ENTERIC-COATED PHARMACEUTICAL COMPOSITIONS OF MYCOPHENOLATE

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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. 45–9O cP.