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(54) **USE OF FUMARIC ACID DERIVATIVES**

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(58) **Field of Search** ..... 514/547, 546, 514/549

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(57) **ABSTRACT**

Disclosed is a method of treating auto-immune diseases by the administration of certain fumaric acid monoalkyl esters as salts or free acids thereof either alone or in combination with a dialkyl fumarate.

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Article entitled "Elevation of Gluthathione Levels by Phase II Enzyme Inducers: Lack of Inhibition of Human Immunodeficiency Virus Type 1 Replication in Chronically Infected Monocytoid Cells", by Hans J. Prochaska, et al., taken from Mol. Pharmacol, No. XP002088942, pp 916–921.

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# USE OF FUMARIC ACID DERIVATIVES

This Application is a 371 of PCT/EP98/01894 filed Apr. 1, 1998 which claims priority from German Patent Application no. 197,21,099.5 filed May 20, 1997.

## BACKGROUND OF THE INVENTION

The present invention relates to the use of certain fumaric acid monoalkyl esters as salt either alone or in combination with a dialkyl fumarate for preparing pharmaceutical compositions for the treatment of poly-arthritis, multiple sclerosis and graft-versus-host reactions. The invention also relates to medicaments containing one or several fumaric acid monoalkyl esters in the form of free acids, optionally in combination with dialkyl fumarate, as active ingredient for the treatment of polyarthritis, multiple sclerosis, graft-versus-host reactions and other auto-immune diseases. These compositions do not contain fumaric acid per se. The use according to the invention also extends to the treatment of juvenile diabetes, Hashimoto's thyroiditis, Grave's disease, systemic Lupus erythematosus (SLE), Sjogren's syndrome, pernicious anaemia and chronically active (=lupoid) hepatitis.

Pharmaceutical compositions which end in the citric acid cycle when decomposed after administration or which belong to the citric acid cycle are increasingly gaining therapeutic value, especially when given in high dosages, because they help relieve or heal diseases with cryptogenetic causes.

Fumaric acid, for example, inhibits the growth of the Ehrlich ascites tumour in mice, reduces the toxic effects of mitomycin C and aflatoxin [K. Kuroda, M. Akao, Biochem. Pharmacol. 29, 2839–2844 (1980)/Gann. 72, 777–782 (1981)/Cancer Res. 36, 1900–1903, (1976)] and displays a anti-psoriatic and anti-microbial activity [C. N. Huhtsnen, J. Food Sci. 48, 1574 (1983)/M. N. Islam, U.S. Pat. No. 4,346,118 dated Aug. 24, 1982/C. A. 97, 161317b (1982)].

When administered parenterally, dermally and especially perorally, high dosages of fumaric acids or its derivatives known so far such as dihydroxy fumaric acid, fumaramide and fumaronitrile have such unacceptably severe side effects and high toxicity [P. Holland, R. G. White, Brit. Dermatol. 85, 259–263 (1971)/M. Hagedorn, K. W. Kalkoff, G. Kiefer, D. Baron. J. Hug, J. Petres, Arch. Derm. Res. 254, 67–73 (1975)] that, in most cases, such a therapy had to be abandoned in the past.

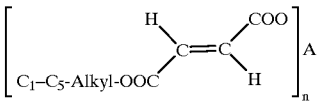
European Patent Application 18 87 49 already describes fumaric acid derivatives and pharmaceutical compositions containing the same for the treatment of psoriasis. Pharmaceutical compositions for the treatment of psoriasis containing a mixture of fumaric acid and other fumaric acid derivatives are known from DE-A-25 30 372. The content of free fumaric acid is obligatory for these medicaments.

DE-A-26 21 214 describes medicaments containing the fumaric acid monoethyl ester and its mineral salts as active ingredient for the treatment of psoriasis. The publication "Hautarzt (Dermatologist) (1987) 279–285" discusses the use of fumaric acid monoethyl ester salts (Ca, Zn, Mg) and of the fumaric acid dimethyl ester for the treatment of psoriasis. Pharmaceutical compositions containing a mixture of fumaric acid monoalkyl ester salts and a fumaric acid diester for the treatment of psoriasis, psoriatic arthritis, neurodermitis and enteritis regionalis Crohn are known from EP 0 312 697 B1.

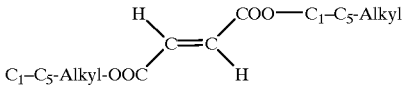
Surprisingly, we have now found in in vitro tests and in animal experiments that it is possible to treat polyarthritis,



multiple sclerosis and graft-versus-host reactions with pharmaceutical compositions using one or several compounds from the group consisting of calcium, magnesium, zinc and iron salts of fumaric acid monoalkyl esters of the general formula



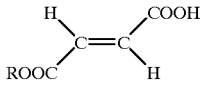

optionally in admixture with dialkyl fumarate of the formula



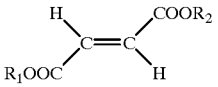

wherein A is a bivalent cation from the series consisting of Ca, Mg, Zn or Fe or a monovalent cation from the series consisting of potassium or sodium, respectively, and n denotes the numeral 1 or 2 depending on the type of cation,

optionally together with commonly used pharmaceutical excipients.

We also found an effect when polyarthritis, multiple sclerosis and graft-versus-host reactions were treated with pharmaceutical compositions containing one or several compounds of alkyl hydrogen fumaric acid of the general formula




optionally in admixture with dialkyl fumarate of the formula




wherein R, $R_1$, $R_2$ may be the same or different and each of R, $R_1$ and $R_2$ is an alkyl group having 1 to 5 carbon atoms ($C_1$–$C_5$ alkyl);

and, optionally, commonly used pharmaceutical excipients and carriers.

Preferred compositions according to the invention contain the calcium salt of the fumaric acid monomethyl ester, the calcium salt of the fumaric acid monomethyl ester in admixture with dimethyl fumarate or the relevant salts of the fumaric acid monoethyl ester.

Preparations containing the calcium salt of the fumaric acid monoalkyl ester or the fumaric acid alkyl ester in the form of the free acid in an amount of 10 to 300 mg are especially suitable for administration, the total weight of the active ingredients being 10 to 300 mg.

Other preferred oral forms of administration contain 10 to 290 parts by weight of the calcium salt of the fumaric acid monoalkyl ester and 290 to 10 parts by weight of dimethyl fumarate as well as 1 to 50 parts by weight of the zinc salt of the fumaric acid monoalkyl ester or 1 to 250 parts by weight of the calcium salt of the fumaric acid monoalkyl

ester, 250 to 10 parts by weight of dimethyl fumarate, 1 to 50 parts by weight of the magnesium salt of the fumaric acid monoalkyl ester and 1 to 50 parts by weight of the zinc salt of the fumaric acid monoalkyl ester or the monomethyl ester, respectively, the total weight of the active ingredients being 30 to 300 mg.

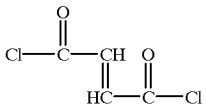
Preferred compositions according to the invention also contain the methyl hydrogen fumarate in an amount of 10 to 300 mg.

For commencement of a systemic therapy and, vice versa, termination of the treatment by gradual reduction of the dosage, low doses containing, for example, 30.0 mg of dimethyl fumarate, 20.0 mg of the calcium salt of monoethyl fumarate and 3.0 mg of the zinc salt of monoethyl fumarate or monomethyl fumarate, respectively, are advantageous.

For therapeutic dosing after an initial phase, for example, a dosage of 120.0 mg of dimethyl fumarate, 87.0 mg of the calcium salt of the monoethyl fumarate and 3.0 mg of the zinc salt of the mono ethyl fumarate or the monomethyl fumarate may be used.

The fumaric acid derivatives contained in the compositions according to the invention, are obtained by

a) condensation of a compound of the formula



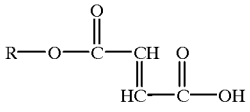
with 2 moles of alkyl alcohol (ROH) by a known method to obtain a diester, followed by controlled hydrolysation to obtain a monoester, or

b) condensation of 1 mole of the relevant alkyl alcohol (ROH) in the usual manner followed by hydrolysis of the monoacid chloride thus obtained to obtain an acid, or

c) direct condensation of the fumaric acid with 2 moles of alkyl alcohol (ROH) by a known method to obtain the relevant diester followed by controlled hydrolysation to obtain the monoester, or

d) direct condensation of maleic acid or maleic anhydride with 1–2 moles of the relevant alkyl alcohol (ROH) by a known method to obtain a mono- or diester followed by catalytic isomerisation to obtain the respective fumaric acid derivative.

The salts of the fumaric acid monoalkyl esters may also be obtained by reacting a compound of the general formula



wherein R is a $C_1$–$C_5$ alkyl group with equivalent mole amounts of Na, K, Fe, Ca, Mg or Zn hydroxide or oxide in toluene and removing the water generated during the reaction.

For particularly preferred applications, preparations containing the following active ingredients in the stated dosages and proportions are used:

as a pharmaceutical composition for oral administration in the form of tablets or capsules, characterised in that they contain the calcium salt of the fumaric acid monomethyl ester in an amount of 10 to 300 mg, the total weight of the active ingredients being 10 to 300 mg; or

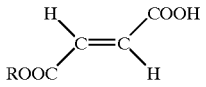
as a pharmaceutical composition for oral administration in the form of tablets or capsules, characterised in that they contain 10 to 290 parts by weight of the calcium salt of the fumaric acid monomethyl ester and 290 to 10 parts by weight of dimethyl fumarate, the total weight of the active ingredients being 20 to 300 mg; or

additionally, as a pharmaceutical composition for oral administration in the form of tablets or capsules characterised in that they contain 10 to 250 parts by weight of the calcium salt of the fumaric acid monomethyl ester, 1 to 50 parts by weight of dimethyl fumarate and 1 to 50 parts by weight of the zinc salt of the fumaric acid monomethyl ester, the total weight of the active ingredients being 20 to 300 mg, or as a pharmaceutical composition for oral administration in the form of tablets or capsules, characterised in that they contain 10 to 250 parts by weight of the calcium salt of the fumaric acid mono methyl ester, 250 to 10 parts by weight of dimethyl fumarate, 1 to 50 parts by weight of the magnesium salt of the fumaric acid monomethyl ester and 1 to 50 parts by weight of the zinc salt of the fumaric acid monomethyl ester, the total weight of the active ingredients being 30 to 300 mg, or, alternatively,

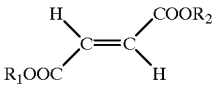
as a pharmaceutical composition for oral administration which may be provided with a coating resistant to gastric acid,

as a pharmaceutical preparation for the treatment of polyarthritis, multiple sclerosis or graft-versus-host reactions for peroral administration in the form of pellets, micro-tablets, capsules, granules and tablets, in the form of ointments, plasters or lotions for cutaneous and transdermal administration, in the form of aqueous micro-dispersions, oil-in-water emulsions or oily solutions for parenteral administration, or suppositories or micro-enemas for rectal administration, and

as a pharmaceutical composition for the treatment of polyarthritis, multiple sclerosis or graft-versus-host reactions, characterised in that it contains one or several compounds selected from the group consisting of free acids of fumaric acid monoalkyl esters of the general formula



optionally in combination with dialkyl fumarate of the formula



and R, $R_1$ and $R_2$ are as defined above.

and carriers, said composition not containing fumaric acid in its free form, or

as a pharmaceutical composition for oral administration in the form of tablets, capsules or micro-tablets, characterised in that they contain alkyl hydrogen fumarate in an amount of 10 to 300 mg, the total weight of the active ingredients being 10 to 300 mg, or

as a pharmaceutical composition for oral administration in the form of tablets, capsules or micro-tablets, characterised in that they contain 10 to 290 parts by weight of

alkyl hydrogen fumarate and 290 to 10 parts by weight of dialkyl fumarate, the total weight of the active ingredients being 20 to 300 mg, or as pharmaceutical compositions containing the free acid of the fumaric acid monomethyl ester (methyl hydrogen fumarate), or

as a pharmaceutical composition for oral administration in the form of tablets, capsules or micro-tablets, characterised in that they each contain the methyl hydrogen fumarate in an amount of 10 to 300 mg, the total weight of the active ingredients being 10 to 300 mg,

or as a pharmaceutical composition for oral administration in the form of tablets, capsules or micro-tablets containing 10 to 290 parts by weight of methyl hydrogen fumarate and 290 to 10 parts by weight of dimethyl fumarate, the total weight of the active ingredients being 20 to 300 mg, or,

as a pharmaceutical composition for the treatment of polyarthritis, multiple sclerosis or graft-versus-host reactions for peroral administration in the form of micro-pellets, micro-tablets, capsules, granulates and tablets, in the form of ointments, plasters, lotions or shower preparations for cutaneous and transdermal administration, in the form of aqueous micro-dispersions, oil-in-water emulsion or oily solutions for parenteral administration, or suppositories or micro-enemas for rectal administration.

According to a preferred form of administration, the size or mean diameter of the pellets or micro-tablets is in the range of 300 to 2,000 μm, especially in the range of 500 μm to 1,500 μm or 1,000 μm.

Another special benefit of the use according to the invention is to alternate a treatment regimen with cyclosporin sequentially with administration of the fumaric acid derivatives described above. In other words, an application of fumaric acid derivatives according to the above definitions for a period of one or several weeks could follow a cyclosporin therapy extending over one or several weeks. As a result, the well-known severe side effects of a long-term cyclosporin therapy can be reduced dramatically and unexpectedly.

In order to illustrate the use according to the invention, various examples for the preparation of preferred medicaments are given below:

## PRODUCTION EXAMPLES

### Example 1

Production of enteric-coated film tablets containing 100.0 mg of monoethyl fumarate-Ca salt, which corresponds to 71 mg of fumaric acid

Taking the necessary precautions (breathing mask, gloves, protective clothing, etc.), 10.000 kg of monoethyl fumarate-Ca salt are crushed, mixed intensely and homogenised by means of an 800 sieve. Then an excipient mixture of the following composition is prepared: 21.000 kg of starch derivative (STA-RX 1500®), 2.000 kg of microcrystalline cellulose (Avicel PH 101®), 0.600 kg of polyvinyl pyrrolidone (PVP, Kollidon® 25), 4.000 kg of Primogel®, 0.300 kg of colloidal silicic acid (Aerosil®).

The active ingredient is added to the entire powder mixture, mixed, homogenised by means of a 200 sieve and processed with a 2% aqueous solution of polyvinyl pyrrolidone (PVP, Kollidon® 25) in the usual manner into binder granules, and then mixed with the outer phase in a dry state. The latter consists of 2.000 kg of a so-called FST complex containing 80% of talcum, 10% of silicic acid and 10% of magnesium stearate.

Afterwards the mixture is pressed into convex tablets with a weight of 400 mg and a diameter of 10.0 mm by the usual method. Instead of these classic compaction methods, other methods such as direct compaction or solid dispersions according to the melting and spray drying method may also be used for preparing tablets.

Enteric Coating

A solution of 2.250 kg of hydroxy propyl methyl cellulose phthalate (HPMCP, Pharmacoat HP® 50) is dissolved in a solvent mixture consisting of 2.50 liters of demineralised water, 13.00 liters of acetone (Ph. Helv. VII) and 13.00 liters of ethanol (94% by weight) and then 0.240 kg of castor oil (Ph. Eur. II) added to the solution. The solution is poured or sprayed in portions onto the tablet cores in a coating pan in a conventional manner or applied by means of a fluidised bed apparatus of the appropriate structure.

After drying, the film coating is applied. Said coating consists of a solution of Eudragit E 12.5%® 4.800 kg, talcum (Ph. Eur. II) 0.340 kg, titanium(VI) oxide Cronus RN 56® 0.520 kg, coloured lacquer ZLT-2 blue (Siegle) 0.210 kg, and polyethylene glycol 6000 (Ph. Helv. VII) 0.120 kg in a solvent mixture of 8.200 kg of 2-propanol (Ph. Helv. VII), 0.060 kg of glycerine triacetate (Triacetin®) and 0.200 kg of demineralised water. After homogenous distribution in the coating pan or the fluidised bed, the mixture is dried and polished in the usual manner.

### Example 2

Preparation of enteric coated capsules containing 86.5 mg of monoethyl fumarate-Ca salt and 110.0 mg of dimethyl fumarate, which corresponds to a total of 150 mg of fumaric acid

Taking the necessary precautions (breathing mask, gloves, protective clothing, etc.), 8.650 kg of monoethyl fumarate-Ca salt and 11.000 kg of dimethyl fumarate are intensely mixed with a mixture consisting of 15.000 kg of starch, 6.000 kg of lactose (Ph. Helv. VII), 2.000 kg of micro-crystalline cellulose (Avicel®), 1.000 kg of polyvinyl pyrrolidone (Kollidon® 25) and 4.000 kg of Primogel® and homogenised by means of a 800 sieve.

Together with a 2% aqueous solution of polyvinyl pyrrolidone (Kollidon® 25) the entire powder mixture is processed in the usual manner into a binder granulate and mixed with the outer phase in the dried state. Said outer phase consists of 0.350 kg of colloidal silicic acid (Aerosil®), 0.500 kg of Mg stearate and 1.500 kg of talcum (Ph. Helv. VII). The homogeneous mixture is then filled in portions of 500.0 mg into appropriate capsules which are then provided with a enteric-coated coating consisting of hydroxy propyl methyl cellulose stearate and castor oil as softening agent by a known method. Instead of hard gelatine capsules, the mixture may also be filled into appropriate gastric acid-resistant capsules, which consist of a mixture of cellulose acetate phthalate (CAP) and hydroxy propyl ethyl cellulose phthalate (HPMCP).

### Example 3

Preparation of enteric-coated capsules containing 203.0 mg of monoethyl fumarate-Ca salt, 5.0 mg of monoethyl fumarate-Mg salt and 3.0 mg of monoethyl fumarate-Zn salt, which corresponds to a total of 150 mg of fumaric acid

Taking the necessary precautions (breathing mask, gloves, protective clothing, etc.), 20.300 kg of mono ethyl

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