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(54) **UTILIZATION OF DIALKYFUMARATES**

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- (58) **Field of Search** **514/547, 960**

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(57) **ABSTRACT**

The present invention relates to the use of certain dialkyl fumarates for the preparation of pharmaceutical preparations for use in transplantation medicine or for the therapy of autoimmune diseases and said compositions in the form of micro-tablets or pellets. For this purpose, the dialkyl fumarates may also be used in combination with conventional preparations used in transplantation medicine and immunosuppressive agents, especially cyclosporines.

16 Claims, No Drawings



UTILIZATION OF DIALKYL FUMARATES

REFERENCE TO RELATED APPLICATIONS

This application is a 371 continuation of PCT Application PCT/EP99/08215, filed Oct. 29, 1999, the text of which is not in English, which PCT Application claims priority on German Application No. 198 53 487.6 filed Nov. 19, 1998, the text of which is not in English.

DESCRIPTION

The present invention relates to the use of dialkyl fumarates for preparing pharmaceutical preparations for use in transplantation medicine or the therapy of autoimmune diseases and pharmaceutical preparations in the form of micro-tablets or micro-pellets containing dialkyl fumarates.

On the one hand, therefore, it relates especially to the use of dialkyl fumarates for preparing pharmaceutical preparations for the treatment, reduction or suppression of rejection reactions of the transplant by the recipient, i.e. host-versus-graft reactions, or rejection of the recipient by the transplant, i.e. graft-versus-host reactions. On the other hand, it relates to the use of dialkyl fumarates for preparing pharmaceutical preparations for treating autoimmune diseases such as polyarthritis, multiple sclerosis, juvenile-onset diabetes, Hashimoto's thyroiditis, Grave's disease, systemic Lupus erythematosus (SLE), Sjogren's syndrome, pernicious anaemia and chronic active (=lupoid) hepatitis.

Both graft rejection and autoimmune diseases are based on medically undesirable reactions or dysregulation of the immune system. Cytokins such as interleukins or tumour necrose factor α (TNF- α) are substantial mediators influencing the immune system. In general, both are treated by the administration of immunosuppressive agents such as cyclosporine.

In the overall result, autoimmune diseases may be defined as the failure of the tolerance of endogenous substances or antigens. As a rule, this tolerance can be maintained only if the antigens keep coming into contact with immunological cells. When this tolerance is lost, autoantibodies are formed, i.e. a humoral immunoresponse against endogenous tissue. The exact nature of the involvement of TNF- α is not known.

Transplantations are tissue or organ transplantations, i.e. the transfer of tissues such as cornea, skin, bones (bone chips), vessels or fasciae, of organs such as kidney, heart, liver, lung, pancreas or intestines, or of individual cells such as islet cells, α -cells and liver cells, the kidney having the greatest significance as a transplanted organ.

According to the degree of relationship between the donor and the recipient we differentiate between auto-transplantation (transfer to another part of the body of the same individual), iso-transplantation (transfer to another, genetically identical individual) and allogenic transplantation (transfer to another individual of the same species). Depending on the site of origin and transplantation, we further differentiate between homotopic transplantation (transfer to the same site) and heterotopic transplantation (transfer to a different site). The above-mentioned transplantations play an important role in modern medicine.

A major problem in transplantation medicine is graft rejection after transplantation of the tissue, organ or cell by immunological defence reactions of the recipient. Such a graft rejection is also called host-versus-graft reaction. The immunological defence reaction of the organism against the heteroprotein often results in rejection or dissolution of the grafts. In host-versus-graft reactions, different stages may be

distinguished. Depending on the degree of difference between the recipient and the donor, this reaction takes place at different speeds so that we speak of an acute, subacute or chronic reaction. The acute rejection process is accompanied by the irreversible loss of the transplant (necrotisation) as a result of arteriitis or arteriolitis within 48 hours and cannot be influenced by the administration of drugs. The sub-acute rejection reaction becomes manifest as a rejection crisis from day 12 to month 4 with reversible functional disorders as a result of a transplant vasculopathy. Finally, the loss of function of the transplant as a result of vascular changes such as obliterating arteriopathy, which proceeds over weeks or years and can practically not be influenced by drugs, is termed a chronic rejection reaction.

Vice-versa, rejection reactions of the transplant against the recipient, the so-called graft-versus-host reactions, may occur when immunocompetent tissues are transplanted, i.e. primarily in bone marrow transplantation. Again, the severity of the reaction is graded, and substantially similar complications result as in host-versus-graft-reactions, namely arteriopathies and necroses.

To avoid such rejection reactions, i.e. the host-versus-graft reaction and the graft-versus-host reaction, transplantation medicine essentially makes use of immunosuppression, i.e. a weakening of the normal immunoresponse. For this purpose, anti-lymphocyte sera are often used in combination with corticosteroids and so-called antimetabolites, e.g. purine analogues such as 6-mercaptopurine and thioguanine which affect the nucleic acid and protein synthesis and thus prevent cell division and proliferation. This leads to suppression or the production of antibodies and the cellular immune response. The immunosuppressive agents used for therapy are substances which suppress or weaken the immunoreaction in the body either specifically or non-specifically. Non-specific immunosuppressive agents are cytostatic agents such as, for example, alkylating agents or antimetabolites.

In addition, active ingredients are known which cause at least partial specific immunosuppression, such as corticosteroids, antisera, antibodies FK-506, tacrolimus, mycophenolatemofetil and primarily cyclosporines such as cyclosporine A. As a result of using modern immunosuppressive agents, the most important representatives of which are the cyclosporines, especially cyclosporine A, it was possible to improve the results of transplantation considerably over the last few years. At present, the survival rate after one year is about 60% for liver transplantations, about 80% for heart transplantations and over 90% for kidney transplantations.

Autoimmune diseases where the endogenous immune system attacks endogenous organs, tissues and cells are comparable to graft-versus-host reactions. These are also medically undesirable reactions of the immune system which may be treated with immunosuppressive agents, too.

The danger in using immunosuppressive agents lies in weakening the body's defence against infectious diseases and the increased risk of malignant diseases. Therefore, it is the object of the invention to provide a pharmaceutical preparation to be employed in transplantation medicine which may be used to treat, especially to suppress, weaken and/or alleviate host-versus-graft reactions and graft-versus-host reactions, but does not have the above disadvantage.

It is another object of the invention to provide a pharmaceutical preparation which may be employed for treating autoimmune diseases, particularly polyarthritis, multiple sclerosis, juvenile-onset diabetes, Hashimoto's thyroiditis,

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Grave's disease, systemic Lupus erythematoses (SLE), Sjogren's syndrome, pernicious anaemia and chronic active (=lupoid) hepatitis, without the disadvantages of immunosuppression.

The object of the invention is achieved by using certain dialkyl fumarates for preparing pharmaceutical preparations for use in transplantation medicine and for the therapy of autoimmune diseases and pharmaceutical preparations in the form of micro-tablets and micro-pellets containing these dialkyl fumarates. The individual subject matters of the invention are characterised in detail in the claims. The preparations according to the invention do not contain any free fumaric acids per se.

It is known that pharmaceutical preparations which, upon biological degradation after administration, enter into the citric acid cycle or are part thereof gain increasing therapeutic significance—especially when given in high dosages—since they can alleviate or heal diseases caused cryptogenetically.

Fumaric acid, for example, inhibits the growth of the Ehrlich ascites tumour in mice, reduces the toxic effects of mitomycin C and aflatoxin and displays anti-psoriatic and anti-microbial activity. When administered parenterally, transdermally and especially perorally, high dosages of fumaric acid or its derivatives known so far such as dihydroxyl fumaric acid, fumaramide and fumaronitrile have such unacceptably severe side effects and high toxicity that, in most cases, such a therapy had to be abandoned in the past.

Surprisingly, investigations carried out by the applicant have shown that methyl hydrogen fumarate, a metabolite of the dimethyl fumarate, initially increases the endotoxin-stimulated TNF- α secretion in human mono-nuclear cells of periphery blood (periphery blood mono-nuclear cells=PBMC cells) and in isolated monocytes. In addition, the applicant was able to show that fumaric acid has an effect on in vitro and in vivo haemagglutination which is comparable to that of cyclosporine.

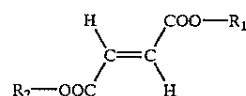
Surprisingly, it has now been found that dialkyl fumarates are advantageous for preparing pharmaceutical compositions for use in transplantation medicine and for the therapy of autoimmune diseases. This is because compositions containing such dialkyl fumarates surprisingly permit a positive modulation of the immune system in host-versus-graft reactions, graft-versus-host reactions and other autoimmune diseases.

European Patent Application 0 188 749 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. Pharmaceutical preparations containing a mixture of fumaric acid monoalkyl ester salts and a fumaric acid diester for the treatment of psoriasis, psoriatic arthritis, neurodermatitis and enteritis regionalis Crohn are known from EP 0 312 697 B1.

Specifically, the object of the invention is achieved by the use of one or more dialkyl fumarates of the formula

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wherein R_1 and R_2 , which may be the same or different, independently represent a linear, branched or cyclic, saturated or unsaturated C_{1-20} alkyl radical which may be optionally substituted with halogen (Cl, F, I, Br), hydroxy, C_{1-4} alkoxy, nitro or cyano for preparing a pharmaceutical preparation for use in transplantation medicine or for the therapy of autoimmune diseases.

The C_{1-20} alkyl radicals, preferably C_{1-8} alkyl radicals, most preferably C_{1-5} alkyl radicals are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, pentyl, cyclopentyl, 2-ethyl hexyl, hexyl, cyclohexyl, heptyl, cycloheptyl, octyl, vinyl, allyl, 2-hydroxy ethyl, 2 or 3-hydroxy propyl, 2-methoxy ethyl, methoxy methyl or 2- or 3-methoxy propyl. Preferably at least one of the radicals R_1 or R_2 is C_{1-5} alkyl, especially methyl or ethyl. More preferably, R_1 and R_2 are the same or different C_{1-5} alkyl radicals such as methyl, ethyl, n-propyl or t-butyl, methyl and ethyl being especially preferred. Most preferably, R_1 and R_2 are identical and are methyl or ethyl. Especially preferred are the dimethyl fumarate, methyl ethyl fumarate and diethyl fumarate.

The dialkyl fumarates to be used according to the invention are prepared by processes known in the art (see, for example, EP 0 312 697).

Preferably, the active ingredients are used for preparing oral preparations in the form of tablets, micro-tablets, pellets or granulates, optionally in capsules or sachets. Preparations in the form of micro-tablets or pellets, optionally filled in capsules or sachets are preferred and are also a subject matter of the invention. The oral preparations may be provided with an enteric coating. Capsules may be soft or hard gelatine capsules.

The dialkyl fumarates used according to the invention may be used alone or as a mixture of several compounds, optionally in combination with the customary carriers and excipients. The amounts to be used are selected in such a manner that the preparations obtained contain the active ingredient in an amount corresponding to 10 to 300 mg of fumaric acid.

Preferred preparations according to the invention contain a total amount of 10 to 300 mg of dimethyl fumarate and/or diethyl fumarate.

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

In addition to graft-versus-host reactions (see above), the following autoimmune diseases to be treated may be named: polyarthritis, multiple sclerosis, graft-versus-host reactions, juvenile-onset diabetes, Hashimoto's thyroiditis, Grave's disease, systemic Lupus erythematoses (SLE), Sjogren's syndrome, pernicious anaemia and chronic active (lupoid) hepatitis. Autoimmune diseases in a wider meaning also comprise psoriasis, psoriatic arthritis, neurodermatitis and enteritis regionalis Crohn.

In addition to the preparations for peroral administration in the form of micro-pellets, micro-tablets, capsules (such as soft and hard gelatine capsules), granulates and tablets cited above, suitable pharmaceutical preparations are preparations for cutaneous and transdermal administration in the form of ointments, plasters, lotions or shower preparations and for

parenteral administration in the form of aqueous micro-dispersions, oil-in-water emulsions or oily solutions for rectal administration of suppositories or micro-enemas. Pharmaceutical preparations in the form of micro-tablets or micro-pellets are preferred for the therapy of all autoimmune diseases mentioned above, including psoriasis, psoriatic arthritis, neurodermatitis and enteritis regionalis Crohn and are also a subject matter of the invention.

According to the invention, a therapy with dialkyl fumarates may also be carried out in combination with one or more preparations of the triple drug therapy customarily used in organ transplantations or with cyclosporine A alone. For this purpose, the preparations administered may contain a combination of the active ingredients in the known dosages or amounts, respectively. Likewise, the combination therapy may consist of parallel administration of separate preparation same or different routes. Optionally, the dosage of the active ingredient contained in addition to the dose of the fumaric acid derivative administered in accordance with the invention may be reduced advantageously.

Another embodiment of the use according to the invention is to alternate the drug therapy with immunosuppressive agents such as cyclosporine in sequence with an application of the above-mentioned dialkyl fumarate. This means that an application of fumaric acid derivatives as defined above over one or more weeks may follow a cyclosporine therapy of one or more weeks. This permits reduction of the Cyclosporine A dosage resulting in a considerable decrease of the rate of side effects in long-term therapy.

By administration of the dialkyl fumarates in the form of micro-tablets, which is preferred, gastrointestinal irritations and side effects, which are reduced already when conventional tablets are administered but is still observed, may be further reduced vis-à-vis fumaric acid derivatives and salts.

It is presumed that, upon administration of conventional tablets, the ingredients of the tablet are released in the intestine in a concentration which is too high, causing local irritation of the intestinal mucous membrane. This local irritation results in a short-term release of very high TNF- α concentrations which may be responsible for the gastrointestinal side effects. In case of application of enteric-coated micro-tablets in capsules, on the other hand, very low local concentrations of the active ingredients in the intestinal epithelial cells are achieved. The micro-tablets are incrementally released by the stomach and passed into the small intestine by peristaltic movements so that distribution of the active ingredients is improved.

This means that enteric-coated micro-tablets in the same dosage are distributed already in the stomach and passed to the intestine in portions, where the active ingredients are released in smaller dosages. This avoids local irritation of the intestinal epithelial cells and the release of TNF- α . It is assumed that this results in the improved tolerance of micro-tablets in the gastrointestinal tract vis-à-vis conventional tablets.

In addition, resorption is improved, because the dialkyl fumarates to be used according to the invention are not the active ingredient per se, but a so-called pro-drug, which must be converted into the active ingredient in the body.

In order to illustrate the use according to the invention, different examples for preparing preferred drugs are given below.

PRODUCTION EXAMPLES

In principle, the oral preparations according to the invention in the form of tablets or micro-tablets may be prepared by classical tableting processes. Instead of such classical

tableting processes, other methods for the preparation of tablets may be used, such as direct tableting and processes for preparing solid dispersions in according with the melt method and the spray drying method.

The tablets may be provided with an enteric coating. The enteric coating may be applied in a classical coating pan or sprayed on or applied in a fluidised bed apparatus. The tablet may also be provided with a film coat.

EXAMPLE 1

Preparation of Enteric-coated Micro-tablets in Capsules Containing 120.0 mg of Dimethyl Fumarate, which Corresponds to 96 mg of Fumaric Acid

Taking the necessary precautions (breathing mask, gloves, protective clothing, etc.), 12.000 kg of dimethyl fumarate are crushed, mixed and homogenised by means of a sieve 800. Then an excipient mixture with the following composition is prepared: 17.50 kg of starch derivative (STA-RX® 1500), 0.30 kg of micro-crystalline cellulose (Avicel® PH 101), 0.75 kg of PVP (Kollidon® 120), 4.00 kg of Primogel®, 0.25 kg of colloidal silicic acid (Aerosil®). The active ingredient is added to the entire powder mixture, mixed, homogenised by means of a sieve 200, processed in the usual manner with a 2% aqueous solution of polyvidon pyrrolidone (Kollidon® K25) to obtain a binder granulate and then mixed in the dry state with the outer phase. Said outer phase consists of 0.50 kg of Mg stearate and 1.50 kg of talcum.

Then the powder mixture is compressed in the usual manner to obtain convex tablets having a gross weight of 10.0 mg and a diameter of 2.0 mm.

One example to achieve resistance to gastric acid is to dissolve a solution of 2.250 kg of hydroxy propyl methyl cellulose phthalate (HPMCP, Pharmacoat® HP 50) in portions in a mixture of the following solvents: 13.00 l of acetone, 13.50 l of ethanol (94 wt.-%, denatured with 2% of ketone) and 1.50 l of demineralised water. As a plasticiser, castor oil (0.240 kg) is added to the finished solution and applied in portions onto the tablet cores in the customary manner.

After drying is completed, a suspension of the following composition is applied as a film coat in the same apparatus: 0.340 kg of talcum, 0.400 kg of titanium(VI) oxide Cronus RN 56, 0.324 kg of coloured lacquer L-Rotlack 86837, 4.800 kg of Eudragit E 12.5% and 0.120 kg of polyethylene glycol 6000, pH 11 XI in a solvent mixture of the following composition: 8.170 kg of 2-propanol, 0.200 kg of demineralised water and 0.600 kg of glycerine triacetate (Triacetin).

After that the enteric-coated micro-tablets are filled into hard gelatine capsules having a net weight of 400 mg and sealed.

EXAMPLE 2

Preparation of Enteric-coated Micro-tablets in Capsules Containing 120.0 mg of Dimethyl Fumarate, which Corresponds to 96 mg of Fumaric Acid

12.000 kg of dimethyl fumarate are crushed and homogenised as above. Then an excipient mixture composed as follows is prepared: 23.20 kg of microcrystalline cellulose (Avicel® PH 200), 3.00 kg of Croscarmellose sodium (AC-Di-SOL-SD-711), 2.50 kg of talcum, 0.10 kg of anhydrous silica (Aerosil® 200) and 1.00 kg of Mg stearate. The active ingredient is then added to the entire powder mixture and mixed homogeneously. By means of direct tableting, the powder mixture is then pressed into convex tablets having a gross weight of 10.0 mg and a diameter of 2.00 mm.

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After that, a solution of 0.94 Eudragit® L in isopropanol is prepared which also contains 0.07 kg of dibutyl phthalate. This solution is sprayed onto the tablet cores. After that, a dispersion of 17.32 kg of Eudragit® L D-55 and a mixture of 2.80 kg of micro-talcum, 2.00 kg of Macrogol 6000 and 0.07 kg of dimeticon in water is prepared and sprayed onto the cores.

Next, the enteric-coated micro-tablets are filled into hard gelatine capsules having a net weight of 650 mg and sealed.

EXAMPLE 3

Preparation of Micro-pellets in Capsules Containing 50.0 mg of Dimethyl Fumarate, which Corresponds to 40 mg of Fumaric Acid

5.000 kg of dimethyl fumarate are crushed and homogenised as above. In addition, 2 l of a 20% (m/v) polyvinyl pyrrolidone solution (Kollidon K-30) in ethanol are prepared. 7.250 kg of nonpareilles pellets in a coating pan are sprayed with part of the Kollidon K-30 solution until slightly humid. Then the active ingredient is added in portions until the pellets are dry. This procedure of humidification/drying is continued until all of the active ingredient mixture has been added. Then the pellets are moved around until completely dry.

After that, the pellets are filled into hard gelatine capsules (126.5 mg pellets/capsule).

EXAMPLE 4

Preparation of Enteric-coated Capsules Containing 110.0 mg of Dimethyl Fumarate, which Corresponds to 88 mg of Fumaric Acid

11.000 kg of dimethyl fumarate are intensely mixed in a mixture consisting of 14.00 kg of starch, 5.65 kg of lactose, 2.00 kg of microcrystalline cellulose (Avicel®), 1.00 kg of polyvinyl pyrrolidone (Kollidon® 25) and 2.443 kg of Primogel® and, taking the necessary precautions (breathing mask, gloves, protective clothing), homogenised by means of a sieve 800.

Using a 2% aqueous solution of polyvinyl pyrrolidone (Kollidon® K25), the entire powder mixture is processed into a binder granulate in the customary manner and mixed with the outer phase when dry. 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. The homogenous mixture is filled into suitable capsules in portions of 400 mg which are then provided with an enteric coating consisting of hydroxy propyl methyl cellulose stearate and castor oil as plasticiser in the customary manner. Instead of using hard gelatine capsules, the product may also be filled into suitable enteric-coated capsules consisting of a mixture of cellulose acetate phthalate (CAP) and hydroxy propyl methyl cellulose phthalate (HPMCP).

In comparison with substances of the prior art such as cyclosporine, which may cause massive kidney disorders or diseases of the lymphoproliferative system, a therapy with fumaric acid derivatives according to the invention for the indications listed above rarely results in serious side effects.

Among other things, the immunosuppressive effect of cyclosporine is caused by the inhibition of Th-1 cell formation. As in vitro experiments of the applicant have shown, fumarates cause a shift of the cytokine pattern of the Th1 type to the cytokine pattern of the Th2 type.

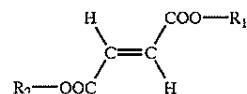
Especially in view of the long-term therapy and prevention which is always necessary in graft-versus-host reactions and host-versus-graft reactions or other immune diseases such as multiple sclerosis, the unexpected effect of the use according to the invention is of the greatest interest. In a combination therapy of cyclosporine with the fumaric acid

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derivatives, the toxic side effects of the former compounds may be unexpectedly reduces to a substantial degree. In addition, the use according to the invention is also significant in the substitution of the corticosteroid therapy of autoimmune diseases which is known to be accompanied by severe side effects.

What is claimed is:

1. Pharmaceutical preparation in the form of microtablets or micropellets comprising one or more dialkyl fumarates of the formula



wherein R₁ and R₂, which may be the same or different, independently represent a linear, branched or cyclic, saturated or unsaturated C₁₋₂₀ alkyl radical which may be optionally substituted with halogen (Cl, F, I, Br), hydroxy, C₁₋₄ alkoxy, nitro or cyano, and optionally suitable carriers and excipients for use in transplantation medicine or for the therapy of autoimmune diseases such as polyarthritis, multiple sclerosis, juvenile-onset diabetes, Hashimoto's thyroiditis, Grave's disease, systemic Lupus erythematoses (SLE), Sjogren's syndrome, pernicious anaemia, chronic active (lupoid) hepatitis, psoriasis, psoriatic arthritis, neurodermatitis and enteritis regionalis Crohn.

2. A preparation according to claim 1 comprising dimethyl fumarate, diethyl fumarate or methylethyl fumarate.

3. A preparation according to claim 1 or 2 comprising an amount of the active ingredient corresponding to 10 to 300 mg of fumaric acid.

4. A preparation according to claim 1 wherein the one or more dialkylfumarates is diethylfumarate.

5. A preparation according to claim 1 wherein the one or more dialkylfumarates is dimethylfumarate.

6. A preparation according to claims 4 or 5 wherein the amount of dialkylfumarate in said preparation corresponds to 10 to 300 mg of fumaric acid.

7. A preparation according to any of claims 1, 2, 4 or 5 wherein the preparation is formulated into an oral preparation in which the microtablets or micropellets are in capsules or sachets.

8. A preparation according to any of claims 1, 2, 4 or 5 wherein the preparation is formulated into an oral preparation in which the microtablets or micropellets are in soft or hard gelatine capsules.

9. A preparation according to any of claims 1, 2, 4 or 5 wherein the microtablets or micropellets are provided with an enteric coating.

10. A preparation according to claim 1 wherein the preparation is formulated into an oral preparation in which the microtablets or micropellets are in capsules or sachets and wherein the amount of dialkylfumarate in said preparation corresponds to 10 to 300 mg of fumaric acid.

11. A preparation according to claim 1 wherein the preparation is formulated into an oral preparation in which the microtablets or micropellets are in soft or hard gelatine capsules and wherein the amount of dialkylfumarate in said preparation corresponds to 10 to 300 mg of fumaric acid.

12. A preparation according to claim 1 wherein the microtablets or micropellets are provided with an enteric coating and wherein the amount of dialkylfumarate in said preparation corresponds to 10 to 300 mg of fumaric acid.

13. A pharmaceutical composition in which the active ingredient consists of one or more dialkyl fumarates, said composition being in the form of microtablets or micropellets wherein the size or mean diameter, respectively of said

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