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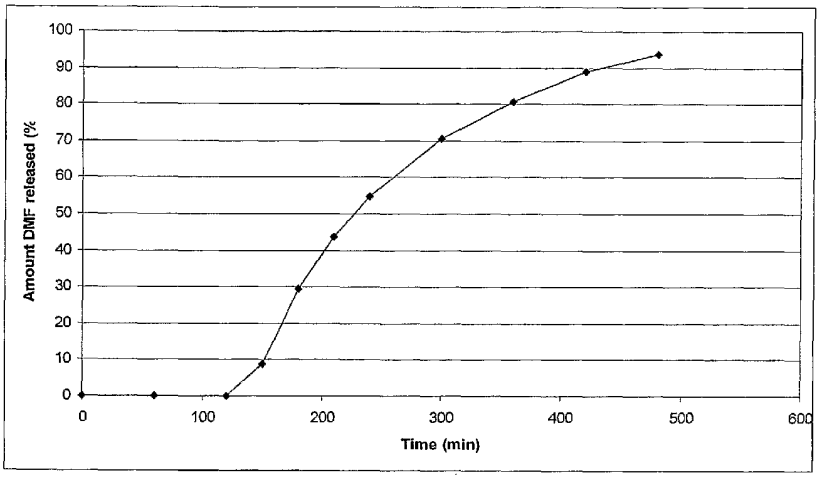
(54) Title: CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS COMPRISING A FUMARIC ACID ESTER



(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.

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CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS COMPRISING A FUMARIC ACID ESTER

Field of the invention

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

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

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.

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 dimethylfumarate 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.

US 6,277,882 and US 6,355,676 disclose respectively the use 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. US 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. US 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.

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.

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.

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.

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 contemplated 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

Fig. 1 shows an example of an in vitro dissolution profile of a capsule prepared as described in example 5.

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.

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

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.

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