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REPUBLICATION

(54) **CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS COMPRISING A FUMARIC ACID ESTER**

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(57) **ABSTRACT**

The present invention relates to controlled release pharmaceutical compositions comprising fumaric acid ester(s) as active substance(s). The compositions are suitable for use in the treatment of e.g. psoriasis or other hyperproliferative, inflammatory or autoimmune disorders and are designated to release the fumaric acid ester in a controlled manner so that local high concentrations of the active substance within the gastrointestinal tract upon oral administration can be avoided and, thereby, enabling a reduction in gastro-intestinal related side-effects.

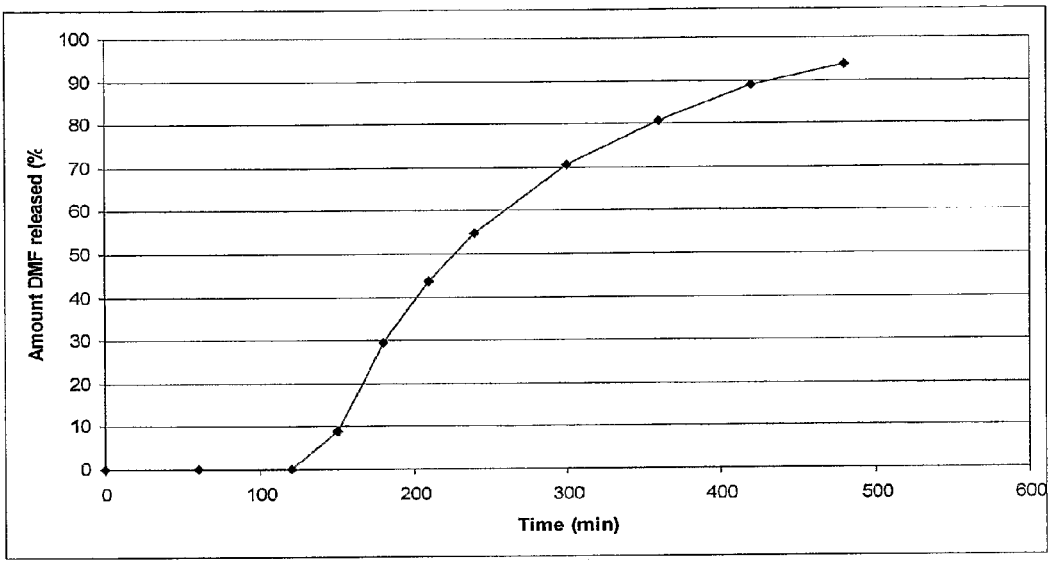
Amount DMF released (%
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
Time (min)

Fig. 1

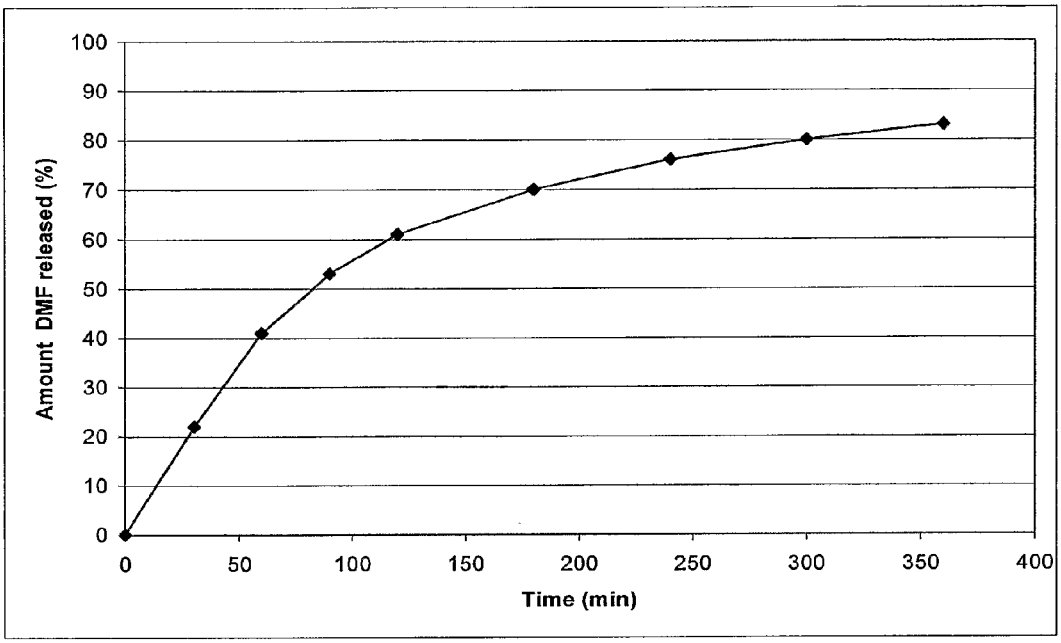
Amount DMF released (%)
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
Time (min)

Fig. 2

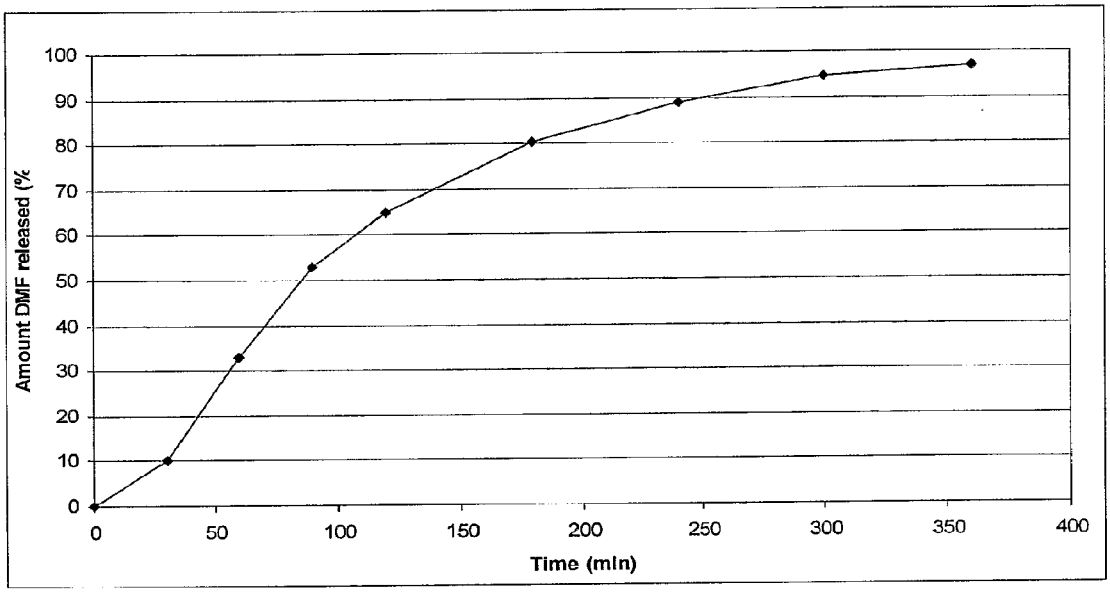
Amount DMF released (%
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
Time (min)

Fig. 3

CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS COMPRISING A FUMARIC ACID ESTER

FIELD OF THE INVENTION

[0001] The present invention relates to controlled release pharmaceutical compositions comprising a fumaric acid ester as an active substance. The compositions are suitable for use in the treatment of e.g. psoriasis or other hyperproliferative, inflammatory or autoimmune disorders and are designed to release the fumaric acid ester in a controlled manner so that local high concentrations of the active substance within the gastrointestinal tract upon oral administration can be avoided and, thereby, enabling a reduction in gastro-intestinal related side-effects.

BACKGROUND OF THE INVENTION

[0002] Fumaric acid esters, i.e. dimethylfumarate in combination with ethylhydrogenfumarat have been used in the treatment of psoriasis for many years. The combination is marketed under the tradename Fumaderm®. It is in the form of tablets intended for oral use and it is available in two different dosage strengths (Fumaderm® initial and Fumaderm®):

	Fumaderm ® Initial	Fumaderm ®
Dimethylfumarate	30 mg	120 mg
Ethylhydrogenfumarate, calcium salt	67 mg	87 mg
Ethylhydrogenfumarate, Magnesium salt	5 mg	5 mg
Etylhydrogenfumarate, Zinc salt	3 mg	3 mg

[0003] The two strengths are intended to be applied in an individually based dose regimen starting with Fumaderm® initial in an escalating dose, and then after e.g. three weeks of treatment switching to Fumaderm®. Both Fumaderm® initial and Fumaderm® are enteric coated tablets.

[0004] Another marketed composition is Fumaraat 120® containing 120 mg of dimethylfumarate and 95 mg of calcium monoethylfumarate (TioFarma, Oud-Beijerland, Netherlands). In a recent publication (Litjens et al. Br. J. Clin. Pharmacol. 2004, vol. 58:4, pp. 429-432), the pharmacokinetic profile of Fumaraat 120® is described in healthy subjects. The results show that a single oral dose of Fumaraat 120® is followed by a rise in serum monomethylfumarate concentration and only negligible concentrations of dimethylfumarate and fumaric acid is observed. The results indicate that dimethylfumarate is rapidly hydrolyzed to monomethylfumarate in an alkaline environment, but according to the authors not in an acid environment. As the composition is enteric coated, it is contemplated that the uptake of fumarate takes place mainly in the small intestine, where di methylfumarate before uptake is hydrolysed to the monoester due to an alkaline environment, or it may rapidly be converted due to esterases in the circulation. Furthermore, the study shows that t_{max} and C_{max} are subject to food effect, i.e. t_{max} is prolonged (mean for fasted conditions is 182 min, whereas for fed conditions mean is 361 min) [lag time is 90 min for fasted and 300 min for fed] and C_{max} is decreased (fasted: 0.84 mg/l, fed: 0.48 mg/l) by concomitant food-intake. Another study (Reddingius W.G. Bioanalysis and Pharmacokinetics of Fumarates in Humans. Dissertation ETH Zurich No. 12199 (1997)) in healthy subjects with two tablets of Fumaderm® P forte revealed C_{max} values (determined as monoethyl- or monomethylfumarate) in a range from 1.0 to 2.4 μg/ml and a t_{max} in a range of from 4.8 to 6.0 hours.

[0005] U.S. Pat. No. 6,277,882 and U.S. Pat. No. 6,355,676 disclose respectively the u se of alkyl hydrogen fumarates and the use of certain fumaric acid mono alkyl ester salts for preparing micro tablets for treating psoriasis, psoriatic arthritis, neurodermatitis and enteritis regionalis Crohn. U.S. Pat. No. 6,509,376 discloses the use of certain dialkyl fumarates for the preparation of pharmaceutical preparations for use in transplantation medicine or the therapy of autoimmune diseases in the form of micro tablets or pellets. U.S. Pat. No. 4,959,389 disclose compositions containing different salts of fumaric acid monoalkyl ester alone or in combination with dialkyl fumarate. GB 1,153,927 relates to medical compositions comprising dimethylmaleic anhydride and/or dimethylmaleic acid and/or a dimethylfumaric acid compounds. The Case report "Treatment of disseminated granuloma annulare with fumaric acid esters" from BMC Dermatology, vol. 2, no. 5, 2002, relates to treatment with fumaric acid esters.

[0006] However, therapy with fumarates like e.g. Fumaderm® frequently gives rise to gastro-intestinal side effects such as e.g. fullness, diarrhea, upper abdominal cramps, flatulence and nausea.

[0007] Accordingly, there is a need to develop compositions comprising one or more therapeutically or prophylactically active fumaric acid esters that provide an improved treatment with a reduction in gastro-intestinal related side effects upon oral administration.

[0008] Furthermore, the present commercially available products contain a combination of two different esters of which one of the esters (namely the ethylhydrogenfumarate which is the monoethylester of fumaric acid) is present in three different salt forms (i.e. the calcium, magnesium and zinc salt). Although each individual form may have its own therapeutic profile it would be advantageous to have a much simpler product, if possible, in order to obtain a suitable therapeutic effect.

[0009] The present inventors contemplate that an improved treatment regimen may be obtained by administration of a pharmaceutical composition that is designed to deliver the active substance in a controlled manner, i.e. in a manner that is prolonged, slow and/or delayed compared with the commercially available product. Furthermore, it is contem plated that instead of using a combination of different fumaric acid esters, a suitable therapeutic response may be achieved by use of a single fumaric acid ester alone such as dimethylfumaric acid.

SHORT DESCRIPTION OF THE FIGURES

[0010] FIG. **1** shows an example of an in vitro dissolution profile of a capsule prepared as described in example 5.

[0011] FIG. **2** shows an example of an in vitro dissolution profile of a sample of a tablet (before the enteric coating is applied) prepared as described in example 16.

[0012] FIG. **3** shows an example of an in vitro dissolution profile of a sample of a tablet (before the enteric coating is applied) prepared as described in example 17.

DISCLOSURE OF THE INVENTION

[0013] Accordingly, the present invention relates to a pharmaceutical composition comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, which—upon oral administration and in comparison to that obtained after oral administration of Fumaderm® tablets in an equivalent dosage—gives a reduction in GI (gastro-intestinal) related side-effects.

[0014] As mentioned above, the present inventors contemplate that a suitable way of reducing the gastro-intestinal related side-effects is by administration of the active substance in the form of a controlled release composition.

[0015] Accordingly, the present invention relates in a further aspect to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test employing 0.1 N hydrochloric acid as dissolution medium during the first 2 hours of the test and then 0.05 M phosphate buffer pH 6.5 as dissolution medium—is as follows:

[0016] within the first 3 hours after start of the test at the most about 70% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0017] within the first 4 hours after start of the test at the most about 92% w/w of the total amount of the fumaric acid ester is released, and/or

[0018] within the first 5 hours after start of the test at the most about 94% w/w of the total amount of the fumaric acid ester is released, and/or

[0019] within the first 6 hours after start of the test at the most about 95% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0020] within the first 7 hours after start of the test at the most about 98% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0021] within the first 9 hours after start of the test at the most about 99% w/w of the total amount of the fumaric acid ester contained in the composition is released and/or

[0022] within the first 12 hours after start of the test at the most about 99% w/w of the total amount of the fumaric acid ester contained in the composition is released.

[0023] In the present context, a controlled release composition is a composition that is designed to release the fumaric acid ester in a prolonged, slow and/or delayed manner compared to the release of the commercially available product Fumaderm®, when tested under comparable conditions (e.g. for in vivo studies: dose equivalents, with or without standardized meal etc., or for in vitro studies: dose equivalents, dissolution test apparatus and working conditions including e.g. composition, volume and temperature of dissolution medium employed, rotation speed etc.).

[0024] The release in vivo may be tested by measuring the plasma concentration at predetermined time periods and thereby obtaining a plasma concentration versus time profile for the fumaric acid ester in question or, if relevant, a metabolite thereof. (E.g. in the case of dimethylfumarate, the active substance is envisaged to be methylhydrogenfumarate, i.e. the monomethyl ester of fumaric acid). Furthermore, it is contemplated that metabolism already takes place within the gastro-intestinal tract or during passage of the gastro-intestinal mucosa, or upon first passage through the hepatic circulation. Accordingly, when dimethylfumarate is administered, the relevant component to search for in the plasma may be the monomethyl ester and not the dimethylester of fumaric acid.

[0025] Other tests may also be used to determine or to give a measure of the release of the active substance in vivo. Thus, animals (e.g. mice, rats, dogs etc.) may be used as a model. The animals receive the compositions under investigation and after specified periods of time, the animals are sacrificed and the content of the active ingredient (or metabolite thereof, if relevant) is determined in plasma or specific organs or extracted from the intestinal contents.

[0026] Another test involves the use of a specific segment of an animal intestine. The segment is placed in a suitable dissolution apparatus containing two compartments (a donor and a receiver) separated by the segment, and the composition under investigation is placed in a suitable medium in one compartment (the donor compartment). The composition will release the active substance that subsequently is transported across the intestinal segment. Accordingly, at suitable time intervals, the concentration of the active substance (or, if relevant, the metabolite) is measured in the receiver compartment.

[0027] A person skilled in the art will be able to adapt the above-mentioned method to the specific composition.

[0028] With respect to in vitro methods, well-established methods are available, especially methods described by official monographs like e.g. United States Pharmacopeia (USP) or the European Pharmacopoeia. A person skilled in the art will know which method to choose and how to select the specific conditions to carry out the in vitro test. For instance, the USP prescribes in vitro tests be carried out at 37+/−1.0 such as 37+/−0.5 degrees Celsius/Centigrade. A suitable dissolution test is, for example as described in example 29, for capsules, wherein the dissolution profile is determined as described in the United States Pharmacopoeia at 37° C. using a rotating basket at 100 rpm employing 0.1 N hydrochloric acid as dissolution medium during the first 2 hours of the test and then followed by 0.05 M phosphate buffer pH 6.5 as dissolution medium for the remaining test period, and, for example as described in example 30, for tablets wherein the dissolution profile is determined as described in the United States Pharmacopoeia at 37° C. using a paddle dissolution apparatus at 100 rpm employing 0.1 N hydrochloric acid as dissolution medium during the first 2 hours of the test and then followed by 0.05 M phosphate buffer pH 6.5 as dissolution medium for the remaining test period.

[0029] As mentioned above, the in vivo release of the active substance is prolonged, slow and/or delayed compared with the commercially available Fumaderm® composition. In the present context, the term "prolonged" is intended to indicate that the active substance is released during a longer time period than Fumaderm® such as at least during a time period that is at least 1.2 times, such as, e.g., at least 1.5 times, at least 2 times, at least 3 times, at least 4 times or at least 5 times greater than that of Fumaderm®.

Thus, if e.g. 100% of dimethylfumarate is released from Fumaderm® tablets 3 hours after the start of a suitable test, then 100% of dimethylfumarate in a composition according to the invention is released at least 3.6 hours after the start of a suitable test.

[0030] In the present context the term "delayed" is intended to indicate that the release of the active substance starts at a later point in time compared with that of Fumaderm® (such as at 30 min or more later such as, e.g., 45 min or more later, 1 hour or more later or 1.5 hours or more later, alternatively, that the initial release during the first 2 hours is much less compared with that of Fumaderm® (i.e. less than 80% w/w such as, e.g., less than 70% w/w, less than 60% w/w or less than 50% of that of Fumaderm®).

[0031] As used in the present invention, a gastrointestinal (GI) side effect may include, but is not limited to diarrhea, stomach ache, stomach pain, abdominal pain, abdominal cramps, nausea, flatulence, tenesmus, meteorism, an increased frequency of stools, a feeling of fullness and upper abdominal cramps.

[0032] In the present context, a reduction of GI related side effects is intended to denote a decrease in severity and/or incidence among a given treated patient population, compared to the GI side effects observed after administration of the composition according to the invention compared with that of Fumaderm®. A reduction in GI related side effects according to this definition could thus be construed as a substantial reduction in incidence of any of the GI side effect listed above, such as at least a 10% reduction in incidence or more preferably at least 20% reduction in incidence or even more preferable a more than 30% reduction in incidence. A reduction in GI related side effect can also be expressed as a substantial reduction in severity in any of the GI side effects listed above, such as a reduction in severity and/or frequency of diarrhea, stomach ache, stomach pain, abdominal pain, abdominal cramps, nausea, flatulence, tenesmus, meteorism, increased frequency of stools, a feeling of fullness or upper abdominal cramps. The reduction of GI related side effects, as described above, can be monitored in a clinical trial setting, either comparing the administration of the composition according to the invention head on with Fumaderm® or with placebo. In case of a placebo controlled trial, the incidence of GI related side effects in the patients receiving the composition according to the invention compared to the placebo group, can be compared to historical trials comparing Fumaderm® to placebo (see e.g. Altmeyer et al, J. Am. Acad. Dermatol. 1994; full reference: Altmeyer P J et al, Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. J. Am. Acad. Dermatol. 1994; 30:977-81). Typically, patients suffering from psoriasis are included in such a study, and typically more than 10% of the body surface area will be affected by psoriasis (severe psoriasis). However, patients in whom between 2 and 10 percent of the body surface area is affected can also be included (moderate psoriasis). Patients can also be selected based on the psoriasis area severity index (PASI). Typically, patients within a certain range of PASI are included, such as between 10 and 40, or such as between 12 and 30, or such as between 15 and 25. Patients with any type of psoriasis may be included (chronic plaque type, exanthematic guttate type, pustular type, psoriatic erythroderma or palmoplantar type), but in some cases only patients with the chronic plaque type are included. About 15 to 20 patients in each treatment group (composition according to the invention and Fumaderm® or placebo) are sufficient in most cases, but more preferably about 30 to 50 patients are included in each arm of the study. Total study duration can be as short as one day to one week, but more preferably the study will run for 8 weeks to 12 weeks or up to 16 weeks. The side effects can e.g. be assessed as the total number of times a certain side effect was reported in each group (irrespective of how many patients have experienced the side effect), or the side effects can be assessed as the number of patients that have experienced a certain side effect a certain number of times, such as at least once or at least twice or at least three times during the duration of the study. Furthermore, the severity of a side effect can be monitored, or a certain severity of a side effect can be required for it to qualify as a side effect in the study. A convenient way of assessing the severity of a side effect is via a visual analogue (VAS) scale.

Active Substance

[0033] The active substance in a composition of the invention is any fumaric acid ester. In one embodiment of the invention the fumaric acid ester is preferably selected from the group consisting of dimethylfumarate, diethylfumarate, dipropylfumarate, dibutylfumarate, dipentylfumarate, methyl-ethylfumarate, methyl-propylfumarate, methyl-butylfumarate, methyl-pentylfumarate, monomethylfumarate, monoethylfumarate, monopropylfumarate, rnonobutylfumarate and monopentylfumarate, including pharmaceutically acceptable salts thereof.

[0034] In a specific embodiment of the invention, the fumaric acid ester is a mono-(C_1-C_5)alkylester of fumaric acid that is present in the form of a pharmaceutically acceptable salt. Suitable salts are e.g. metal salts such as a salt selected from alkali metal salts and alkaline earth metal salts including sodium, potassium, calcium, magnesium or zinc salt.

[0035] The term (C_1-C_5)alkyl refers to a branched or un-branched alkyl group having from one to five carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl and pentyl.

[0036] In another embodiment, the composition according to the invention comprises dimethylfumarate as the active substance.

[0037] In a further embodiment, the composition according to the invention comprises monomethylfumarate as the active substance optionally in the form of a pharmaceutically acceptable salt like e.g. its sodium, potassium, calcium, magnesium and/or zinc salt.

[0038] In another embodiment, the composition according to the invention consists essentially of dimethylfumarate as the active substance.

[0039] In another embodiment, the composition according to the invention consists of dimethylfumarate as the active substance.

[0040] In a further embodiment, the composition according to the invention consists essentially of monomethylfumarate as the active substance optionally in the form of a pharmaceutically acceptable salt like e.g. its sodium, potassium, calcium, magnesium and/or zinc salt.

[0041] In a further embodiment, the composition according to the invention consists of monomethylfumarate as the

active substance optionally in the form of a pharmaceutically acceptable salt like e.g. its sodium, potassium, calcium, magnesium and/or zinc salt.

[0042] In a further embodiment, the composition according to the invention comprises dimethylfumarate and monomethylfumarate (optionally in the form of a pharmaceutically acceptable salt like e.g. its sodium, potassium, calcium, magnesium and/or zinc salt) as the active substances, in a weight ratio between about 1:10 and about 10:1.

[0043] In a further embodiment, the composition according to the invention consists essentially of dimethylfumarate and monomethylfumarate (optionally in the form of a pharmaceutically acceptable salt like e.g. its sodium, potassium, calcium, magnesium and/or zinc salt) as the active substances, in a weight ratio between about 1:10 and about 10:1.

[0044] In a further embodiment, the composition according to the invention consists of dimethylfumarate and monomethylfumarate (optionally in the form of a pharmaceutically acceptable salt like e.g. its sodium, potassium, calcium, magnesium and/or zinc salt) as the active substances, in a weight ratio between about 1:10 and about 10:1.

Cosmetic and/or Pharmaceutical Compositions

[0045] The problem the invention solves is related to the appearance of gastro-intestinal side-effects upon oral administration of fumaric acid esters. By prolonging and/or delaying the release of the active substance from the composition it is envisaged that the local concentration of the active substance at specific sites of the gastro-intestinal tract is reduced (compared with that of Fumaderm®) which in turn leads to a reduction in gastro-intestinal side-effects. Accordingly, compositions that enable a prolonged and/or a slow release of a fumaric acid ester as defined above are within the scope of the present invention.

[0046] Such compositions are well-known to the skilled artisan and include e.g. diffusion-controlled drug delivery systems, osmotic pressure controlled drug delivery systems, erodible drug delivery systems etc. Moreover, there are pharmaceutical companies that based on a specific technology (such as mentioned above) can provide a specific composition with specific release characteristics of the active substance. Accordingly, a person skilled in the art will know how to obtain a suitable product once he has realized a specific need in respect of a particular drug substance. By way of example, Eurand is one of such companies that offer technical solutions in order to obtain a controlled release pharmaceutical composition containing a specific active substance and having specific requirements with respect to the release of the active substance from the composition (see e.g. http://www.eurand.com). Another company is MacroMed, Inc. that has developed a technology involving a so-called SQZgel™ (http://macromed.com, SQZgel™'s mechanism of action is a pH-sensitive polymer mixture combined with an outer coating. In the acidic environment of the stomach the polymer imbibes with water and swells, entrapping the drug. Upon entering the higher pH of the intestines, the polymer slowly shrinks, or "squeezes" at a "dialed-in" rate releasing the active composition in a sustained manner), or Egalet a/s that has a specific extrusion based technology (httd://www.egalet.com, Key elements of the Egalet® technology are a biodegradable coat and a matrix, comprising the active drug, which is surface erodible, hydrophobic and composed of PEG-stearate. One of the Egalet® technologies is the 2K Egalet® constant release system, which is a 2-component production model consisting of coat and matrix. The drug is evenly distributed throughout the Egalet® matrix for constant release over time. Also of interest in the present context are technologies like e.g. the Eurand technologies Diffucaps (Drug release profiles are created by layering active drug onto a neutral core such as sugar spheres, crystals or granules followed by a rate-controlling, functional membrane. Diffucaps/Surecaps beads are small in size, approximately 1 mm or less in diameter. By incorporating beads of differing drug release profiles into hard gelatin capsules, combination release profiles can be achieved), Diffutabs (The Diffutab technology incorporates a blend of hydrophilic polymers that control drug release through diffusion and erosion of a matrix tablet), Minitabs (Eurand Minitabs are tiny (2 mm×2 mm) tablets containing gel-forming excipients that control drug release rate. Additional membranes may be added to further control release rate), Orbexa (This technology produces beads that are of controlled size and density with a defined-based granulation extrusion and spheronization techniques. The resultant beads can be coated with release rate controlling membranes for additional release rate control and may be filled into capsules or provided in sachet form) and SDS (Eurand's SDS technology uses functional polymers or a combination of functional polymers and specific additives, such as composite polymeric materials, to deliver a drug to a site of optimal absorption along the intestinal tract. In order to achieve this, Eurand first produces multiparticulate dosage forms such as Diffucaps or Eurand Minitabs, which incorporate the active drug. These dosage forms are then coated with pH dependent/independent polymeric membranes that will deliver the drug to the desired site. These are then filled into hard gelatin capsules).

[0047] Another interesting technology for use in formulating compositions according to the present invention is the so-called MeltDose® technology as described in WO 03/004001 (see http://www.lifecyclepharma.com. MeltDose® involves formulating solubilized, individual molecules into tablets. By formulating individual molecules, the primary limitation of oral absorption of drugs with low water-solubility is removed, and a superior bioavailability can be attained). By employing this technology it is possible to obtain a particulate material that is suitable for processing into various pharmaceutical dosage forms e.g. in the form of pellets or tablets. Furthermore, the technology is suitable for use as it is possible to obtain a suitable release profile of the active substance, e.g. such as those release profiles described herein. In one embodiment, pellets suitable for use may have a mean particle size larger than 2000 μm.

[0048] In another embodiment, pellets suitable for use may have a mean particle size of from about 0.01 μm to about 250 μm.

[0049] Another specific suitable formulation principle for use in the present context is formulation in a lipophilic environment such as, e.g., soft gelatin capsules. A suitable example of this formulation principle is Vegicaps Soft from Scherer (a soft capsule technology based on carrageenan and starch, which despite being 100% plant-derived, still offers all the key attributes of traditional soft gelatin capsules. These include a soft and flexible dosage form that provides ease of swallowing.) (For further information see http://www.rpscherer.de/page.php?pageID=94).

[0050] A further specific example of a suitable formulation comprises the formulation of the active substance together with Vitamin E concentrate in soft or hard gelatin capsules.

This formulation, in a modified form, is the basis of the commercial cyclosporine product, Neoral®, containing, among other things, corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-a-tocopherol USP (part of the vitamin E family), gelatin NF, glycerol, iron oxide black, propylene glycol USP, titanium dioxide USP, carmine, and alcohol in addition to cyclosporine.

[0051] Another specific example of a suitable formulation comprises the formulation of active substance together with ethanol, tocopherolethylene glycol 1000 succinate (TPGS), corn oil and wax in soft or hard gelatin capsules. This product can be a semi-solid or solid dosage form. The release rate of this formulation is dependent on degradation due to lipases in the intestine.

[0052] A further example of a suitable formulation comprises the formulation of the active substance together with ethanol, tocopherolethylene glycol 1000 succinate (TPGS), corn oil and polyglycolized glycerides (e.g. Gelucire) in soft or hard gelatin capsules. This product can be a semi-solid or solid dosage form. The release rate of this formulation is dependent on degradation due to lipases in the intestine.

[0053] A further example of a suitable formulation is an oral pulsed dose drug delivery system. This dosage form can be perceived as a modified form of the Schering Repetab tablets. A portion of the composition of the present invention is put in the core of a tablet.

[0054] The core can for example be made by conventional wet granulation or continuous granulation such as extrusion followed by compaction of the granulate into tablets. The core is then coated using an appropriate technology, preferably by airsuspension using an enteric coating polymer such as Eudragits.

[0055] The first releasing dose is compression coated on the core or air-suspension coated either with the enteric coat or on top of the enteric coat. In a embodiment of the invention, the first releasing dose is air-suspension coated with the enteric coat. In a further embodiment of the invention, the first releasing dose is compression coated on the core, in order to avoid release of the composition according to the invention prior to the degradation of the enteric coat, such degradation typically occurring at pH values higher than those found in the gastric ventricle; i.e. the degradation of the enteric coat typically occurs after passage of the gastric ventricle.

[0056] A further example of a suitable formulation is an oral sustained drug delivery system. A portion of the composition of the present invention is put in the core of a tablet.

[0057] The core can for example be made by conventional wet granulation or continuous granulation such as extrusion followed by compaction of the granulate into tablets. The core is coated using an appropriate technology, preferably by airsuspension using ethylcellulose and a hydrophilic excipient such as hydroxyl propyl cellulose (HPC).

[0058] The first releasing dose is compression coated on the core or air-suspension coated either with the enteric coat or on top of the enteric coat. In a preferred embodiment of the invention, the first releasing dose is air-suspension coated with the enteric coat. In a further embodiment of the invention, the first releasing dose is compression coated on the core, in order to avoid release of the composition according to the invention prior to the degradation of the enteric coat, such degradation typically occurring at pH values higher than those found in the gastric ventricle; i.e. the degradation of the enteric coat typically occurs after passage of the gastric ventricle.

[0059] A further example of a suitable formulation is obtained via crystal engineering, such as e.g. described in WO 03/080034, which is hereby incorporated by reference.

[0060] Accordingly, in another embodiment the composition of the invention comprises the active substance in the form of micro-crystals with hydrophilic surfaces. Furthermore, in another embodiment of the invention, the microcrystals are filmcoated directly, in order to achieve a sustained release formulation.

[0061] Another specific example of a suitable formulation comprises complexation of the composition according to the present invention with genuine cyclodextrins and cyclodextrin-derivatives (e.g. alkyl- and hydroxyalkyl-derivatives or sulfobutyl-derivatives). The complexation is achieved in accordance with well known methods. It is contemplated that such a complexation leads to a higher solubility and a higher dissolution rate of the composition according to the invention, compared to the composition prior to complexation. Furthermore, it is contemplated that such a complexation leads to a higher bioavailability of the composition according to the invention, compared to the composition prior to complexation.

[0062] In specific embodiments, the invention relates to a controlled release pharmaceutical composition that may be administered one, two or more times daily, such as once or twice or three times daily. Furthermore, the composition may be designed so that it releases the fumaric acid ester relatively independent on pH, i.e. the release is not dependent on pH in the gastrointestinal tract. Examples of such compositions are e.g. compositions in the form of solid dosages forms (e.g. tablets, capsules, pellets, beads etc.) that a re coated with a controlled release coating. Suitable materials for controlled release coatings are e.g. cellulose and cellulose derivatives including methylcellulose, ethylcellulose and cellulose acetate, or poly(ethylene-co-vinyl acetate), poly (vinyl chloride).

[0063] The release of the fumaric acid ester typically takes place in three steps from a composition coated with a diffusion controlled membrane:

[0064] i) firstly, water (from the GI tract) diffuses into the dosage form from the surroundings,

[0065] ii) secondly, at least some of the fumaric acid ester present in the dosage form dissolves by the action of water,

[0066] iii) the dissolved fumaric acid ester diffuses out of the dosage form and into the surroundings (i.e. the GI tract)

[0067] Other examples include e.g. matrix tablets or dosage form containing a multiplicity of units each in the form of a matrix system. The active substance is embedded in a matrix containing e.g. cellulose and cellulose derivatives including microcrystalline cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose and methylcellulose, povidone, poly(ethyleneoxide) (PEO), polyethylene glycol (PEG), poly (vinyl alcohol) (PVA), xanthan gum, carrageenan and other synthetic materials. Substances normally used as pharmaceutically acceptable excipients or additives may be added to a matrix composition.

[0068] Other examples of suitable compositions are e.g. hydrogels, i.e. monolithic systems wherein the active substance is embedded in a water-swellable network polymer.

Materials suitable for use include e.g. hydrophilic vinyl and acrylic polymers, polysaccharides like alginates, and poly (ethylene oxide).

[0069] In specific embodiments, a composition according to the invention has a pH controlled release (also known as a pH dependent release) of the fumaric acid ester. Normally, the release is designed so that only a small amount, if any, of the fumaric acid ester is released in the stomach (pH up to about 3), whereas the fumaric acid ester is released in the intestines (pH shifts to about 6-7). Such a pH controlled release can be obtained by providing a composition of the invention with an enteric coating (the whole composition or, if the composition is a multiparticulate composition, the individual units) or by providing a composition that releases the fumaric acid by a pH-dependent osmotic mechanism, or by employment of suitable enzymes.

[0070] Examples of suitable substances for use as enteric coating materials include polyacrylamides, phthalate derivatives such as acid phthalates of carbohydrates, amylose acetate phthalate, cellulose acetate phthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate, hydroxypropylethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, methylcellulose phthalate, polyvinyl acetate phthalate, poly acrylic methacrylic acid copolymers, shellac and vinyl acetate and crotonic acid copolymers, etc.

[0071] The compositions mentioned above having a pH independent release may also be formulated to release the fumaric acid ester e.g. by providing the composition with an outer layer of an enteric coating.

[0072] Furthermore, the compositions may be formulated in such a manner that an initial delay in release of the fumaric acid ester is obtained. Such a delay may be obtained e.g. by choosing an outermost coating that in a time-controlled manner degrades (e.g. erodes) and only when this outermost coating is eroded away, the release of the fumaric acid ester starts.

[0073] In the following is given a description of various compositions according to the invention that are designed to obtain a suitable release of the fumaric acid ester. Based on the description above and handbooks within the field of controlled release of pharmaceutics, a person skilled in the art will know how to choose different formulation principles in order to achieve the required release profile.

Compositions Designed to be Administered Two or more Times Daily

pH Independent Release

[0074] In the following is given a description of specific embodiments, wherein the fumaric acid ester is released independently of pH and wherein the release pattern is suitable for compositions that are administered two or more times daily. Examples of suitable formulation principles are e.g. compositions provided with a diffusion coating such as a controlled release diffusion coating, matrix particulates or matrix tablets, hydrogels, pulsed dose drug delivery systems, co-formulation with vitamin E concentrate or ethanol, TPGS, corn oil and wax etc., including any of the formulation principles mentioned above.

[0075] Accordingly, in one aspect the invention relates to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test employing water as dissolution medium—is as follows:

[0076] within the first 6 hours after start of the test at the most about 60% w/w such as, e.g., from about 30% to about 60% w/w, from about 40% to about 55% w/w, or about 50% of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0077] within the first 9 hours after start of the test at the most about 85% w/w such as, e.g., from about 50% to about 85% w/w, from about 60% to about 80% w/w, or about 75% of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0078] within the first 12 hours after start of the test at least about 80% w/w such as, e.g., about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0079] the total amount of the fumaric acid ester contained in the composition is released within the first 12 hours after start of the test.

pH Controlled Release

[0080] In the following is given a description of specific embodiments, wherein the fumaric acid ester is released depending on pH and wherein the release pattern is suitable for compositions that are administered two or more times daily. Examples of suitable formulation principles are e.g. compositions provided with an enteric coating or hydrogels of a type described by Zentner et al (U.S. Pat. No. 6,537,584) and Bae (U.S. Pat. No. 5,484,610), which hereby are incorporated by reference. Further examples of suitable formulation principles are e.g. compositions provided with a diffusion coating such as a controlled release diffusion coating, matrix particulates or matrix tablets, hydrogels, pulsed dose drug delivery systems, co-formulation with vitamin E concentrate or ethanol, TPGS, corn oil and wax etc., including any of the formulation principles mentioned above, optionally with an enteric coating.

[0081] Accordingly, in one aspect the invention relates to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test employing 0.1 N hydrochloric acid as dissolution medium during the first 2 hours of the test and then 0.05 M phosphate buffer pH 6.5 or 6.8 as dissolution medium—is as follows:

[0082] within the first 2 hours after start of the test at least about 1% w/w such as, e.g. at least about 2% w/w, at least about 3% w/w, or about 5% w/w of the total amount of the fumaric acid ester is released, and/or

[0083] within the first 3 hours after start of the test at the most about 35% w/w such as, e.g., from about 15% to about 35% w/w, from about 20% to about 30% w/w, or about 25% w/w of the total amount of the fumaric acid ester is released, and/or

[0084] within the first 3 hours after start of the test from about 10% to about 70% w/w, from about 10% to about 65% w/w, from about 10% to about 60% w/w, from about 15% to about 50% w/w, from about 15% to about

35% w/w, from about 20% to about 30% w/w, or about 20% w/w, or about 25% w/w of the total amount of the fumaric acid ester is released, and/or

[0085] within the first 4 hours after start of the test at the most about 92% w/w such as, e.g., from about 10% to about 92% w/w, from about 20% to about 85% w/w, from about 20% to about 80% w/w, from about 20% to about 70% w/w, from about 25% to about 60% w/w, from about 25% to about 55% w/w, from about 30% to about 50% w/w, or about 35% w/w, or about 40% w/w, or about 45% w/w of the total amount of the fumaric acid ester is released, and/or

[0086] within the first 5 hours after start of the test at the most about 94% w/w such as, e.g., from about 15% to about 94% w/w, from about 25% to about 90% w/w, from about 30% to about 85% w/w, from about 35% to about 80% w/w, from about 35% to about 75% w/w, from about 40% to about 70% w/w, from about 45% to about 70% w/w, from about 55% to about 70% w/w, from about 60% to about 70% w/w, or about 45% w/w, or about 50% w/w, or about 55% w/w, or about 60% w/w, or about 65% w/w of the total amount of the fumaric acid ester is released, and/or

[0087] within the first 6 hours after start of the test at the most about 60% w/w such as, e.g., from about 30% to about 60% w/w, from about 40% to about 55% w/w, or about 50% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0088] within the first 6 hours after start of the test at the most about 95% w/w such as, e.g., from about 35% to about 95% w/w, from about 40% to about 90% w/w, from about 45% to about 85% w/w, from about 50% to about 85% w/w, from about 55% to about 85% w/w, from about 60% to about 85% w/w, from about 65% to about 85% w/w, from about 70% to about 85% w/w, from about 75% to about 85% w/w, or about 65% w/w, or about 70% w/w, or about 75% w/w, or about 80% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0089] within the first 7 hours after start of the test at the most about 98% w/w such as, e.g., from about 45% to about 98% w/w, from about 50% to about 98% w/w, from about 55% to about 98% w/w, from about 60% to about 98% w/w, from about 65% to about 98% w/w, from about 70% to about 98% w/w, from about 75% to about 95% w/w, from about 80% to about 95% w/w, from about 85% to about 95% w/w, or about 75% w/w, or about 80% w/w, or about 85% w/w, or about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0090] within the first 9 hours after start of the test at the most about 85% w/w such as, e.g., from about 50% to about 85% w/w, from about 60% to about 80% w/w, or about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0091] within the first 9 hours after start of the test at the most about 99% w/w such as, e.g., from about 60% to about 99% w/w, from about 70% to about 99% w/w, from about 80% to about 99% w/w, from about 90% to about 99% w/w, or about 95% w/w of the total amount of the fumaric acid ester contained in the composition is released.

[0092] In another aspect of the invention a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, characterized in that it consists of a controlled-release dosage form adapted to release di-(C_1-C_5)alkylester and/or a mono-(C_1-C_5)alkylester of fumaric acid or a pharmaceutically acceptable salt thereof over a predetermined time period, according to a in vitro profile of dissolution when measured according to USP in 0.1 N hydrochloric acid during the first 2 hours and then 0.05 M phosphate buffer at a pH 6.5 or 6.8,

[0093] wherein at the most 5% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 2 hours after start of the test, and/or

[0094] wherein from about 20% to about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 3 hours after start of the test, and/or

[0095] wherein from about 50% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 4 hours after start of the test, and/or

[0096] wherein from about 60% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 5 hours after start of the test, and/or

[0097] wherein from about 70% to about 95% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 6 hours after start of the test, and/or

[0098] wherein from about 75% to about 97% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 7 hours after start of the test, is provided.

[0099] In a further aspect of the invention a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, characterized in that it consists of a controlled-release dosage form adapted to release di-(C_1-C_5)alkylester and/or a mono-(C_1-C_5)alkylester of fumaric acid or a pharmaceutically acceptable salt thereof over a predetermined time period, according to a in vitro profile of dissolution when measured according to USP in 0.1 N hydrochloric acid during the first 2 hours and then 0.05 M phosphate buffer at a pH 6.5 or 6.8, wherein at the most 5% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 2 hours after start of the test, wherein from about 20% to about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 3 hours after start of the test, wherein from about 50% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 4 hours after start of the test, wherein from about 60% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 5 hours after start of the test, wherein from about 70% to about 95% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 6 hours after start of the test, wherein from about 75% to about 97% w/w of the total amount of the fumaric acid ester

contained in the composition is released within the first 7 hours after start of the test, and wherein at least 85% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 8 hours after start of the test, is provided.

[0100] In another further aspect of the invention a controlled release pharmaceutical composition comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, characterized in that it consists of a controlled-release dosage form adapted to release di-(C_1-C_5)alkylester and/or a mono-(C_1-C_5)alkylester of fumaric acid or a pharmaceutically acceptable salt thereof over a predetermined time period, according to a in vitro profile of dissolution when measured according to USP in 0.1 N hydrochloric acid during the first 2 hours and then 0.05 M phosphate buffer at a pH 6.5 or 6.8,

[0101] wherein at the most 5% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 2 hours after start of the test and/or,

[0102] wherein from about 20% to about 50% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 3 hours after start of the test, and/or

[0103] wherein from about 45% to about 70% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 4 hours after start of the test, and/or

[0104] wherein from about 65% to about 85% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 5 hours after start of the test, and/or

[0105] wherein from about 75% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 6 hours after start of the test, is provided.

[0106] In yet another aspect of the invention a controlled release pharmaceutical composition comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5) alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, characterized in that it consists of a controlled-release dosage form adapted to release di-(C_1-C_5)alkylester and/or a mono-(C_1-C_5)alkylester of fumaric acid or a pharmaceutically acceptable salt thereof over a predetermined time period, according to a in vitro profile of dissolution when measured according to USP in 0.1 N hydrochloric acid during the first 2 hours and then 0.05 M phosphate buffer at a pH 6.5 or 6.8, wherein at the most 5% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 2 hours after start of the test, wherein from about 20% to about 50% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 3 hours after start of the test, wherein from about 45% to about 70% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 4 hours after start of the test, wherein from about 65% to about 85% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 5 hours after start of the test, wherein from about 75% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 6 hours after start of the test, and wherein at least 80% of the total amount of the fumaric acid ester contained in the composition is released within the first 7 hours after start of the test, is provided.

[0107] In yet another aspect of the invention a controlled release pharmaceutical composition comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5) alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, characterized in that it consists of a controlled-release dosage form adapted to release di-(C_1-C_5)alkylester and/or a mono-(C_1-C_5)alkylester of fumaric acid or a pharmaceutically acceptable salt thereof over a predetermined time period, according to a in vitro profile of dissolution when measured according to USP in 0.1 N hydrochloric acid during the first 2 hours and then 0.05 M phosphate buffer at a pH 6.5 or 6.8,

[0108] wherein at the most 5% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 2 hours after start of the test, and/or

[0109] wherein from about 50% to about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 3 hours after start of the test, and/or

[0110] wherein from about 70% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 4 hours after start of the test, and/or

[0111] wherein from about 80% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 5 hours after start of the test, is provided.

[0112] In yet another aspect of the invention a controlled release pharmaceutical composition comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5) alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, characterized in that it consists of a controlled-release dosage form adapted to release di-(C_1-C_5)alkylester and/or a mono-(C_1-C_5)alkylester of fumaric acid or a pharmaceutically acceptable salt thereof over a predetermined time period, according to a in vitro profile of dissolution when measured according to USP in 0.1 N hydrochloric acid during the first 2 hours and then 0.05 M phosphate buffer at a pH 6.5 or 6.8, wherein at the most 5% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 2 hours after start of the test, wherein from about 50% to about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 3 hours after start of the test, wherein from about 70% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 4 hours after start of the test, wherein from about 80% to about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 5 hours after start of the test and wherein from about at least 90% w/w of the total amount of the fumaric acid ester contained in the composition is released within the first 6 hours after start of the test, is provided.

Release Over Gradually Shifting pH ("Half-Change" Method)

[0113] In the following is given a description of specific embodiments, wherein the fumaric acid ester is released depending on pH and wherein the release pattern is suitable for compositions that are administered two or more times daily. Examples of suitable formulation principles are e.g. compositions provided with an enteric coating or hydrogels of a type described by Zentner et al (U.S. Pat. No. 6,537,584) and Bae (U.S. Pat. No. 5,484,610), which hereby are incorporated by reference. Further examples of suitable formulation principles are e.g. compositions provided with a diffusion coating such as a controlled release diffusion coating, matrix particulates or matrix tablets, hydrogels, pulsed dose drug delivery systems, co-formulation with vitamin E concentrate or ethanol, TPGS, corn oil and wax etc., including any of the formulation principles mentioned above, optionally with an enteric coating.

[0114] The "half-change" method has specifically been developed for enteric-coated or sustained release preparations. This method encompasses hourly replacing half of the dissolution medium by an aliquot of neutral dissolution medium (to simulate the GI passage with respect to the slightly shifting pH values from duodenum to ileum). The approach is described in the following table:

Time from start (hours)	Ratio of simulated gastric fluid/simulated Intestinal fluid (%)	pH value
0-1	100/0	1.3
1-2	50/50	2.4
2-3	25/75	6.2
3-4	12.5/87.5	6.8
4-5	6.25/93.75	7.1
5-6	~3/97	7.2
6-7	~1/99	7.3
7-8	~0/100	7.3

[0115] The composition of the simulated gastric fluid can e.g. be found in the United States Pharmacopeia (USP) 2005:

[0116] 2.0 g of NaCl and 3.2 g of purified pepsin, derived from porcine gastric mucosa, with an activity of 800 to 2500 units per mg of protein, is dissolved in 7.0 mL of hydrochloric acid and sufficient water to make 1000 mL. The resulting test solution has a pH of about 1.2.

[0117] Another composition of the simulated gastric fluid is found in the German E DIN 19738 (Deutsche Industrie Norm):

[0118] 100 mL of synthetic/simulated gastric fluid contains 290 mg of NaCl, 70 mg of KCl, 27 mg of KH_2PO_4 and enough HCl to adjust the pH to 2.0. In addition, it contains 100 mg pepsin and 300 mg of mucin.

[0119] The composition of the simulated intestinal fluid can e.g. be found in the United States Pharmacopeia (USP) 2005:

[0120] 6.8 g of monobasic potassium phosphate is dissolved in 250 mL of water. Mix and add 77 mL of 0.2 N sodium hydroxide and 500 mL of water. 10.0 g of pancreatin is added, the solution is mixed and adjusted to a pH of 6.8±10.1 by adding either 0.2 N sodium hydroxide or 0.2 N hydrochloric acid. The resulting solution is diluted with water to 1000 mL.

[0121] Another composition of the simulated intestinal fluid is found in the German E DIN 19738 (Deutsche Industrie Norm):

[0122] 100 mL of synthetic/simulated intestinal fluid contains 30 mg of KCl, 50 mg of $CaCl_2$, 20 mg of $MgCl_2$ and sufficient $NaHCO_3$ to adjust the pH to 7.5. Furthermore, it contains 30 mg of trypsin, 900 mg of pancreatin, 900 mg of lyophilized bile and 30 prig of urea.

[0123] In a preferred embodiment of the present invention, the "half-change" method is carried out with the simulated gastric fluid and the simulated intestinal fluid as defined by the USP 2005.

[0124] In another embodiment of the present invention, the "half-change" method is carried out with the simulated gastric fluid and the simulated intestinal fluid as defined by the USP 2005, but without the proteins (i.e. without the pepsin in the simulated gastric fluid, and without the pancreatin in the simulated intestinal fluid).

[0125] Accordingly, in one aspect the invention relates to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test according to the "half-change" method—is as follows:

[0126] within the first 3 hours after start of the test from about 20% to about 40% w/w, from about 20% to about 35% w/w, or about 30% w/w of the total amount of the fumaric acid ester is released, and/or

[0127] within the first 3 hours after start of the test at least about 12% w/w such as, e.g., from about 12% to about 50% w/w, from about 15% to about 45% w/vv, from about 20% to about 40% w/w, from about 20% to about 35% w/w, from about 22% to about 35% w/w, or about 25% w/w, or about 30% w/w of the total amount of the fumaric acid ester is released, and/or

[0128] within the first 4 hours after start of the test from about 25% to about 40% w/w, from about 30% to about 40% w/w, or about 40% w/w of the total amount of the fumaric acid ester is released, and/or

[0129] within the first 4 hours after start of the test at least about 76% w/w such as, e.g., from about 76% to about 95% w/w, from about 80% to about 90% w/w, or about 80% w/w, or about 85% w/w of the total amount of the fumaric acid ester is released, and/or

[0130] within the first 4 hours after start of the test at the most about 40% w/w such as, e.g., from about 10% to about 40% w/w, from about 15% to about 35% w/w, from about 20% to about 30% w/w, or about 25% w/w, or about 30% w/w of the total amount of the fumaric acid ester is released, and/or

[0131] within the first 6 hours after start of the test at least about 81% w/w such as, e.g., from about 81% to about 96% w/w, from about 85% to about 95% w/w, from about 85% to about 90% w/w, or about 80% w/w, or about 85% w/w, or about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0132] within the first 6 hours after start of the test at the most about 50% w/w such as, e.g., from about 20% to about 50% w/w, from about 25% to about 45% w/w, from about 30% to about 45% w/w, or about 40% w/w,

or about 45% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0133] within the first 7 hours after start of the test at least about 82% w/w such as, e.g., from about 82% to about 99% w/w, from about 85% to about 99% w/w, from about 85% to about 95% w/w, or about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0134] within the first 7 hours after start of the test at the most about 65% w/w such as, e.g., from about 25% to about 65% w/w, from about 30% to about 65% w/w, from about 35% to about 60% w/w, from about 40% to about 60% w/w, from about 50% to about 60% w/w, or about 55% w/w, or about 60% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0135] within the first 8 hours after start of the test at the most about 85% w/w such as, e.g., from about 50% to about 85% w/w, from about 60% to about 80% w/w, or about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0136] within the first 8 hours after start of the test at the most about 92% w/w such as, e.g., from about 30% to about 92% w/w, from about 35% to about 90% w/w, from about 40% to about 85% w/w, from about 45% to about 80% w/w, from about 50% to about 75% w/w, from about 55% to about 75% w/w, from about 60% to about 75% w/w, or about 65% w/w, or about 70% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0137] within the first 12 hours after start of the test at least about 80% w/w such as, e.g., about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of the total amount of the fumaric acid ester contained in the composition is released.

Slow Release

[0138] In the following is given a description of specific embodiments, wherein the fumaric acid ester is released in a slow or delayed manner wherein the release pattern is suitable for compositions that are administered two or more times daily. Examples of suitable formulation principles are any of those described above.

[0139] Accordingly, in one aspect the invention relates to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test employing water as dissolution medium—is as follows:

[0140] within the first 6 hours after start of the test at the most about 35% w/w such as, e.g., from about 15% to about 35% w/w such as, e.g., from about 20% to about 30% w/w, or about 25% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0141] within the first 8 hours after start of the test at the most about 60% w/w such as, e.g., from about 30% to about 60% w/w such as, e.g., from about 40% to about 55% w/w, or about 50% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0142] within the first 10 hours after start of the test at the most about 85% w/w such as, e.g., from about 50% to about 85% w/w such as, e.g., from about 60% to about 80% w/w, or about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0143] within the first 12 hours after start of the test at least about 80% w/w such as, e.g., about 80% w/w or more such as, e.g., about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of the total amount of the fumaric acid ester contained in the composition is released.

Compositions Designed to be Administered Once Daily

pH Independent Release

[0144] In the following is given a description of specific embodiments, wherein the fumaric acid ester is released independent of pH and wherein the release pattern is suitable for compositions that are administered once daily. Examples of suitable formulation principles are e.g. compositions provided with a diffusion coating such as a controlled release diffusion coating, matrix particulates or matrix tablets, hydrogels, pulsed dose drug delivery systems, co-formulation with vitamin E concentrate or ethanol, TPGS, corn oil and wax etc., including any of the formulation principles mentioned above.

[0145] Accordingly, in one aspect the invention relates to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test employing water as dissolution medium—is as follows:

[0146] within the first 9 hours after start of the test at the most about 60% w/w such as, e.g., from about 30% to about 60% w/w, from about 40% to about 55% w/w, or about 50% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0147] within the first 13.5 hours after start of the test at the most about 85% w/w such as, e.g., from about 50% to about 85% w/w, from about 60% to about 80% w/w, or about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0148] within the first 18 hours after start of the test at least about 80% w/w such as, e.g., about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0149] the total amount of the fumaric acid ester contained in the composition is released within the first 18 hours after start of the test.

pH Controlled Release

[0150] In the following is given a description of specific embodiments, wherein the fumaric acid ester is released dependently of pH and wherein the release pattern is suitable

for compositions that are administered once daily. Examples of suitable formulation principles are e.g. compositions provided with an enteric coating or hydrogels of a type described by Zentner et al (U.S. Pat. No. 6,537,584) and Bae (U.S. Pat. No. 5,484,610). Further examples of suitable formulation principles are e.g. compositions provided with a diffusion coating such as a controlled release diffusion coating, matrix particulates or matrix tablets, hydrogels, pulsed dose drug delivery systems, co-formulation with vitamin E concentrate or ethanol, TPGS, corn oil and wax etc., including any of the formulation principles mentioned above, optionally with an enteric coating.

[0151] Accordingly, in one aspect the invention relates to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test employing 0.1 N hydrochloric acid as dissolution medium during the first 2 hours of the test and then 0.05 M phosphate buffer pH 6.5 or 6.8 as dissolution medium—is as follows:

[0152] within the first 2 hours after start of the test at least about 1% w/w such as, e.g. at least about 2% w/w, at least about 3% w/w, or about 5% w/w of the total amount of the fumaric acid ester is released, and/or

[0153] within the first 4 hours after start of the test at the most about 90% w/w such as, e.g., from about 5% to about 90% w/w, from about 5% to about 85% w/w, from about 10% to about 80% w/w, from about 10% to about 70% w/w, from about 10% to about 65% w/w, from about 10% to about 60% w/w, from about 15% to about 50% w/w, from about 15% to about 35% w/w, from about 20% to about 30% w/w, or about 20% w/w, or about 25% w/w of the total amount of the fumaric acid ester is released, and/or

[0154] within the first 4.5 hours after start of the test at the most about 35% w/w such as, e.g., from about 15% to about 35% w/w, from about 20% to about 30% w/w, or about 25% w/w of the total amount of the fumaric acid ester is released, and/or

[0155] within the first 5 hours after start of the test at the most about 92% w/w such as, e.g., from about 10% to about 92% w/w, from about 20% to about 85% w/w, from about 20% to about 80% w/w, from about 20% to about 70% w/w, from about 25% to about 60% w/w, from about 25% to about 55% w/w, from about 30% to about 50% w/w, or about 35% w/w, or about 40% w/w, or about 45% w/w of the total amount of the fumaric acid ester is released, and/or

[0156] within the first 6 hours after start of the test at the most about 94% w/w such as, e.g., from about 15% to about 94% w/w, from about 25% to about 90% w/w, from about 30% to about 85% w/w, from about 35% to about 80% w/w, from about 35% to about 75% w/w, from about 40% to about 70% w/w, from about 45% to about 70% w/w, from about 55% to about 70% w/w, from about 60% to about 70% w/w, or about 45% w/w, or about 50% w/w, or about 55% w/w, or about 60% w/w, or about 65% w/w of the total amount of the fumaric acid ester is released, and/or

[0157] within the first 7 hours after start of the test at the most about 95% w/w such as, e.g., from about 35% to about 95% w/w, from about 40% to about 90% w/w, from about 45% to about 85% w/w, from about 50% to about 85% w/w, from about 55% to about 85% w/w, from about 60% to about 85% w/w, from about 65% to about 85% w/w, from about 70% to about 85% w/w, from about 75% to about 85% w/w, or about 65% w/w, or about 70% w/w, or about 75% w/w, or about 80% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0158] within the first 9 hours after start of the test at the most about 98% w/w such as, e.g., from about 45% to about 98% w/w, from about 50% to about 98% w/w, from about 55% to about 98% w/w, from about 60% to about 98% w/w, from about 65% to about 98% w/w, from about 70% to about 98% w/w, from about 75% to about 95% w/w, from about 80% to about 95% w/w, from about 85% to about 95% w/w, or about 75% w/w, or about 80% w/w, or about 85% w/w, or about 90% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0159] within the first 9 hours after start of the test at the most about 60% w/w such as, e.g., from about 30% to about 60% w/w, from about 40% to about 55% w/w, or about 50% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0160] within the first 12 hours after start of the test at the most about 99% w/w such as, e.g., from about 60% to about 99% w/w, from about 70% to about 99% w/w, from about 80% to about 99% w/w, from about 90% to about 99% w/w, or about 95% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0161] within the first 13.5 hours after start of the test at the most about 85% w/w such as, e.g., from about 50% to about 85% w/w, from about 60% to about 80% w/w, or about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released,.

Release Over Gradually Shifting pH ("Half-Change" Method)

[0162] In the following is given a description of specific embodiments, wherein the fumaric acid ester is released depending on pH and wherein the release pattern is suitable for compositions that are administered once daily. Examples of suitable formulation principles are e.g. compositions provided with an enteric coating or hydrogels of a type described by Zentner et al (U.S. Pat. No. 6,537,584) and Bae (U.S. Pat. No. 5,484,610), which hereby are incorporated by reference. Further examples of suitable formulation principles are e.g. compositions provided with a diffusion coating such as a controlled release diffusion coating, matrix particulates or matrix tablets, hydrogels, pulsed dose drug delivery systems, co-formulation with vitamin E concentrate or ethanol, TPGS, corn oil and wax etc., including any of the formulation principles mentioned above, optionally with an enteric coating.

[0163] Accordingly, in one aspect the invention relates to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test according to the "half-change" method—is as follows:

[0164] within the first 3 hours after start of the test at least about 12% w/w such as, e.g., from about 12% to about 60% w/w, from about 15% to about 50% w/w, from about 20% to about 40% w/w, from about 20% to about 35% w/w, or about 25% w/w, or about 30% w/w of the total amount of the fumaric acid ester is released, and/or

[0165] within the first 4 hours after start of the test at the most about 35% w/w such as, e.g., from about 15% to about 35% w/w, from about 20% to about 30% w/w, or about 25% w/w of the total amount of the fumaric acid ester is released, and/or

[0166] within the first 5 hours after start of the test at the most about 45% w/w such as, e.g., from about 10% to about 45% w/w, from about 15% to about 40% w/w, from about 15% to about 35% w/w, from about 20% to about 30% w/w, or about 25% w/w, or about 30% w/w of the total amount of the fumaric acid ester is released, and/or

[0167] within the first 7 hours after start of the test at the most about 65% w/w such as, e.g., from about 20% to about 65% w/w, from about 20% to about 60% w/w, from about 20% to about 50% w/w, from about 25% to about 45% w/w, from about 30% to about 45% w/w, or about 40% w/w, or about 45% w/w of the total amount of the fumaric acid ester is released, and/or

[0168] within the first 8 hours after start of the test at the most about 92% w/w such as, e.g., from about 25% to about 92% w/w, from about 25% to about 90% w/w, from about 30% to about 80% w/w, from about 35% to about 70% w/w, from about 40% to about 65% w/w, from about 45% to about 60% w/w, from about 50% to about 60% w/w, or about 55% w/w, or a bout 60% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0169] within the first 8 hours after start of the test at the most about 60% w/w such as, e.g., from about 30% to about 60% w/w, from about 40% to about 55% w/w, or about 50% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0170] within the first 12 hours after start of the test at the most about 99% w/w such as, e.g., from about 30% to about 99% w/w, from about 30% to about 95% w/w, from about 35% to about 90% w/w, from about 40% to about 85% w/w, from about 45% to about 80% w/w, from about 50% to about 75% w/w, from about 55% to about 75% w/w, from about 60% to about 75% w/w, or about 65% w/w, or about 70% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0171] within the first 12.5 hours after start of the test at the most about 85% w/w such as, e.g., from about 50% to about 85% w/w, from about 60% to about 80% w/w, or about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0172] within the first 18 hours after start of the test at least about 80% w/w such as, e.g., about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of the total amount of the fumaric acid ester contained in the composition is released.

Slow Release

[0173] In the following is given a description of specific embodiments, wherein the fumaric acid ester is released in a slow or delayed manner wherein the release pattern is suitable for compositions that are administered once daily. Examples of suitable formulation principles are any of those described above.

[0174] Accordingly, in one aspect the invention relates to a controlled release pharmaceutical composition for oral use comprising as an active substance one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of furnaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, wherein the release of the fumaric acid ester—when subjected to an in vitro dissolution test employing water as dissolution medium—is as follows:

[0175] within the first 7 hours after start of the test at the most about 35% w/w such as, e.g., from about 15% to about 35% w/w, from about 20% to about 30% w/w, or about 25% w/w of the total amount of the furnaric acid ester contained in the composition is released, and/or

[0176] within the first 11 hours after start of the test at the most about 60% w/w such as, e.g., from about 30% to about 60% w/w, from about 40% to about 55% w/w, or about 50% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0177] within the first 14 hours after start of the test at the most about 85% w/w such as, e.g., from about 50% to about 85% w/w, from about 60% to about 80% w/w, or about 75% w/w of the total amount of the fumaric acid ester contained in the composition is released, and/or

[0178] within the first 18 hours after start of the test at least about 80% w/w such as, e.g., about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of the total amount of the fumaric acid ester contained in the composition is released.

[0179] Typically, as described above, the compositions according to the invention are designed to deliver the active substance (i.e. the monoalkylester of fumaric acid, which in turn is metabolised to fumaric acid and, which subsequently is subjected to a rapid elimination process) in a prolonged manner. Apart from the characteristic in vitro release patterns described herein, such a prolonged release is reflected in the pharmacokinetic parameters obtained after a clinical study as well. Accordingly, it is contemplated that the C_{max} of the monoalkylester of furnaric acid (which appears in the plasma upon hydrolysis or metabolism of the dialkylester administered) is of the same order of magnitude as previously described in the literature provided that a similar or equivalent dose is administered (i.e. C_{max} of monomethylfumarate in a range of from about 0.4 to about 2.0 mg/l corresponding to an oral dose of 120 to 240 mg dimethylfumarate). However, in order to avoid many frequent daily administrations (2-4 tablets 1-3 times daily) it is an aim to prolong the time period where the concentration is within the therapeutic window. Accordingly, it is contemplated that W_{50} (i.e. the time period in which the plasma concentration is 50% of C_{max} or more) is prolonged compared to the marketed treatment with at least 10% such as, e.g. at least 20%, at least 30%, at least 40% or at least 50%. A suitable W_{50} is believed to be at least 2 hours such as in a range of

from about 2 to about 15 hours or from about 2.5 to about 10 hours or from about 3 to about 8 hours.

[0180] Furthermore, it is contemplated that a controlled release composition according to the invention may lead to a reduced interindividual and/or intraindividual variation in the plasma profile and to a reduced dependency on whether the composition is taken together with or without food (a reduced variation of the plasma concentration profile of monomethylfumarate when the pharmaceutical composition is administered with or without concomitant food intake). Therefore, the controlled release composition according to the invention may lead to a reduced frequency of dosing and/or a reduced average total daily dose, and/or an increased efficacy at the same total daily dose of the active substance compared to Fumaderm®.

[0181] Different kinetic models, such as zero-order (1), first-order (2), square-root (Higuchi's equation) (3) can be applied to the interpretation of the drug release kinetic.

$$M_t = M_0 + k_0 * t \quad 1:$$

$$InM_t = InM + k_1 * t \quad 2:$$

$$M_t = M_0 + k_H * t^{1/2} \quad 3:$$

[0182] In these equations, M_t is the cumulative amount of drug released at any specified time point and M_0 is the dose of active substance incorporated in the pharmaceutical composition. k_0, k_1 and k_H are rate constants for zero-order, first-order and Higuchi's equation, respectively.

[0183] One aspect of the invention relates to a zero-order dissolution release profile. Another aspect relates to a first-order dissolution release profile. A further aspect relates to a square-root (Higuchi's equation) dissolution release profile.

[0184] In one aspect of the invention a controlled release pharmaceutical composition comprising as an active substance from 10% to 90% by weight of one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, from 2% to 40% by weight pharmaceutically acceptable polymer(s), and from 1% to 40% by weight hydrophilic excipient(s), and optionally pharmaceutically acceptable excipients or additives, is provided.

[0185] In another aspect of the invention a controlled release pharmaceutical composition comprising as an active substance from 40% to 60% by weight of one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, from 15% to 25% by weight pharmaceutically acceptable polymer(s), and from 2% to 15% by weight hydrophilic excipient(s), and optionally pharmaceutically acceptable excipients or additives, is provided.

[0186] In a further aspect of the invention a controlled release pharmaceutical composition comprising as an active substance from 65% to 80% by weight of one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, from 10% to 25% by weight pharmaceutically acceptable polymer(s), and from 2% to 15% by weight hydrophilic excipient(s), and optionally pharmaceutically acceptable excipients or additives, is provided.

[0187] Examples of "pharmaceutically acceptable polymer(s)" comprises but are not limited to ethylcellulose, or methacrylic/acrylic acid copolymers, such as ammonio methacrylate copolymer type A and B or methacrylic acid copolymer A and B.

[0188] Examples of "hydrophilic excipient(s)" comprises but are not limited to polyethylene glycol (PEG), povidone, hydroxyl propyl cellulose (HPC), hydroxyethyl starch (HES) or hydroxypropyl methyl cellulose (HPMC) or a material with similar properties, or a combination thereof.

[0189] In a further aspect of the invention a controlled release pharmaceutical composition, wherein the pharmaceutically acceptable polymer is ethyl cellulose, is provided.

[0190] In another aspect of the invention a controlled release pharmaceutical composition, wherein the hydrophilic excipient is hydroxyl propyl cellulose, is provided.

[0191] In another aspect of the invention a controlled release pharmaceutical composition, wherein the hydrophilic excipient is polyethylene glycol, is provided.

[0192] In yet another aspect of the invention a controlled release pharmaceutical composition comprising as an active substance as an active substance from 10% to 90% by weight of one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5) alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, and 2% to 40% by weight methacrylic acid copolymer A and B in a weight ratio between 1:9 and 9:1, and optionally pharmaceutically acceptable excipients or additives, is provided.

[0193] In a further aspect of the invention a controlled release pharmaceutical composition comprising from 50% to 90% of one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5) alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, is provided.

[0194] Various controlled release formulations, not limiting the scope of the present invention, illustrating the invention are described hereafter (all concentrations based on the final tablet):

1) Granules

[0195] Granules may be prepared by mixing and/or granulating the active substance at a concentration of about 10 to about 90%, especially from about 50 to about 70%, with granulating excipients, such as pharmaceutical acceptable polymers, e.g. ethylcellulose such as Ethocel® NF premium, or methacrylic/acrylic acid copolymers, such as ammonio methacrylate copolymer type A and B (in a weight ratio of 1:9 to 9:1) or methacrylic acid copolymer A and B (in a weight ratio of 1:9 to 9:1), incorporated at a concentration between about 2 to about 40%. Hydrophilic excipients such as polyethylene glycol (PEG), povidone, hydroxyl propyl cellulose (HPC), hydroxyethyl starch (HES) or hydroxypropyl methyl cellulose (HPMC) at a concentration of about 1 to about 40% and/or pharmaceutical acceptable surfactants with HLB values above 8 at a concentration of about 0.01 to about 3% may be incorporated.

2) Micro-Crystal Formulation

[0196] Crystallization is performed in any suitable organic solvent for re-crystallisation, such as isopropanol, at an appropriate temperature such as e.g. between +70° C. and −20° C. A hydrocolloid (e.g. HPMC) or a surfactant (e.g.

polysorbate) can be used at an appropriate concentration to manipulate the growth of the crystals during recrystallization. Any granulating/coating excipient, such as pharmaceutically acceptable polymers, may be used e.g. ethylcellulose at a concentration of about 10 to about 50%, especially about 20 to about 35%, polymethacryllates such as ammonio methacrylate copolymer type A and B or methacrylic acid copolymer A and B. As a hydrophilic excipient mention can be made of e.g PEG 400.

3) Capsules and Sachets

[0197] A capsule (e.g. a capsule of gelatine, HPMC or a starch derivative) or a sachet may be filled with coated micro-crystals or coated granules and if necessary appropriate amounts of filling excipients such as sugaralcoholes e.g. mannitol, and/or glidants.

4) Tablets

[0198] Tablets may be based on either micro-crystals or granules. When it comes to producing tablets in large scale, especially on a rotary machine, further excipients to increase flow ability or to improve tabletting-behaviour may be needed. As filling and binding excipients, if required, mention can be made of e.g. microcrystalline cellulose, such as Avicel® 102, and cellulose at a concentration of about 1 to about 60%, crystalline, spray dried or granulated lactose monohydrate e.g. Tablettose®, as well as anhydrous lactose monohydrate, at a concentration of about 5 to about 60%, sugar alcohols, such as sorbitol and mannitol, at a concentration of about 0 to about 40% and modified starch at a concentration of about 0 to about 40%. Furthermore disintegration agents such as starch and starch-derivates such as sodium starch glycolate (at a concentration of about 0.2 to about 10%), crospovidone (at a concentration of about 0.2 to about 10%), sodium carboxymethylcellulose (at a concentration of about 0.1 to about 10%), glidants such as colloidal anhydrous and hydrous silica (at a concentration of about 0.2 to about 4%), and lubricants, e.g. magnesium stearate, calcium behenate, and calciumarachinate (at a concentration of about 0.2 to about 3%) or sodium stearyl fumarate (at a concentration of about 1 to about 8%) can be added.

Dosage

[0199] Apart from providing compositions having different content of fumaric acid present, the invention also provides e.g. kits containing two or more containers e.g. with compositions having various amounts of the fumaric acid included. Such kits are suitable for use in those situations where an increasing dosage is required over time. A normal up-scale of the dosage is given below:

Week	Morning	Noon	Evening	Strength
1	1	—	—	A
2	1	—	1	A
3	1	—	1	B
4	1	—	—	B
5	1	—	1	B
6	1	1	1	B
7	2	1	1	B
8	2	1	2	B
9	2	2	2	B

A corresponds to a low strength such as about 30 mg dimethylfumarate (or a corresponding effective dose of another fumaric acid ester)
B corresponds to a higher strength such as about 120 mg dimethylfumarate (or a corresponding effective dose of another fumaric acid ester)

[0200] In one aspect of the invention a controlled release pharmaceutical composition, wherein the amount of one or more fumaric acid esters selected from di-(C_1-C_5)alkylesters of fumaric acid and mono-(C_1-C_5)alkylesters of fumaric acid, or a pharmaceutically acceptable salt thereof, in a dosage form is from 90 mg to 360 mg active substance, such as 90, 120, 180, 240 or 360 mg active substance, is provided. In a further aspect of the invention the amount of active substance is 120, 180 or 240 mg active substance. In yet a further aspect of the invention, the amount of active substance is 180 or 360 mg.

[0201] The daily dosage of the controlled release pharmaceutical composition according to the invention that is administered to treat a patient depends on a number of factors among which are included, without limitation, weight and age and the underlying causes of the condition or disease to be treated, and is within the skill of a physician to determine. In one aspect of the invention the daily dosage can be e.g. from 240 to 360 mg active substance given in one to three doses, in another aspect from 360 to 480 mg active substance given in one to three doses, in another aspect 480 to 600 mg active substance given in one to three doses, in another aspect 600 to 720 mg active substance given in one to three doses, in another aspect 720 to 840 mg active substance given in one to three doses, in another aspect 840 to 960 mg active substance given in one to three doses and in yet another aspect 960 to 1080 mg active substance given in one to three doses.

[0202] In one aspect of the invention the controlled release pharmaceutical composition is in the form of a capsule.

[0203] In another aspect of the invention the controlled release pharmaceutical composition in the form of a tablet is provided, such as a tablet which has a shape that makes it easy and convenient for a patient to swallow e.g. a tablet which has a rounded or a rod-like shape without any sharp edges.

[0204] In another aspect of the invention a pharmaceutical composition in the form of a tablet designed to be divided into two or more parts, is provided.

[0205] The compositions according to the invention may be administered together with a meal or in relation to a meal such as e.g. in a time period corresponding to a range from at least about 30 minutes before a meal to about 2 hours after the meal, or the composition may be administered at any specific point(s) in time during the day.

[0206] In one embodiment, the total daily dose is given at bedtime, such as up to or about 30 minutes before bedtime, up to or about 60 minutes before bedtime, up to or about 90 minutes before bedtime, up to or about 120 minutes before bedtime or up to or about 180 minutes before bedtime.

[0207] The compositions and kits according to the invention are contemplated to be suitable to use in the treatment of one or more of the following conditions:

[0208] a. Psoriasis
[0209] b. Psoriatic arthritis
[0210] c. Neurodermatitis
[0211] d. Inflammatory bowel disease, such as
[0212] i. Crohn's disease
[0213] ii. Ulcerative colitis
[0214] e. autoimmune diseases:
[0215] i. Polyarthritis
[0216] ii. Multiple sclerosis (MS)
[0217] iii. Juvenile-onset diabetes mellitus
[0218] iv. Hashimoto's thyroiditis
[0219] v. Grave's disease
[0220] vi. SLE (systemic lupus erythematosus)
[0221] vii. Sjögren's syndrome
[0222] viii. Pernicious anemia
[0223] ix. Chronic active (lupoid) hepatitis
[0224] x. Rheumatoid arthritis (RA)
[0225] xi. Optic neuritis

[0226] Moreover, the novel composition or kit according to the invention may be used in the treatment of

[0227] 1. Pain such as radicular pain, pain associated with radiculopathy, neuropathic pain or sciatica/sciatic pain
[0228] 2. Organ transplantation (prevention of rejection)
[0229] 3. Sarcoidosis
[0230] 4. Necrobiosis lipoidica
[0231] 5. Granuloma annulare

[0232] Psoriasis has been proposed to potentially be associated with Crohn's disease (Najarian D J, Gottlieb A B, Connections between psoriasis and Crohn's disease. 3 Am Acad Dermatol. 2003 June;48(6):805-21), celiac disease (Ojettl V et al, High prevalence of celiac disease in psoriasis. Am J Gastroenterol. 2003 November;98(11):2574-5.), psychiatric or psychological disease, such as depression or a life crisis (Gupta M A, Gupta A K, Psychiatric and psychological co-morbidity in patients with dermatologic disorders: epidemiology and management. Am J Clin Dermatol. 2003;4 (12):833-42. and Mallbris L et al, Psoriasis phenotype at disease onset: clinical characterization of 400 adult cases. J Invest Dermatol. 2005 March; 124(3):499-504.), overweight, diabetes mellitus, excess consumption of alcohol/alcoholism, as well as psoriatic arthritis.

[0233] The present invention thus relates in one aspect to a method of treating psoriasis, psoriatic arthritis, neurodermatitis, inflammatory bowel disease, such as Crohn's disease and ulcerative colitis, autoimmune diseases, such as polyarthritis, multiple sclerosis (MS), juvenile-onset diabetes mellitus, Hashimoto's thyroiditis, Grave's disease, SLE (systemic lupus erythematosus), Sjögren's syndrome, Pernicious anemia, Chronic active (lupoid) hepatitis, Rheumatoid arthritis (RA) and optic neuritis, pain such as radicular pain, pain associated with radiculopathy, neuropathic pain or sciatica/sciatic pain, organ transplantation (prevention of rejection), sarcoidosis, necrobiosis lipoidica or granuloma annulare, which method comprises administering orally to a patient in need thereof, an effective dosage of a controlled release pharmaceutical composition according the invention.

[0234] The present invention relates in another aspect to the use of a controlled release pharmaceutical composition according to the invention for the preparation of a medicament for the treatment of psoriasis, psoriatic arthritis, neurodermatitis, inflammatory bowel disease, such as Crohn's disease and ulcerative colitis, autoimmune diseases, such as polyarthritis, multiple sclerosis (MS), juvenile-onset diabetes mellitus, Hashimoto's thyroiditis, Grave's disease, SLE (systemic lupus erythematosus), Sjögren's syndrome, Pernicious anemia, Chronic active (lupoid) hepatitis, Rheumatoid arthritis (RA) and optic neuritis, pain such as radicular pain, pain associated with radiculopathy, neuropathic pain or sciatica/sciatic pain, organ transplantation (prevention of rejection), sarcoidosis, necrobiosis lipoidica or granuloma annulare.

[0235] Furthermore, the invention also relates to treating an individual suffering from one of the conditions in the abovementioned lists, more specifically psoriasis or psoriatic arthritis, with a composition or kit according to the invention, said individual further being in treatment with

[0236] a) a topical anti-psoriatic drug such as 1) vitamin D or derivatives thereof (calcipotriol, calcipotriene), 2) a corticosteroid (such as e.g. betamethasone, desoximethasone, fluocinolone, momethasone, hydrocortisone aceponate, fluticasone, clobethasol, clobethasone, hydrocortisone butyrate, desonide, triamcinolone or hydrocortisone), 3) tazaroten, 4) ditranol, 5) tacrolimus (FK-506), and other calcineurin inhibitors, such as pimecrolimus or 6) any combination of 1-5 and/or

[0237] b) an oral anti-psoriatic drug such as 1) an oral retinoid (such as acitretin or etretinate) combined or not combined with PUVA, 2) cyclosporine and other calcineurin inhibitors, such as ISA247, tacrolimus and pimecrolimus, 3) methotrexate, 4) hydroxyurea, 5) azathioprine, 6) sulphasalazine, 7) a fumarate derivative (such as e.g. Fumaderm® or BG-12), 8) rosiglitazone (Avandia) and other peroxisome proliferator-activated-γ (PPARγ) agonists or modulators, such as pioglitazone, farglitazar, GW1929, GW7845, MC-555, MBX-102/MBX-10, MBX-1828, MBX-2044, CLX-0921, R-483, reglitazar, naveglitazar (LY-519818/LY-818), netoglitazone (MCC-555), CS-7017, troglitazone, ciglitazone, tesaglitazar, isaglitazone, balaglitazone, muraglitazar, TAK-654, LBM642, DRF 4158, EML 4156, T-174, TY-51501, TY-12780, VDO-52 or AMG-131(T131) or any combination of 1-8 and/or

[0238] c) a parenterally administered anti-psoriatic drug such as 1) alefacept (Amevive), 2) etanercept (Enbrel), 3) efalizumab (Raptiva), 4) onercept, 5) adalimumab (Humira) or any combination of 1-5 and/or

[0239] d) an inhibitor of TNF-α not mentioned in the list under section c) above (e.g. CDP 870 or infliximab (Remicade)), administered via an enteral or parenteral route and/or

[0240] e) tisocalicitrate and/or NCX 1022 and/or IDEC-131 and/or MEDI-507, and/or

[0241] f) An NSAID or a COX or a LOX inhibitor such as e.g. a COX-2 inhibitor or a COX/5-LOX inhibitor, and/or

[0242] g) an anti-diabetic or anti-obesity drug, such as biguanides such as metformin; metformin XR; a sulphonylurea such as chlorpropamide, glipizide, gliclazide, glyburide/glibenclamide or glimepiride; Glucovance (metformin+glyburide); Metaglip (glipizide+metformin); a peroxisome proliferator-activated-γ (PPARγ) agonist or modulator, such as rosiglitazone (Avandia), pioglitazone, farglitazar, GW1929, GW7845, MC-555, MBX-102/MBX-10, MBX-1828,

MBX-2044, CLX-0921, R-483, reglitazar, naveglitazar (LY-519818/LY-818), netoglitazone (MCC-555), CS-7017, troglitazone, ciglitazone, tesaglitazar, isaglitazone, balaglitazone, muraglitazar, TAK-654, LBM642, DRF 4158, EML 4156, T-174, TY-51501, TY-12780, VDO-52 or AMG-131(T131); Avandamet (rosiglitazone+metformin); Actos (pioglitazone+metformin); Avandaryl (rosiglitazone maleate+glimepiride); a benzoimidazole such as FK-614; CS-917; TA-1095; ONO-5129; TAK-559; TAK-677/AJ-9667; a d-phenylalanine inducer such as senaglinide; c-3347; NBI-6024; ingliforib; BVT 3498; LY 929; SGLT2 inhibitors; CS 011; BIM 51077; R1438; R1439; R1440; R1498; R1499; AVE 0847; AVE 2268; AVE 5688; AVE 8134; TA-6666; AZD 6370; SSR 162369; TLK-17411; NN 2501; MK 431; KGA-2727; MK-767; CS-872; a beta-3 receptor antagonist such as N-5984; an alpha-glucosidase inhibitor such as acarbose, voglibose or miglitol; a glinitide/meglitinide analogue or carbamoylmethylbensoeic acid derivative such as mitiglinide, repaglinide or nateglinide; a DPP-IV inhibitor such as LAF 237 (vildagliptin), DPP728, P93/01, P32/98, PT-630 or saxagliptin; GLP-1 or GLP-1 analogues, such as exenatide, Exenatide-LAR, liraglutide (NN 2211), ZP 10/AVE 0010, LY 307161, betatropin, CJC-1131, GTP-010, SUN E7001 or AZM 134; pramlinitide acetate; insulin or insulin analogues, such as Humalog (insulin lispro), Humulin, Novolin, Novolog/NovoRapid (insulin aspart), Apidra (insulin glulisine), Lantus (insulin glargine), Exubera, Levemir/NN 304 (insulin detemir), AERx/NN 1998, Insuman, Pulmonary insulin or NN 344; sibutramine or other blockers of the presynaptic reuptake of serotonin and noradrenalin; orlistat and other inhibitors of GI lipases; β3-adrenergic receptor agonists; uncoupling proteins; (specific) antagonists of PPARγ (Peroxisome Proliferator-Activated Receptor γ); insulin secretagogues; rimonabant and other CB1 endocannabinoid receptor antagonists; bupropion; topiramate; leptin agonists; ciliary neurotrophic factor; peptide analogues of the human growth hormone fragment 177-191; cholecystokinin-A receptor agonists; melanocortin-3 agonists; noradrenergic drugs such as phentermine, diethylpropion, phendimetrazine or benzphetamine; or any combination of the anti-diabetic or anti-obesity drugs mentioned above, and/or

[0243] h) a drug potentially useful in the treatment of substance abuse e.g. alcohol abuse such as naltrexone, acamprosate, disulphiram or Vivitrex (naltrexone long acting injection), and/or,

[0244] i) a drug potentially useful in the treatment of Crohn's disease such as

[0245] 1. 5-ASA compounds such as sulfasalazine, oral 5-ASA formulations or rectal 5-ASA formulations,

[0246] 2. glucocorticosteroids such as systemic steroids (e.g. budesonide or prednisolone) or topically acting steroids (e.g. budesonide),

[0247] 3. antibiotics such as metronidazole or quinolones (e.g. ciprofloxacine, ofloxacine, norfloxacine, levofloxacine or moxifloxacine),

[0248] 4. immunosuppressives such as azathioprine, 6-mercaptopurine or methotrexate,

[0249] 5. nutritional therapies such as elemental or polymeric formulas or pre- and probiotics,

[0250] 6. biological therapies e.g. TNF-α inhibitors such as infliximab, adalimumab, CDP870, CDP571, etanercept or onercept,

[0251] 7. symptomatic agents such as anti-diarrheals or anti-spasmodics.

[0252] Examples of suitable NSAIDs are piroxicam, diclofenac, nabumetone, propionic acids including naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates including mefenamic acid, paracetamol, indomethacin, sulindac, meloxicam, apazone, pyrazolones including phenylbutazone, salicylates including aspirin.

[0253] Examples of suitable COX-2 inhibitors are rofecoxib (Vioxx), valdecoxib (Bextra), celecoxib (Celebrex), etoricoxib (Arcoxia), lumiracoxib (Prexige), parecoxib (Dynastat), deracoxib (Deram), tiracoxib, meloxicam, nimesolide, (1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-l-hydroxy-6,6dimethyl-6H-dibenzo[b,d]pyran carboxylic acid (CT-3), 2(5H)-Furanone, 5,5-dimethyl (l-methylethoxy) [4(methylsulfonyl)phenyl]-(DFP); Carprofen (RIMADYL), (Acetyloxy)-benzoic acid, 3-[(nitrooxy)methyl]phenyl ester (NCX4016), P54 (CAS Reg. No. 130996 0) 2,6-Bis(1,1-dimethylethyl) [(E)-(2-ethyl-1,1-dioxo isothiazolidinylidene)methyl]phenol (S-2474), 5(R)-Thio sulfonamide-3(2H)-benzofuranone (SVT-2016) and N-[3-(Fonnyl-amino) oxo phenoxy-4H benzopyran yl] methanesulfonamide ("T-614"); or a pharmaceutically acceptable salt thereof.

[0254] Examples of suitable COX/5-LOX inhibitors are licofelone (ML-3000 or [2,2-dimethyl-6-(4-chlorophenyl)-7-phenyl-2,3,dihydro-1H-pyrrolizine-5-yl]-acetic acid), di-tert-butylphenols, such as (E)-(5)-(3,5-di-tert-butyl-4-hydroxybenzylidence)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474), darbufelone or tebufelone and pharmacologically active metabolites as well as derivatives such as dihydrodimethyl-benzofuran and PGV-20229, dihydro-dimethylbenzofuran, thiophene derived compounds such as RWJ-63556, N-hydroxy-N-methyl-4-(2,3-bis-(4-methoxyphenyl)-thiophen-5-yl)-butanamide (S19812), methoxytetrahydropyran derivatives, oxygenated xanthones such as 1,3,6,7-Tetrahydroxyxanthone (norathyriol)—pyrazole thiocarbamates, pyrazoles such as modified forms of phenidone containing compounds or the tri-flouro-benzole substituted pyrazoline derivative BW-755C, tepoxaline and derivatives and di-tert-butylpyrimidines.

[0255] It is contemplated that such combination therapy leads to an improved therapeutic response and/or an increased convenience for the individual, compared to said individual being treated without the composition or kit according to the invention.

[0256] In a further aspect, the i nvention relates to a method of reducing side effects associated with oral treatment of any of the conditions a-e and 1-5 listed above, in which method the active pharmaceutical ingredient for treating said condition is used in combination with one or more of the following agents:

[0257] a) an antacid such as 1) magnesium hydroxide, 2) magnesium trisilicate, 3) aluminium hydroxyde gel, 3) sodium hydrogencarbonate, 4) magaldrat or any combination of 1-5 and/or

[0258] b) a histamine H-2 antagonist such as 1) cimetidine, 2) ranitidine, 3) nizatidine, 4) famotidine, 5) roxatidine, 6) lafutadine or any combination of 1-6 and/or

[0259] c) a cytoprotective agent such as 1) sucralfate, 2) tripotassium dictitratobismuthate, 3) carbenoxolone, 4) prostaglandin E-2 analogues such as misoprostol, 5) ecabet, 6) cetraxate HCl, 7) teprenone, 8) troxipide, 9) dicyclomine hydrochloride, 10) sofalcon or any combination of 1-10 and/or

[0260] d) a proton pump inhibitor (PPI) such as 1) omeprazole, 2) esomeprazole, 3) lansoproazole, 4) pantoprazole, 5) rabeprazole, 6) CS-526/R-105266, 7) AZD 0865, 8) soraprazan or any combination of 1-8, and/or

[0261] e) an NSAID or a COX or a LOX inhibitor such as e.g. a COX-2 inhibitor or a COX/5-LOX inhibitor, and/or

[0262] f) pentoxifylline, e.g. at a dose range of from 400 to 800 mg/day.

[0263] In a specific embodiment, the active substance is a fumaric acid ester containing compound. In particular, the fumaric ester containing compound is any and all of the salts contained in Fumaderm® or Fumaraat® or Panaclar® (BG-12) or described in U.S. Pat. No. 6,277,882, U.S. Pat. No. 6,355,676 or U.S. Pat. No. 6,509,376 or a formulation according to the present invention. The active pharmaceutical ingredient may be provided in a formulation according to the present invention, or any Fumaderm® or Fumaraat® or Panaclar® formulation or as e.g. described in U.S. Pat. No. 6,277,882, U.S. Pat. No. 6,355,676 or U.S. Pat. No. 6,509,376.

[0264] It is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims. Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are encompassed within the invention, subject to any specifically excluded limit i n the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used i n the practice or testing of the present invention, the preferred methods and materials are described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. The patents and publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present i nvention is not entitled to antedate such patent or publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed. As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. The figures shown herein are not necessarily drawn to scale, with some components and features being exaggerated for clarity.

[0265] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

EXAMPLES

Example 1

Preparation of Tablets

[0266] 200 g granules are mixed with 150 g microcrystalline cellulose (e.g. Avicel® 102), 97.5 g lactose (e.g. Tablettose®), 10 g sodium carboxymethylcellulose (e.g. Ac-Di-Sol®) and 25 g starch for 30 min. Then 10 g magnesium stearate and 7.5 g amorphous silicium dioxide (e.g. Aerosil® 200) is added and the powder mixture is mixed for 5 min.

[0267] This powder mixture is compressed to tablets in tabletting equipment (tablet diameter 10 mm, surface about 280-300 mm^2). The tablets are enteric coated in a pan-coating or in a fluid-bed coating process as described in Example 4.

Example 2

Preparation of Tablets

[0268] 200 g micro-crystals are mixed with 150 g microcrystalline cellulose (e.g. kvicel® 102), 130 g lactose (e.g. Tablettose®), 10 g of sodium carboxymethylcellulose (e.g. Ac-Di-Sol®) and 25 mg starch for 30 min. Then 10 g magnesium stearate and 7.5 g of amorphous silicium dioxide is added and the powder mixture is mixed for 5 min. This powder mixture is compressed to tablets in tabletting equipment (tablet diameter 10 mm, surface about 280-300 mm^2). The tablets are enteric coated in a pan-coating or in a fluid-bed coating process as described in Example 4.

Example 3

Preparation of Capsules

[0269] Granules or micro-crystals are filled in HPMC capsules and these capsules are enteric coated as described in the following. In a pan coater Eudragit® L30D-55 is sprayed at drying temperatures of 60° C. to 80° C. onto the capsules in an amount of 20 mg polymeric material per mm^2. Pigments and talc are added in an appropriate amount.

Example 4

Enteric Coating of Tablets

[0270] In a pan coater Eudragit® L30D-55 is sprayed at drying temperatures of 60° C. to 80° C. onto the tablets in an amount of 6 mg polymeric material per mm^2. Pigments and talc are added in an appropriate amount.

Example 5

Preparation of Capsules

[0271] 156 mg of micro-crystals, prepared as described in Example 15, is filled in a hard-gelatine-capsule size 0. The capsules are enteric coated by dipping them into a solution of 5% HPMCP (Pharmacoat HP 50®) in acetone four times each capsule-side.

Example 6

Preparation of Granules

[0272] In a granulation process 50 g dimethylfumarate (in the following DMF) is mixed with 1 g ethyl cellulose (e.g. Ethocel® NF premium) which is dissolved in 10 ml ethanol 96%, passed through a sieve 1.0 mm and dried at 50° C. to 60° C. for 30 min. These granules are manufactured to tablets and capsules using the same process as described in Examples 1 a nd 3.

Example 7

Preparation of Granules

[0273] In a granulation process 50 g DMF is mixed with 1 g polyvinylacetate (PVA) (e.g. Kollicoat® SR30) which is dissolved in 10 ml ethanol 96%, passed through a sieve 1.00 mm and dried at 50° C. to 60° C. for 30 min.

Example 8

Preparation of Granules

[0274] In a granulation process 50 g DMF is mixed with 15 g of powdered Eudragit® RL 100. After adding an appropriate amount of 2-propanol and passing through a 1.00 mm sieve, the granules are dried at 60° C. These granules are manufactured to tablets and capsules using the same process as described in Examples 1 and 3.

Example 9

Preparation of Coated Granules

[0275] In a granulation process 50 g DMF is directly mixed with 5 g Eudragit® RL30D, passed through a sieve (1.00 mm) and dried at 80° C. After sieving the granules are coated in a fluid-bed coater (Mini-Glatt) with 15 g of a 1:1 mixture Eudragit® RL30D/RS30D. The coated granules can be manufactured to tablets and capsules using the same process as described in Examples 1 and 3.

Example 10

Preparation of Coated Granules

[0276] In a granulation process 50 g DMF is mixed with 20% ethyl cellulose (e.g. Ethocel® NF premium) which is dissolved in an appropriate amount of ethanol 96%. 15% polyethylene glycole 6000 are added to the granulation liquid. The mixture is passed through a sieve 1.00 mm and dried at 50° to 60° C. for 30 min. After sieving the granules are coated in a fluid-bed coated (Mini-Glatt) with a 2:1 mixture of ethyl cellulose and polyethylene glycole 6000 in an amount of 20 mg per mm^2 granules surface area. These granules can be manufactured to tablets or capsules using the processes described in Examples 1 and 3.

Example 11

Preparation of Coated Granules

[0277] In a granulation process 50 g DMF is mixed with 10% ethyl cellulose (e.g. Ethocel® NF premium) which is dissolved in an appropriate amount of ethanol 96%. 6% povidone (e.g. Kollidon® 25) is added to the granulation liquid. The mixture is passed through a sieve 1.00 mm and dried at 50° to 60° C. for 30 min. After sieving the granules are coated in a fluid-bed coated (Mini-Glatt) with a 3:2 mixture of ethyl cellulose and povidone in an amount of 20 mg per mm^2 granule surface area.

[0278] These granules can be manufactured to tablets or capsules using the processes described in Examples 1 and 3.

Example 12

Preparation of Coated Granules

[0279] In a granulation process 50 g DMF is mixed with 10% ethyl cellulose (e.g. Ethocel® NF premium) which is dissolved in an appropriate amount of ethanol 96%. 5% hydroxypropyl cellulose (HPC) (e.g. Klucel®) are added to the granulation liquid. The mixture is passed through a sieve 1.00 mm and dried at 50° to 60° C. for 30 min. After sieving, the granules are coated in a fluid-bed coater (mini-Glatt) with a 2:1 mixture of ethyl cellulose and HPC in an amount of 20 mg per mm^2 granule surface area.

[0280] These granules can be manufactured to tablets or capsules using the processes described in Examples 1 and 3.

Example 13

Preparation of Coated Granules

[0281] In a granulation process 50 g DMF is directly mixed with an appropriate amount of an aqueous dispersion of Eudragit® NE30D, passed through a sieve (1.00 mm) and dried at 80° C. After sieving the granules are coated in a fluid-bed coater (Mini-Glatt) with 15 g of a 1:1 mixture Eudragit® RL30D/RS30D. The coated granules can be manufactured to tablets and capsules using the processes described in Examples 1 and 3.

Example 14

Preparation of Coated Granules

[0282] In a granulation process 50 g DMF is directly mixed with an appropriate amount of an aqueous dispersion of Eudragit® RL30D, passed through a sieve (1.00 mm) and dried at 80° C. After sieving, the granules are coated in a fluid-bed coater (Mini-Glatt) with Eudragit® NE30D. The coated granules can be manufactured to tablets and capsules using the processes described in Examples 1 and 3.

Example 15

Preparation of Coated Micro-Crystals

[0283] A saturated solution of 50 g DMF in 300 ml 2-propanol is prepared at 60° C. and slowly cooled under permanent stirring. The precipitated crystals are filtered off and dried at 50° C. The crystals are sieved and the 315-710 μm fraction is used for a coating process in either a pan coater or a fluid-bed coater (Mini-Glatt). A coating solution of 12 g ethyl cellulose (e.g. Ethocel® NF premium) and 3 g polyethylene glycole 400 in 500 g ethanol is sprayed at 60° C. onto the powder surface. After drying, the coated crystals are sieved through a 1.00 mm sieve. These coated DMF crystals can be manufactured to tablets and capsules using the processes described in Examples 2 and 3.

Example 16

Preparation of Tablets

[0284] In a granulation process 50 g DMF is mixed with 12 g Ethylcellulose (e.g. Ethocel® NF premium) and 3 g Polyethylenglycole 400 which is dissolved in 150 ml Ethanol 96%, passed through a 1.0 mm sieve, dried at 50° to 60° C. over 30 min and again passed through a sieve 1.0 mm. A placebo granulate is prepared as follows: Tablettose® and Avicel® 102 are mixed in equal shares and granulated with 2% povidone (e.g. Kollidon® 25) dissolved in water (q.s.), passed through a 1.0 mm sieve, dried at 50° to 60° C. over 30 min and again passed through a 1.0 mm sieve. 60 parts of the DMF-granulate and 38 parts of the placebo-granulate are mixed for 30 minutes in a Turbula Shaker Mixer. One part Aerosil® 200 and one part magnesium stearate are added and the blend is mixed again for 5 minutes. The blend is compressed to tablets with a diameter of 10 mm, a weight of about 260 mg and a hardness of about 50 N. The tablets are enteric coated using the processes described in Example 4.

Example 17

Preparation of Tablets

[0285] In a granulation process 50 g DMF is mixed with 12 g Ethylcellulose (e.g. Ethocel® NF premium) and 3 g Polyethylenglycole 400 which is dissolved in 150 ml Ethanol 96%, passed through a 1.0 mm sieve, dried at 50° to 60° C. over 30 min and again passed through a sieve 1.0 mm. A placebo granulate is prepared as follows: Tablettose® and Avicel® 102 are mixed in equal shares and granulated with 2% povidone (e.g. Kollidon® 25) dissolved in water (q.s.), passed through a 1.0 mm sieve, dried at 50° to 60° C. over 30 min and again passed through a 1.0 mm sieve. 60 parts of the DMF-granulate and 37 parts of the placebo-granulate are mixed for 30 minutes in a Turbula Shaker Mixer. One part carboxymethylcellulose (e.g. Ac-Di-Sol®), one part Aerosil® 200 and one part magnesium stearate are added and the blend is mixed again for 5 minutes.

[0286] The blend is compressed to tablets with a diameter of 10 mm, a weight of about 260 mg and a hardness of about 50 N. The tablets are enteric coated using the processes described in Example 4.

Example 18

Preparation of Coated Micro-Crystals

[0287] A saturated solution of 50 g DMF in 300 ml 2-propanol is prepared at 60° C. and slowly cooled under permanent stirring. The precipitated crystals are filtered off and dried at 50° C. The crystals are sieved and the 315-710 μm fraction is used for a coating process in either a pan coater or a fluid-bed coater (Mini-Glatt). A coating solution of 12 g ethyl cellulose (e.g. Ethocel® NF premium) and 3 g povidone (PVP) in 500 g ethanol is sprayed at 60° C. onto the surface of the crystals. After drying the coated crystals are sieved through a 1.00 mm sieve.

[0288] The coated DMF crystals can be manufactured to tablets and capsules using the processes described in Example 2 and 3.

Example 19

Preparation of Coated Micro-Crystals

[0289] A saturated solution of 50 g DMF in 300 ml 2-propanol is prepared at 60° C. and slowly cooled under permanent stirring. The precipitated crystals are filtered off and dried at 50° C. The crystals are sieved and the 315-710 μm fraction is used for a coating process in either a pan coater or a fluid-bed coater (Mini-Glatt). A coating solution of 12 g ethyl cellulose (e.g. Ethocel® NF premium) and 3 g hydroxylpropylcellulose (HPC) in 500 g ethanol is sprayed at 60° C. onto the powder surface. After drying the coated crystals are sieved through a 1.00 mm sieve. These coated DMF crystals can be manufactured to tablets and capsules using the processes described in Examples 2 and 3.

Example 20

Preparation of Micro-Crystals

[0290] DMF-crystals are prepared as described in Example 15, but 2% of ethyl cellulose, related to the mass of the crystals, is added directly to the 2-propanol before precipitation of the crystals.

Example 21

Preparation of Coated Micro-Crystals

[0291] 50 g DMF crystals prepared as described in Example 15 are coated in a fluid-bed coater (Mini-Glatt) at a temperature of 80° C. with 20 g of an aqueous dispersion of a 1:1 mixture of Eudragit® RL30D/RS30D. These coated DMF crystals are manufactured to tablets and capsules using the processes described in Examples 2 and 3.

Example 22

Preparation of Tablets

[0292] DMF crystals prepared as described in Example 15 are directly mixed with 25% solid Eudragit® RS PO/RL PO in a ratio of 1:2 and manufactured to tablets as described in Example 2.

Example 23

Preparation of Coated Micro-Crystals

[0293] DMF crystals prepared as described in Example 15 are coated in a fluid-bed coater (Mini-Glatt) with an amount of 5% (related to the mass of the crystals) aqueous dispersion of polyvinyl acetate (e.g. Kollicoat® SR 30D). These coated DMF crystals can be manufactured to tablets and capsules using the processes described in Examples 2 and 3.

Example 24

Preparation of Granules

[0294] In a granulation process, 50 g DMF is mixed with 15% ethyl cellulose (e.g. Ethocel® NF premium) which is dissolved in an appropriate amount of ethanol 96%. 10% polyethylene glycole 6000 is added to the granulation liquid. The mixture is passed through a sieve 1.00 mm and dried at 50° to 60° C. for 30 min. These granules can be manufactured to tablets or capsules using the processes described in Examples 1 and 3.

Example 25

Preparation of Granules

[0295] In a granulation process, 50 g diethylfumarate (DEF) is mixed with 15% ethyl cellulose (e.g. Ethocel® NF premium) which is dissolved in an appropriate amount of ethanol 96%. 10% polyethylene glycole 6000 is added to the granulation liquid. The mixture is passed through a sieve 1.00 mm and dried at 50° to 60° C. for 30 min. These granules can be manufactured to tablets or capsules using the processes described in Examples 1 and 3.

Example 26

Preparation of Tablets

[0296] A granulate is prepared as described in Example 24 but instead of PEG 6000, 10% of povidone (e.g. Kollidon® 25) is added. This mixture can be manufactured to tablets or capsules using the processes described in Examples 1 and 3.

Example 27

Preparation of Tablets

[0297] A granulate is prepared as described in Example 24 but instead of PEG 6000, 10% hydroxyl propyl methylcellulose is added. This mixture can be manufactured to tablets or capsules using the processes described in Examples 1 and 3.

Example 28

[0298] 50 g DMF crystals prepared as described in Example 15 are coated in a fluid-bed coater (Mini-Glatt) at a temperature of 80° C. with 20 g of an aqueous dispersion of a 1:1 mixture of Eudrag it® RL30D/RS30D. The coated crystals are enteric coated in a pan coater as described in the following. Eudragit® L30D-55 are sprayed at drying temperatures of 60° C. to 80° C. onto the coated crystals in an amount of 6 mg polymeric material per mm^2

[0299] These double coated DMF crystals are either filled into hard gelatine or soft gelatine capsules or manufactured to tablets using the process described in Example 2.

Example 29

Preparation of Tablets

[0300] In a granulation process 50g DMF is mixed with 12 g Ethylcellulose (e.g. Ethocel® NF premium) and 3 g hydroxypropyl cellulose (e.g. Klucel®) which is dissolved in 150 ml Ethanol 96%, passed through a sieve 1.0 mm, dried at 50° to 60° C. over 30 min and again passed through a sieve 1.0 mm.

[0301] Tablettose® and Avicel® 102 are mixed in equal shares and granulated with 2% povidone (Kollidon® 25) dissolved in water (q.s.). 60 parts of the DMF-granulate and 38 parts of the placebo-granulate are mixed for 30 minutes in a Turbula Shaker Mixer. One part Aerosil® 200 and one part magnesium stearate are added and the blend is mixed again for 5 minutes.

[0302] The blend is compressed to tablets with a diameter of 10 mm, a weight of about 260 mg and a hardness of about 50 N. The tablets are enteric coated using the process described in Example 4.

Example 30

Determination of pH Controlled Release Dissolution Profile of Capsules

[0303] The dissolution profile is determined as described in the United States Pharmacopoeia using a rotating basket with 6 so called Levy-glasses with a capacity of 1 liter and 6 basket stirring elements powered by an electric motor (at 100 rpm). The Levy-glasses are filled with 0.1N HCl (the water bath has a temperature of 37° C+/−0.5° C.) and the capsules are applied to the baskets. After 2 hours, the acid is removed from the vessels and replaced with dissolution medium (USP phosphate buffer, pH 6.5) and tested for another 6 hours. Samples (5ml) are taken after 0, 60 and 120 minutes from the acid medium, and after 30, 60, 90, 120, 180, 240, 300 and 360 minutes from the buffer medium after replacing the dissolution medium with USP buffer. Instead of replacing the amount of drawn buffer solution after each sample, the loss of buffer is taken into account when calculating the amount of released DMF. The amount of DMF is determined by HPLC (Kontron XXX) using a Merck LiChroCART RP8 5 μM, 20 cm column, tempered at 25° C. The mobile phase consists of a mixture (35:65) of acetonitrile and 0.0725 mol/l $NaH_2PO_4*H_20$-buffer adjusted to pH 3.2 with phosphoric acid. The UV detector is set at a wavelength of 230 nm and a flow rate of 1.0 ml per minute. The DMF peak is detectable after a retention time of about 5 min.

Example 31

Determination of pH Controlled Release Dissolution Profile of Non-Enteric Coated Tablets

[0304] The dissolution profile is determined using 6 so called Levy-glasses with a capacity of 1 liter and 6 paddles as stirring elements powered by an electric motor. The rotating speed of the paddles is 100 rpm. The Levy-glasses are filled with USP phosphate buffer, pH 6.5 (the water bath

has a temperature of 37° C+/−0.5° C.) and the tables are into the Levy-glasses. Samples (5ml) are taken after 0, 30, 60, 90, 120, 180, 240, 300 and 360 minutes from the buffer medium after replacing the dissolution medium with USP buffer. Instead of replacing the amount of drawn buffer solution after each sample, the loss of buffer is taken into account when calculating the amount of released DMF. The amount of DMF is determined by HPLC (Kontron XXX) using a Merck LiChroCART RP8 5 μM, 20 cm column, tempered at 25° C. The mobile phase consists of a mixture (35:65) of acetonitrile and 0.0725 mol/l $NaH_2PO_4*H_20$-buffer adjusted to pH 3.2 with phosphoric acid. The UV detector is set at a wavelength of 230 nm and a flow rate of 1.0 ml per minute. The DMF peak is detectable after a retention time of about 5 min.

Example 32

[0305] The dissolution profile of capsules prepared as described in Example 5 is determined as described in Example 30. The dissolution profile is shown in FIG. **1**.

Example 33

[0306] The dissolution profile of the tablets (before the enteric coating is applied) prepared as described in example 16 is determined as described in Example 31. The dissolution profile is shown in FIG. **2**.

Example 34

[0307] The dissolution profile of the tablets (before the enteric coating is applied) prepared as described in example 17 is determined as described in Example 31. The dissolution profile is shown in FIG. **3**.

1-90. (canceled)

91-93. (canceled)

94. An oral pharmaceutical composition comprising (i) dimethylfumarate, (ii) one or more enteric coating polymers, and (iii) one or more pharmaceutically acceptable excipients, said composition being capable of providing controlled release in vivo in humans, wherein said dimethylfumarate is present in an amount of 50-90%, by weight, of said composition.

95. The composition of claim **94**, wherein said composition is in a tablet form.

96. The composition of claim **94**, wherein said composition is contained in a capsule.

97. The composition of claim **96**, wherein said composition is in the form of micro tablets.

98. The composition of claim **96**, wherein said composition is in the form of pellets or beads.

99. The composition of claim **96**, wherein said composition is in the form of granules.

100. The composition of claim **96**, wherein said composition is in the form of micro-crystals.

101. The composition of claim **94**, wherein said dimethylfumarate is present in an amount of 50-60%, by weight, of said composition.

102. The composition of claim **94**, wherein said dimethylfumarate is present in an amount of 50-80%, by weight, of said composition.

103. The composition of claim **94**, wherein said composition comprises a layer containing said one or more enteric coating polymers.

104. The composition of claim **101**, wherein said composition comprises a layer containing said one or more enteric coating polymers

105. The composition of claim **102**, wherein said composition comprises a layer containing said one or more enteric coating polymers.

106. The composition of claim **95**, wherein said tablet comprises a layer containing said one or more enteric coating polymers.

107. The composition of claim **97**, wherein said micro tablets comprise a layer containing said one or more enteric coating polymers.

108. The composition of claim **98**, wherein said pellets or beads comprise a layer containing said one or more enteric coating polymers.

109. The composition of claim **99**, wherein said granules comprise a layer containing said one or more enteric coating polymers.

110. The composition of claim **100**, wherein said micro-crystals comprise a layer containing said one or more enteric coating polymers.

111. The composition of claim **94**, wherein said one or more enteric coating polymers comprises polyacrylamides, phthalate derivatives, acid phthalates of carbohydrates, amylose acetate phthalate, cellulose acetate phthalate, cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate, hydroxypropylethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, methylcellulose phthalate, polyvinyl acetate phthalate, poly acrylic methacrylic acid copolymers, shellac, or vinyl acetate and crotonic acid copolymers.

112. The composition of claim **111**, wherein said one or more enteric coating polymers is a poly acrylic methacrylic acid copolymer.

113. An oral pharmaceutical composition consisting of (i) dimethylfumarate, (ii) one or more enteric coating polymers, and (iii) one or more pharmaceutically acceptable excipients, said composition being capable of providing controlled release in vivo in humans, wherein said dimethylfumarate is present in an amount of 50-90%, by weight, of said composition.

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