions of the invention will of course vary, e.g. depending on the condition to be treated (for example the disease type or the nature of resistance), the MPA salt used, the effect desired and the mode of administration.

In general however satisfactory results are obtained on administration e.g. orally at dosages on the order of from about 1 to about 30 mg salt per kg animal body weight per day, administered once or in divided doses up to 4 times per day. Suitable daily dosages for patients are thus in the order of 200 mg to 3 g p.o. salt e.g. from about 50 to 100% that of mycophenolate mofetil. For the preferred mono sodium salt the dosage of the salt is about two thirds that of mycophenolate mofetil.

Representative unit dosage forms contain from about 50 mg, e.g. 100 mg, to about 1.5 g of the pharmaceutically acceptable mycophenolate salt.

The bioavailability characteristics of compositions of the invention may be determined in conventional manner, e.g. by oral administration to beagle dogs. Dosages are typically 50 mg salt animal e.g. ca 3–5 mg salt /kg animal body weight. Dogs are adult (ca. 10 kg e.g. 6–14 kg) and fasted. Three hours after administration ca. 200 g food is administered. Blood samples are taken from the cephalic vein, before administration and 10, 30, and 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours, after administration. Plasma levels of free MPA are determined by HPLC analysis (with UV detection).

In a relative bioavailability trial as described above in male beagle dogs dosages of 3.8 mg salt/kg animal body weight p.o. were administered with the Example 1 composition as described hereinafter and with a MPA or MMF formulation corresponding to the Example 1 composition but containing an identical amount of MPA or commercially available MMF.

Results are as follows:—

MPA (AUC Relative Bioavailability, Frel [ng.hr.ml^{-1}]	Ex 1	MPA	MMF
Mean	4612 (218)	3579 (174)	2709 (100)
Median	4204 (168)	2911 (182)	2513 (100)
SD	939	1889	1363
CV	20	53	50
Cmax [ng/ml] (Relative Cmax)			
Mean	5391 (313)	3683 (227)	2052 (100)
Median	5359 (367)	2719 (172)	1462 (100)
SD	1847	2504	945
CV (%)	34 (46)	68 (87)	46 (0)

The coefficients of variation (CV) of AUC (20%) and Cmax (34%) of the Example 1 composition are significantly less than those of the reference compositions, indicating less inter-subject and intra-subject variability with the Example 1 composition.

The area under the curve (AUC) and Cmax with the Example 1 composition are higher than those of the reference compositions.

Naturally the advantageous bioavailability characteristics of the present compositions may be ascertained in standard clinical bioavailability trials. For example, doses from 200 mg to 1.5 g of the Example 1 composition and MPA, and MMF may be administered to 12 healthy volunteers in single doses in a cross-over trial. Increased AUC and C_{max} may be observed for the Example 1 composition.

The compositions of the present invention are surprisingly tolerated better than MMF, inducing less gastro-intestinal side effects such as diarrhoea and burning. They show less long term side effects e.g. In the colon.

The compositions of the invention may be administered as the sole active ingredient or with another immunosuppressant e.g. together with simultaneous or separate administration of other immunosuppressants, for example, in immunosuppressive applications such as prevention and treatment of graft vs. host disease, transplant rejection, or immune-mediated disease, the compositions of the invention may be used in combination with cyclosporins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, FK-506 (tacrolimus), etc., rapamycin; corticosteroids; cyclophosphamide; azathioprine; methotrexate; brequinar; leflunomide; mizoribine; deoxyspergualin; analogues thereof, and immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD25, CD28, CTLA4, B7, CD45, or CS58 or their ligands; or other immunomodulatory compounds.

When the compositions of the invention are co-administered with such other immunosuppressants the dosages of the other immunosuppressants may be reduced e.g. to one-half to one-third their dosages when used alone.

Representative doses for ciclosporin to be used are e.g. 1 to 10, e.g. 1 to 2 mg/kg/day.

The present invention provides in another aspect the use, method and compositions as defined hereinafter in the claims.

Insofar as details of excipients are not described herein, these are known, or available e.g. In the Handbook of Pharmaceutical Excipients, Second Edition, edited by Ainley Wade and Paul J. Weller, American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete edited by H. P. Fiedler, 4th Edition, Edito Cantor, Aulendorf and earlier editions.

Following is a description by way of example only of compositions of this invention:

EXAMPLE 1:

Composition

Capsule contents

MPA mono sodium salt	53.43 mg (=50 mg MPA)
Lactose (1:1 mixture of 100/200 mesh)	256.57 mg
Silica (Aerosil)	3.1 mg
Magnesium stearate	1.55 mg
	314.65 mg
Capsule is size 1	
Enteric coating (ca 17 mg)	
Hydroxypropyl methyl cellulose phthalate (HP50)	9 parts
Triacetin	1 part

Procedure

The capsule ingredients are mixed and filled into size 1 capsules. The capsules are coated in a fluidized bed coater with a solution of the enteric coating ingredients in ethanol (containing 10% acetone). The coating on each capsule is about 17 mg. The capsules meet the enteric coating test described herein and do not disintegrate within 2 hours in

artificial gastric juices (pH 1, HCl). The compositions are stable, e.g for 2 years at room temperature,

If desired larger capsules containing 534.3 mg MFA mono sodium salt may be made in analogous manner, reducing the amount of lactose. These are well tolerated in clinical trials.

EXAMPLE 2:

Capsules of size 1 are made up as in Example 1. A solution for enteric coating was made up as follows:

Hydroxypropyl methyl cellulose phthalate (HP50)	270 g
Triacetin	30 g
Acetone	900 g
Ethanol	1800 g

600 g of this enteric coating solution was used for 1 kg of capsules (ca. 2400). The amount of coating applied to each capsule was about 25 mg giving a film thickness of 5–6 mg/cm^2.

What is claimed is:

1. A pharmaceutical composition comprising a mycophenolate salt, the composition being formulated to disintegrate selectively in the intestinal tract to release mycophenolate there.

2. A method of immunosuppressing a subject which comprises administering a therapeutically effective amount of a composition of claim **1** to a subject in need of such immunosuppression, optionally with the simultaneous or separate administration another immunosuppressant, wherein the composition has an enteric coating.

3. A composition containing a composition of claim **1** and another immunosuppressant for simultaneous, sequential or separate administration, wherein the composition has an enteric coating.

4. A composition according to claim **1** wherein the salt is the mono-sodium salt.

5. A composition according to claim **1** wherein said composition further comprises another immunosuppressant.

6. The pharmaceutical composition of claim **1** wherein said composition has an enteric coating and is suitable as an immunosuppressant medicament.

7. The pharmaceutical composition of claim **6** wherein said composition further comprises a second immunosuppressant.

8. The pharmaceutical composition of claim **7** wherein said second immunosuppressant is cyclosporin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO : US 6,172,107 B1
DATED: : January 9, 2001
INVENTOR(S) : HAEBERLIN ET AL.

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

Title page, left column, section [54] should read:

-- [54] **ENTERIC-COATED PHARMACEUTICAL COMPOSITIONS** --

Signed and Sealed this

Twenty-ninth Day of May, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

EXHIBIT C

US006306900B1

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

(10) **Patent No.: US 6,306,900 B1**
(45) **Date of Patent: *Oct. 23, 2001**

(54) **ENTERIC COATED PHARMACEUTICAL COMPOSITIONS**

(75) Inventors: **Barbara Haeberlin**, Riehen; **Ching-Pong Mak**, Therwil, both of (CH); **Armin Meinzer**, Buggingen (DE); **Jacky Vonderscher**, Riedisheim (FR)

(73) Assignee: **Novartis AG**, Basel (CH)

(*) 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.: **09/694,209**

(22) Filed: **Oct. 23, 2000**

Related U.S. Application Data

(62) Continuation of application No. 09/469,536, filed on Dec. 22, 1999, now Pat. No. 6,172,107, which is a continuation of application No. 09/077,398, filed as application No. PCT/EP97/01800 on Apr. 10, 1997, now Pat. No. 6,025,391.

(30) **Foreign Application Priority Data**

Apr. 12, 1996 (GB) 9607564
Oct. 24, 1996 (GB) 9622028

(51) **Int. Cl.**[7] **A61K 31/34**; A01N 43/08

(52) **U.S. Cl.** **514/470**; 514/8; 514/11; 514/570; 514/576; 514/885; 514/960; 514/968; 424/457; 424/458; 424/459; 424/461; 424/462; 424/463; 424/468; 424/474; 424/475; 424/479; 424/480; 424/482; 424/490; 424/493; 424/494; 424/495; 424/497

(58) **Field of Search** 514/470, 8, 11, 514/570, 576, 885, 960, 968; 424/457, 458, 459, 461, 462, 463, 468, 474, 475, 479, 480, 482, 490, 493, 494, 495, 497

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,705,894	12/1972	Gerzon et al.	260/240
3,705,946	12/1972	Dyke et al.	424/279
3,777,020	12/1973	Johnson	424/180
3,825,571	7/1974	Mori et al.	260/343.3
3,853,919	12/1974	Mori et al.	260/343.3
3,868,454	2/1975	Johnson	424/248
3,880,995	4/1975	Jones	424/180
3,903,071	9/1975	Holmes	260/210
4,005,108	1/1977	Kupchan et al.	260/343 R
4,234,684	11/1980	Abbott et al.	435/75
4,680,299	7/1987	Hesson	514/311
4,686,234	8/1987	Nelson et al.	514/469
4,725,622	2/1988	Nelson et al.	514/469
4,727,069	2/1988	Nelson et al.	514/211
4,753,935	6/1988	Nelson et al.	514/233.5
4,786,637	11/1988	Allison et al.	514/233.5
4,808,592	2/1989	Nelson et al.	514/233.5
4,847,381	7/1989	Sutherland et al.	546/156
4,868,153	9/1989	Allison et al.	514/470
4,959,387	9/1990	Nelson et al.	524/469
4,992,467	2/1991	Allison et al.	514/464

FOREIGN PATENT DOCUMENTS

815330	5/1973	(BE) .
0281713	9/1988	(EP) .
551182	7/1993	(EP) .
0691130	1/1996	(EP) .
1157099	7/1969	(GB) .
1157100	7/1969	(GB) .
1158387	7/1969	(GB) .
1203328	8/1970	(GB) .
1261060	1/1972	(GB) .
2117238	10/1983	(GB) .
94/01105	1/1994	(WO) .
94/26265	11/1994	(WO) .
94/26266	11/1994	(WO) .
95/04627	4/1995	(WO) .
95/09626	4/1995	(WO) .
95/13082	5/1995	(WO) .
31237	11/1967	(ZA) .

OTHER PUBLICATIONS

Sweeney et al., Cancer Research 32, pp. 1803–1809, Sep. 1972.

JF Bach et al. The mode of action of immunosuppressive agents, Elsevier Publisher, Amsterdam, 1985, pp. 105–174.

Allison et al., Springer Semin Immunopathol (1993) 14:353–380.

Epinette et al. Journal of the American Academy of Dermatology, pp. 962–971, 1978.

Ohsugi et al. Cancer Research 36, pp. 2923–2927, Aug. 1976.

Franklin et al., Biochem. J. (1969), vol. 113, pp. 515–524.

Mitsui et al., CA 75;150091, Progr. Antimicrob. Anticancer Chemother., Proc. Int. Congr. Chemother., 6th (1970) vol. 2, pp. 130–135.

Schiantarelli et al. Agents and Actions, vol. 14, No. 2 (1984) pp. 247–256.

Suzuki et al. The Journal of Antibiotics, vol. XXIX, No. 3, pp. 275–285, 1980.

Harrison et al. J.C.S. Perkins II, pp. 1542–1544, 1985.

Seki et al. Antimicrobial Agents and Chemotherapy, vol. 33, No. 5, May 1989, pp. 773–775.

Allison et al. In: Immunosuppressive Drugs–Development in anti–rejection therapy, pp. 141–159, 1988.

Mitsui et al., The Journal of Antibiotics, Aug. 1969, pp. 358–363.

James J. Lipsky, The Lancet 1996; vol. 348, Nov. 16, 1996, pp. 1357–1359.

H. Boxenbaum, Journal of Pharmacokinetics and Biopharmaceutics, vol. 10, No. 2, 1982, pp. 201–227.

(List continued on next page.)

Primary Examiner—Frederick Krass
(74) *Attorney, Agent, or Firm*—John D. Thallemer

(57) **ABSTRACT**

This invention provides a pharmaceutical composition comprising a mycophenolate salt, the composition being adapted to release mycophenolate in the upper part of the intestinal tract.

14 Claims, No Drawings

OTHER PUBLICATIONS

Eugui et al. Scand. J. Immunol. 33, pp. 175–183, 1991.
Morris et al. Transplant. Proc. vol. 22, pp. 1659–1662 (1990).
Lee et al., Pharmaceutical Research, vol. 7, No. 2, 1990, pp. 161–165.
Boit, Beilsteins Handbuch der Organischem Chemi, vol. 18, Part 7, p. 6513, 1990.
Luckenbach, Beilstein Handbook of Organic Chemistry, vol. 18, Part 9, p. 239, 1992.
Makara et al., CA 124:139508 (abstract of Journal Med. Chem. 1996, 39, pp. 1236–1242.
Suzuki et al., CA BA62:38453, The Journal of Antibiotics, Mar. 1976, vol. 29, No. 3, pp. 286–291.
Potel, Aus der Bakteriologischen Forschungsabteilung der Asta–Werke AG., pp. 527–532, 1977.
XP 002043101 Fester orale and perorate Arzneiformen, pp. 356–361, 1974.
Nature, vol. 223, Aug. 23, 1969, pp. 848–850.
Aisenberg, The New England Journal of Medicine, May 27, 1965, pp. 1114–1116.
Marinari et al., XP 002043018, Arch Dermatol, vol. 113, Jul. 1977, pp. 930–931.
XP002043019, European Mycophenolate Mofetil Cooperative Study Group, vol. 345, May 27, 1995, pp. 1321–1322.
80538 Chemical Abstracts vol. 73, 1970, p. 230, No. 80540w.
Chemical Abstracts, vol. 80, 1974, p. 338, No. 59722s.
Chemical Abstract, vol. 80, 1974, p. 420, No. 120748y.
Chemical Sbstract, vol. 96, 1982, p. 646, No. 199422x.
Chemical Abstract 7–Enzymes, vol. 124, Nov. 11, 1996, p. 559, No. 139508w.
26–Biomolecules, vol. 96, 1982, p. 647.
Chemical Abstract, vol. 98, 1983, p. 564, No. 143262w.
Chemical Abstract, vol. 98, 1983, p. 632, No. 198004w.
27 Heterocytes, vol. 98, 1983, p. 565.
Schnitzer, Academic Press, vol. 10, 1972, pp. 14–19, 24, 25, 70 and 71.
The Lancet, vol. 345, May 27, 1995, pp. 1323–1325.
Sollinger, H.W., Chem. Abstr. 1996, 95370774, Kidney Int'l, Supplement, 1995, vol. 52, pp. 514–517.
Platz et al., "A new and potent immunosuppressive agent, "Transplantation, vol. 51, No. 1, 1991, pp. 27–31.
Ohsugi, et al., "Antitumor and immunosuppressive effects of mycophenolic acid derivatives", Cancer Rres. vol. 36, No. 1976, pp. 2923–2927.
Chemical Abstract 108174f, Gerzon et al., "Mycophenolic acid and its derivatives, inhibitors of malignant tumor cell growth in warm–blooded mammals", 1976.
Ito et al., Pharmacokinetics of Mycophenolic Acid in Healthy Human Voluteers, J. Med. Soc. Toho, Japan, vol. 29, No. 3, 1982, pp. 412–418.
Kajiwara et al., General Pharmacology of Mycophenolic Acid, J. Med. Soc. Toho, Japan, vol. 29, No. 3, 1982, pp. 419–425.
Kajiwara et al., Species Differences of Mycophenolic Acid, a New Drug for Psoriasis in Acute, Sub–acute and Chronic Toxicity, Journal of the Medical Society of Toho University, Sep. 1, 1982.
Ohsugi et al., CA84:103774, Areugi, (1975) 24 (12) pp. 820–825.
Hasunuma, et al., CA 112:191604 Abstract of Adv. Exp. Med. Biol. (1989) 253A (Purine Pyrimidine Metab. Man 6, Pt. A), pp.455–460.
Derwent Abstract 93–329920/41 corresponding to JP 06256182–A (1994).
Derwent Abstract 94–313614/39 corresponding to JP 06239740–A (1994).
Derwent Abstract 93–220931/28 corresponding to EP 551182–A1 (1993).
Derwent Abstract 84509V/49 corresponding to BE 815–330 (1974).
Derwent Abstract 37140T–B corresponding to BE 775785 (1972).
Derwent Abstract 88322 C/49 corresponding to US 4234–684 (1980).

ENTERIC COATED PHARMACEUTICAL COMPOSITIONS

This application is a continuation of U.S. application Ser. No. 09/469,536, filed Dec. 22, 1999, now U.S. Pat. No. 6,172,107 which is a continuation of U.S. application Ser. No. 09/077,398, filed May 28, 1998, now U.S. Pat. No. 6,025,391 which is a 371 of PCT/EP97/01800, filed Apr. 10, 1997.

This invention relates to mycophenolic acid.

Mycophenolic acid, also referred to herein as MPA, was first isolated in 1896, and has been extensively investigated as a pharmaceutical of potential commercial interest. It is known to have anti-tumor, anti-viral, immunosuppressive, anti-psoriatic, and anti-inflammatory activity [see e.g. W. A. Lee et al, Pharmaceutical Research (1990), 7, p. 161–166 and references cited therein]. Publications have appeared on MPA as an anti-cancer agent by Lilly scientists, see e.g. M. J. Sweeney et al., Cancer Research (1972), 32, 1795–1802, and by ICI scientists, see e.g. GB 1,157,099 and 1,203,328 and as an immunosuppressant agent see e.g. A. Mitsui et al. J. Antibiotics (1969) 22, p. 358–363. In the above-mentioned article by W. A. Lee et al it is stated that attempts have been made to increase the bio-availability or specificity of MPA by making derivatives. The poor bioavailability of the acid was thought to be caused by undetermined factors such as drug complexation in the gastro-intestinal lumen, a narrow absorption window, metabolism before absorption etc.. The preparation of the morpholinoethyl ester, also known as mycophenolate mofetil (sometimes referred to herein as MMF), was described which had considerably higher bioavailability than MPA (100% for MMF and 43% for MPA). This derivative has been recently introduced commercially as an immunosuppressant for the treatment or prevention of organ or tissue transplant rejection, at daily dosages of from about 200 mg to about 3 grams p.o, e.g. about 2 g p.o. Patient compliance with MMF is not ideal, inter alia, because of side-effects e.g. gastro-intestinal side effects, the origin of which is not known.

We have now found, after exhaustive testing, that mycophenolate salts when enteric coated or adapted to be released in the upper part of the intestines, e.g. in the duodenum, jejeunum and/or ileum, are effective, well-tolerated, pharmaceuticals particularly for immunosuppressive indications especially for the treatment or prevention of organ, tissue or cellular allograft or xenograft rejection, e.g. after transplant, or the treatment or prevention of immune-mediated diseases (autoimmune diseases) and have interesting bioavailability and stability characteristics. Moreover fewer unit dosage forms are required to be administered than for MMF, leading to easier administration.

The present invention provides in one aspect a pharmaceutical composition comprising a myophenolate salt, the composition being adapted to release mycophenolate in the upper part of the intestinal tract (hereinafter referred to as a composition of the invention). The composition may be adapted in any conventional manner, preferably with means adapted to prevent release of the myocophenolate in the stomach and to ensure release in the upper part of the intestinal tract. In a further aspect the invention provides a pharmaceutical composition comprising a coated pharmaceutically acceptable mycophenolate salt.

Such salts are cationic salts, e.g. of alkali metals, especially the sodium salts. Sodium mycophenolate salts are known, e.g. in South African Patent 68/4959. We prefer to use the mono-sodium salt. This may be obtained in crystalline form by recrystallization from acetone/ethanol if necessary with water; Mpt. 189–191° C.

The invention provides, more specifically, a solid enteric-coated composition in unit dose form for oral application, the core of the composition containing sodium mycophenolate in solid or liquid form.

The term "core" comprises sodium mycophenolate (or other cationic salt) if desired in admixture with further physiologically acceptable material, that can be surrounded by an enteric-coating. The term "core" comprises, in a wide sense, not only tablets, pellets or granules but also capsules, e.g. soft or hard capsules of gelatine or starch. Such cores may be produced in conventional manner. We have found that the mycophenolate salts, particularly the sodium salt, are particularly interesting for the production of tablets. When tablet cores are used they have preferably a hardness of from ca. 10 to 70 N.

The pellets or granules may, after application of the enteric-coating as described hereinafter may be used as such or to fill capsules, e.g. hard gelatine capsules. If desired the capsules may be alternatively enteric-coated, e.g. in conventional manner.

Other pharmaceutically acceptable ingredients may be present in the cores, e.g. those conventionally used in the preparation of pharmaceutically compositions, e.g. fillers, e.g. lactose, glidants, e.g. silica, and lubricants, e.g. magnesium stearate.

The term "enteric coating" comprises any pharmaceutically acceptable coating preventing the release of the active agent in the stomach and sufficiently disintegrating in the intestine tract (by contact with approximately neutral or alkaline intestine juices) to allow the resorption of the active agent through the walls of the intestinal tract. Various in vitro tests for determining whether or not a coating is classified as an enteric coating have been published in the pharmacopoeia of various countries.

More specifically, the term "enteric coating" as used herein refers to a coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38° C. and preferably thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH_2PO_4 buffered solution of pH 6.8.

The thickness of the coating may vary and depends inter alia on its permeability in water and acids. A typical coating may be about 16–30, e.g. 16–20 or to 25, mg on a size 1 gelatine capsule. Similar thicknesses may be applied in other formulations.

In general satisfactory results are obtained with a coating of 5–100 μm, preferably 20–80 μm thickness. The coating is suitably selected from macromolecular polymers. Suitable polymers are listed in e.g. L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 3rd Ed, 1986, p. 365–373, H. Sucker et al, Pharmazeutische Technologie, Thieme, 1991. p. 355–359, Hagers Handbuch der pharmazeutischen Praxis, 4th Ed. Vol. 7, pages 739 to 742 and 766 to 778, (Springer Verlag, 1971) and Remington's Pharmaceutical Sciences, 13th Ed., pages 1689 to 1691 (Mack Publ., Co., 1970) and comprise e.g. cellulose ester derivatives, cellulose ethers, acrylic resins, such as methylacrylate copolymers and copolymers of maleic acid and phthalic acid derivatives.

The preferred films are made from cellulose acetate phthalate and trimellitate; methacrylic acid copolymers, e.g. copolymers derived from methylacrylic acid and esters thereof, containing at least 40% methylacrylic acid; and especially hydroxypropyl methylcellulose phthalate.

Methylacrylates include those of molecular weight above 100,000 daltons based on, e.g. methylacrylate and methyl or ethyl methylacrylate in a ratio of about 1:1. Typical products include Endragit L, e.g. L 100–55, marketed by Rohm GmbH, Darmstadt, Germany.

Typical cellulose acetate phthalates have an acetyl content of 17–26% and a phthalate content of from 30–40% with a viscosity of ca. 45–90 cP.

Typical cellulose acetate trimellitates have an acetyl content of 17–26%, a trimellityl content from 25–35% with a viscosity of ca. 15–20 cS. An example of an appropriate cellulose acetate trimellitate is the marketed product CAT (Eastman Kodak Company, USA).

Hydroxypropyl methylcellulose phthalates, typically have a molecular weight of from 20,000 to 100,000 daltons e.g. 80,000 to 130,000 daltons, e.g. a hydroxypropyl content of from 5 to 10%, a methoxy content of from 18 to 24% and a phthalyl content from 21 to 35%.

An example of an appropriate cellulose acetate phthalate is the marketed product CAP (Eastman Kodak, Rochester N.Y., USA).

Examples of suitable hydroxypropyl methylcellulose phthalates are the marketed products having a hydroxypropyl content of from 6–10%, a methoxy content of from 20–24%, a phthalyl content of from 21–27%, a molecular weight of about 84,000 daltons known under the trade mark HP50 and available from Shin-Etsu Chemical Co. Ltd., Tokyo, Japan, and having a hydroxypropyl content, a methoxyl content, and a phthalyl content of 5–9%, 18–22% and 27–35% respectively, and a molecular weight of 78,000 daltons, known under the trademark HP55 and available from the same supplier.

A preferred coating is HP 50.

The enteric coating may be carried out in conventional manner, e.g. so that the cores are sprayed with a solution of the enteric-coating.

Suitable solvents for the enteric-coating are for example organic solvents, e.g. an alcohol such as ethanol, a ketone such as acetone, halogenated hydrocarbons such as CH_2Cl_2 or mixtures of such solvents, e.g. ethanol/acetone, e.g. 1:1 to 10:1.

Conveniently a softener such as di-n-butylphthalate or triacetin is added to such a solution, e.g. in a ratio of coating material to softener of from 1: about 0.05 to about 0.3.

If desired for cellulose phthalates and other acidic coating materials an ammonium salt may be found and an aqueous solution may be used.

A fluidized bed coater may be used for coating.

Conveniently the cores are treated at room temperature or warmed up to 40° C. e.g. by means of warm air of 40° up to 70° C., before spraying. To avoid a sticking of the cores the spray procedure is preferably interrupted at certain time intervals and the cores then warmed up again. It is, however, also possible to proceed without interruption of the spray procedure, e.g. by automatic regulation of the spray amount taking into account the temperature of exhaust air and/or cores.

The spray pressure may vary within wide ranges, in general satisfactory results are obtainers with a spray pressure of from about 1 to about 1.5 bar.

The compositions of the invention are useful as immunosuppressants as indicated by standard tests.

The activity and characteristics of the compositions of the invention may be indicated in standard

a) clinical trials, e.g. observing the first acute rejection episodes or treatment failure six months after transplant of kidneys or maintaining a rejection—free state within 6 months after imitation of treatment with the invention. The compositions of the invention are administered at a dose in the range of 0.5 to 2.0 g/day e.g. about 1.5 g/day and decrease the acute rejection rates when administered during the period around transplant surgery, and maintain a rejection-free state in patients who are 3 months or more after transplantation. Thus the compositions of the invention may be administered during the initial 72 hours after transplantation at dose of about 0.5 g administered twice a day in combination with a conventional steroid and cyclosporin, e.g. as NEORAL for which the cyclosporin dose is the conventional dose e.g. ca. 8±3 mg/kg for renal transplants. The steroid dose is to be administered at about 2.5 mg/kg for 4 days after transplant, 1 mg/kg thereafter for 1 week, 0.6 mg/kg thereafter for 2 weeks thereafter 0.3 mg/kg for 1 month for prednisone.

and in

b) animal trials e.g. observing the kidney allograft reaction in rat. In this test one kidney from a female fisher 344 rat is transplanted onto the renal vessel of a unilaterally (left side) nephrectomized WF recipient rat using an end-to-end anastomosis. Ureteric anastomosis is also end-to-end. Treatment commences on the day of transplantation and is continued for 14 days. A contralateral nephrectomy is done seven days after transplantation, leaving the recipient relying on the performance of the donor kidney. Survival of the graft recipient is taken as the parameter for a functional graft. Typical doses of the compositions of the invention are from about 1 to 30 mg/kg p.o.

The compositions of the invention are particularly useful for the following conditions:

a) Treatment and prevention of native or transgenic organ, tissue or cellular allograft or xenograft transplant rejection, e.g. for the treatment of recipients of e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, skin, pancreatic islet cell, neural cell or corneal transplant; including treatment and prevention of acute rejection; treatment and prevention of hyperacute rejection, e.g. as associated with xenograft rejection; and treatment and prevention of chronic rejection, e.g. as associated with graft-vessel disease. The compositions of the invention are also indicated for the treatment and prevention of graft-versus-host disease, such as following bone marrow transplantation.

b) Treatment and prevention of autoimmune diseases, e.g. immune-mediated diseases and inflammatory conditions, in particular inflammatory conditions with an etiology including an immunological component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases. Specific immune-mediated diseases for which the compositions of the invention may be employed include, autoimmune hematological disorders, including, but not limited to hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulosis, dermatomyositis, polymyositis, chronic active hepatitis, primary bilary cirrhosis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, pemphigus, idiophatic sprue, inflammatory bowel diseases (including e.g. ulcerative colitis and Crohn's disease), endocrine ophthalmophathy, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), non-infectious uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, vasculitides, glomerulonephritides (with and without nephrotic syndrome, e.g. including idiophatic nephrotic syn-

drome or minimal change nephropathy) and juvenile dermatomyositis.

Appropriate dosages of the compositions of the invention will of course vary, e.g. depending on the condition to be treated (for example the disease type or the nature of resistance), the MPA salt used, the effect desired and the mode of administration.

In general however satisfactory results are obtained on administration e.g. orally at dosages on the order of from about 1 to about 30 mg salt per kg animal body weight per day, administered once or in divided doses up to 4 times per day. Suitable daily dosages for patients are thus in the order of 200 mg to 3 g p.o. salt e.g. from about 50 to 100% that of mycophenolate mofetil. For the preferred mono sodium salt the dosage of the salt is about two thirds that of mycophenolate mofetil.

Representative unit dosage forms contain from about 50 mg, e.g. 100 mg, to about 1.5 g of the pharmaceutically acceptable mycophenolate salt.

The bioavailability characteristics of compositions of the invention may be determined in conventional manner, e.g. by oral administration to beagle dogs. Dosages are typically 50 mg salt animal e.g. ca 3–5 mg salt/kg animal body weight. Dogs are adult (ca. 10 kg e.g. 6–14 kg) and fasted. Three hours after administration ca. 200 g food is administered. Blood samples are taken from the cephalic vein, before administration and 10, 30, and 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours, after administration. Plasma levels of free MPA are determined by HPLC analysis (with UV detection).

In a relative bioavailability trial as described above in male beagle dogs dosages of 3.8 mg salt/kg animal body weight p.o. were administered with the Example 1 composition as described hereinafter and with a MPA or MMF formulation corresponding to the Example 1 composition but containing an identical amount of MPA or commercially available MMF.

Results are as follows:

	Ex 1	MPA	MMF
MPA (AUC Relative Bioavailability, Frel [ng · hr · ml^{-1}]			
Mean	4612 (218)	3579 (174)	2709 (100)
Median	4204 (168)	2911 (182)	2513 (100)
SD	939	1889	1363
CV	20	53	50
Cmax [ng/ml] (Relative Cmax)			
Mean	5391 (313)	3683 (227)	2052 (100)
Median	5359 (367)	2719 (172)	1462 (100)
SD	1847	2504	945
CV (%)	34 (46)	68 (87)	46 (0)

The coefficients of variation (CV) of AUC (20%) and Cmax (34%) of the Example 1 composition are significantly less than those of the reference compositions, indicating less inter-subject and intra-subject variability with the Example 1 composition.

The area under the curve (AUC) and Cmax with the Example 1 composition are higher than those of the reference compositions.

Naturally the advantageous bioavailability characteristics of the present compositions may be ascertained in standard clinical bioavailability trials. For example, doses from 200 mg to 1.5 g of the Example 1 composition and MPA, and MMF may be administered to 12 healthy volunteers in single doses in a cross-over trial. Increased AUC and C_{max} may be observed for the Example 1 composition.

The compositions of the present invention are surprisingly tolerated better than MMF, inducing less gastro-intestinal side effects such as diarrhoea and burning. They show less long term side effects e.g. in the colon.

The compositions of the invention may be administered as the sole active ingredient or with another immunosuppressant e.g. together with simultaneous or separate administration of other immunosuppressants, for example, in immunosuppressive applications such as prevention and treatment of graft vs. host disease, transplant rejection, or immune-mediated disease, the compositions of the invention may be used in combination with cyclosporins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A; FK-506 (tacrolimus), etc., rapamycin; corticosteroids; cyclophosphamide; azathioprine; methotrexate; brequinar; leflunomide; mizoribine; deoxyspergualin; analogues thereof, and immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD25, CD28, CTLA4, B7, CD45, or CS58 or their ligands; or other immunomodulatory compounds.

When the compositions of the invention are co-administered with such other immunosuppressants the dosages of the other immunosuppressants may be reduced e.g. to one-half to one-third their dosages when used alone.

Representative doses for ciclosporin to be used are e.g. 1 to 10, e.g. 1 to 2 mg/kg/day.

The present invention provides in another aspect the use, method and compositions as defined hereinafter in the claims.

Insofar as details of excipients are not described herein, these are known, or available e.g. in the Handbook of Pharmaceutical Excipients, Second Edition, edited by Ainley Wade and Paul J. Weller, American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik and angrenzende Gebiete edited by H. P. Fiedler, 4th Edition, Edito Cantor, Aulendorf and earlier editions.

Following is a description by way of example only of compositions of this invention:

EXAMPLE 1

Composition

Capsule Contents

MPA mono sodium salt	53.43 mg (= 50 mg MPA)
Lactose (1:1 mixture of 100/200 mesh)	256.57 mg
Silica (Aerosil)	3.1 mg
Magnesium stearate	1.55 mg
	314.65 mg

Capsule is Size 1

Enteric Coating (ca 17 mg)	
Hydroxypropyl methyl cellulose phthalate (HP50)	9 parts
Triacetin	1 part

Procedure

The capsule ingredients are mixed and filled into size 1 capsules. The capsules are coated in a fluidized bed coater

with a solution of the enteric coating ingredients in ethanol (containing 10% acetone). The coating on each capsule is about 17 mg. The capsules meet the enteric coating test described herein and do not disintegrate within 2 hours in artificial gastric juices (pH 1, HCl). The compositions are stable, e.g for 2 years at room temperature,

If desired larger capsules containing 534.3 mg MFA mono sodium salt may be made in analogous manner, reducing the amount of lactose. These are well tolerated in clinical trials.

EXAMPLE 2

Capsules of size 1 are made up as in Example 1. A solution for enteric coating was made up as follows:

Hydroxypropyl methyl cellulose phthalate (HP50)	270 g
Triacetin	30 g
Acetone	900 g
Ethanol	1800 g

600 g of this enteric coating solution was used for 1 kg of capsules (ca. 2400). The amount of coating applied to each capsule was about 25 mg giving a film thickness of 5–6 mg/cm^2.

What is claimed is:

1. A pharmaceutical composition comprising a mycophenolate salt, the composition being adapted to prevent release of mycophenolate in the stomach.

2. The composition of claim **1** wherein the composition has an enteric coating and said enteric coating comprises cellulose acetate phthalate and trimellitate, or methacrylic acid copolymers containing at least 40% methacrylic acid, or hydroxypropyl methylcellulose phthalate.

3. The composition of claim **2** wherein said coating comprises methacrylic acid copolymers containing at least 40% methacrylic acid.

4. The composition of claim **2** wherein said composition is in a tablet form.

5. The composition of claim **4**, wherein said tablet has a hardness between 10 and 70 N.

6. The composition of claim **2** wherein said composition is in a granule or pellet form.

7. The composition of claim **6** wherein said granule or pellet is contained in a capsule.

8. The composition of claim **1** wherein said salt is a mono-sodium salt.

9. The composition of claim **8** wherein said salt is in crystalline form.

10. The composition of claim **1** wherein said composition comprises from about 50 mg to 1.5 g of a pharmaceutically acceptable mycophenolate salt.

11. A pharmaceutical composition comprising a mycophenolate mono-sodium salt, the composition being adapted to prevent release mycophenolate in the stomach, wherein said composition has an enteric coating and said enteric coating comprises cellulose acetate phthalate and trimellitate, or methacrylic acid copolymers containing at least 40% methacrylic acid, or hydroxypropyl methylcellulose phthalate.

12. The composition of claim **11** wherein said mono-sodium salt is in crystalline form.

13. The composition of claim **11** herein said composition is in a tablet form and said tablet form has a hardness between 10 and 70 N.

14. The composition of claim **11** wherein said composition comprises from about 50 mg to 1.5 of a pharmaceutically acceptable mycophenolate salt.

* * * * *