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(54) Title: GALENICAL FORMULATIONS

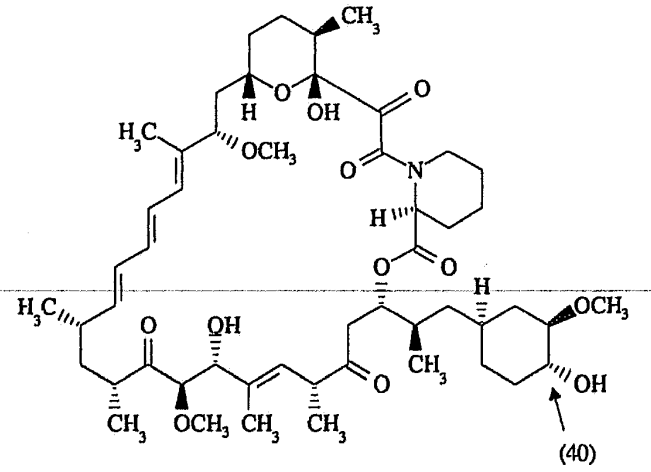
(57) Abrégé/Abstract:
A pharmaceutical composition containing macrolide, e.g. a rapamycin compound in an emulsion preconcentrate or microemulsion preconcentrate for oral administration. The carrier medium for the rapamycin compound includes a hydrophilic phase, a lipophilic phase and a surfactant. The composition is stable and provides high absorption efficiency.

GALENICAL FORMULATIONS **100-8039**

This invention relates to galenic formulations containing macrolides, e.g. compounds of the rapamycin class. In particular this invention relates to galenic formulations which are in the form of micro-emulsions, micro-emulsion preconcentrates, emulsion or emulsion-preconcentrate.

The macrolide may contain e.g. 1, 2 or 3 ring oxygen or nitrogen or other atoms besides carbon atoms. It may have side chains, e.g. in the form of fused rings, or substituents,e.g. oxy groups. It may contain double bonds.
It may contain e.g. from 15 to 35 ring atoms e.g. of carbon.

Rapamycin is a macrolide antibiotic produced by Streptomyces hygroscopicus. It has been found to be pharmaceutically useful in a variety of applications, particularly as an immunosuppressant for use in the treatment and prevention of organ transplant rejection and autoimmune diseases. Rapamycin has the following structure:



(Kesseler, H., et al., Helv. Chim. Acta (1993) 76: 117; US Patent No. 3 929 992). Large numbers of derivatives of rapamycin have been synthesized, including for example those disclosed in US patents 5221670 and 5221740, certain acyl and aminoacyl-rapamycins (see for example US patent 4316885, US patent 4650803, and US patent 5151413), and carbonates and amide esters (see for example EP 509795 and 515140) 27-desmethyl-rapamycin (see for example WO 92/14737), 26-dihydro-rapamycin (see for example US patent 5138051), alkoxyester derivatives (see for example US patent 5233036), and certain pyrazole derivatives (US patent 5164399).

Rapamycin and its structurally similar analogs and derivatives are termed collectively as "compounds of the rapamycin class" in this specification.

Compounds of the rapamycin class are extremely potent immunosuppressants and have also been shown to have antitumor and antifungal activity. However their utility as pharmaceuticals especially on oral administration has been restricted by their very low solubility, low and variable bioavailability and their high toxicity. Little is known concerning the causes of these properties and the site of absorption. Thus low bioavailability may be thought to due to due to extensive metabolism of the macrolide ring and not solvable by a galenical formluation.
Therefore there is a need for an acceptable pharmaceutical composition that contains compounds of the rapamycin class.

FK506 is a macrolide immunosuppressant that is produced by Streptomyces tsukubaensis No 9993. The structure of FK506 is given in the appendix to the Merck Index, as item A5. Also a large number of related compounds which retrain the basic structure and immunological properties of FK506 are also known. These compounds are described in a large number of publications, for example EP 184162, EP 315973, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, WO 93/5059 and the like. Little is known concerning the biopharmaceutical properties of such compounds. These compounds are termed collectively "FK506 compounds" in this

specification.

It has now been surprisingly found that stable compositions containing macrolides that offer high absorption efficiency, can be obtained by formulating the macrolide with certain carrier media.

Accordingly, this invention provides a pharmaceutical composition comprising a macrolide and a carrier medium comprising a hydrophilic phase, a lipophilic phase and a surfactant.

In another aspect the invention provides a pharmaceutical composition which comprises an orally administrable active agent which is other than a cyclosporin and a microemulsion preconcentrate carrier medium therefor which comprises

i) a reaction product of castor oil and ethylene oxide,

ii) a transesterification product of a vegetable oil and glycerol comprising predominantly linoleic acid or oleic acid mono-, di- and tri-glycerides, or a polyoxyalkylated vegetable oil,

iii) 1,2 propylene glycol and

iv) ethanol.

In one particular embodiment there is provided a pharmaceutical composition in the form of a microemulsion preconcentrate comprising rapamycin or 40-O-(2-hydroxy)ethyl rapamycin as an active ingredient in a carrier medium which comprises: i) a hydrophilic phase; ii) a lipophilic phase selected from the group consisting of medium chain fatty acid triglycerides, mixed mono-, di-, and tri-glycerides, and transesterified ethoxylated vegetable oils; iii) a surfactant selected from the group consisting of the reaction product of a natural or hydrogenated castor oil and ethylene oxide; polyethylene-sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, dioctylsulfosuccinate or di(-2-ethylhexyl)-succinate, phospholipids, and propylene glycol mono- and di-fatty acid esters; the relative proportion of the active ingredient and components i), ii) and iii) being such that on dilution with water, a microemulsion having an average particle size of <1,500 Å is spontaneously formed.

In another particular embodiment there is provided a pharmaceutical composition comprising a compound from the FK506 class and a carrier medium comprising a hydrophilic phase, a lipophilic phase and a surfactant.

In a further particular embodiment there is provided a pharmaceutical composition comprising a compound from the rapamycin class and a carrier medium comprising a hydrophilic phase, a lipophilic phase and a surfactant in the form of an emulsion preconcentrate.

The pharmaceutical composition is stable and results in surprisingly high and consistent absorption efficiency when administered orally. Therefore the macrolide may be administered in lower doses, which alleviates toxicity problems. For example, in animal trials in which the pharmaceutical compositions are administered orally, the pharmaceutical compositions resulted in high bioavailabilities. Hence the pharmaceutical compositions have very surprising properties which offer great advantages.

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