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(54) Title: NOVEL ORAL DOSAGE FORMS OF DIMETHYL FUMARATE

(57) Abstract: The present invention relates to granulates of Dimethyl fumarate comprising of gastro resistant or enteric polymers and other excipients. The invention also relates to novel oral dosage forms of Dimethyl fumarate comprising an admixture of Dimethyl fumarate and excipients filled in an enteric coated capsule.

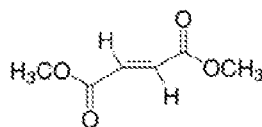


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Complete specification

Background of the invention

Dimethyl fumarate, also known as DMF, is the Dimethyl ester of fumaric acid. The compound has a molecular weight of 144.13 daltons and the following chemical structure:



DMF is also known by the names Dimethyl (E)-butenedioate (IUPAC), trans-1,2-ethylenedicarboxylic acid dimethyl ester and (E)-2-Butenedioic acid dimethyl ester. DMF is typically synthesized by reacting fumaric acid with excess methanol in the presence of an acid catalyst. DMF can also be synthesized according to the methods described in Chinese Patent Publication CN 101318901A.

Fumaric acid esters, i.e. Dimethylfumarate in combination with ethylhydrogen fumarate have been used in the treatment of psoriasis for many years. The combination is marketed as Fumaderm[®] enteric coated tablets in 105mg and 215mg strengths.

Compositions comprising dialkyl fumarates and/or alkyl hydrogen fumarates are known in the art. E.P. patent 0,188,749 discloses fumaric acid derivatives and compositions comprising the same for the treatment of psoriasis. U.S. patent 4,959,389 discloses compositions comprising salts of monoalkyl fumarates alone or in combination with dialkyl fumarates. GB patent 1,153,927 relates to medical compositions comprising dimethylmaleic anhydride and/or dimethylmaleic acid and/or dimethylfumaric acid compounds.

DE patent 3,834,794 discloses pharmaceutical preparations comprising one or more fumaric acid derivatives in the form of e.g. hard gelatin capsules filled with a granulate of said derivatives made in a conventional way with a granulation material.

U.S. patents 6,277,882 and 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 Crohn's disease. U.S. patents 6,509,376; 7,320,999 and 7,803,840 disclose 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 micropellets.

The formulations of DMF described in the prior art for e.g. microtablets and micropellets lead to the requirement of expensive manufacturing procedures. DMF is known to cause allergic reactions resulting in eczema and sofa dermatitis and the like. This makes the manufacturing of such dosage forms even more expensive and time-consuming due to the elaborate precautions that need to be followed in manufacturing. Hence there is a need to develop alternative formulations of Dimethyl fumarate. The present invention addresses this need.

Summary of the Invention

One aspect of the present invention provides granulates comprising Dimethylfumarate, one or more enteric polymers and optionally other excipients.

Another aspect of the invention involves providing tablet or capsule dosage forms comprising of granulates. The dosage forms may further be enteric coated.

Another aspect of the invention relates to a method of manufacturing the Dimethylfumarate granulates.

Yet another aspect of the invention relates to Dimethylfumarate blend comprising of Dimethylfumarate and other pharmaceutically acceptable excipients.

Yet another aspect of the invention involves providing tablet or capsule dosage forms with the Dimethylfumarate blend compositions.

Yet another aspect of the invention relates to the manufacturing process for making the said blend compositions.

Detailed description of the Invention

The term "compact" means a compressed composition comprising Dimethyl fumarate and one or more excipients. The Dimethyl fumarate and excipients can be homogeneously or heterogeneously mixed in the compact.

The term "granulation" refers to the act or process in which primary powder particles are made to adhere using the help of a binder to form larger, multiparticle entities called granules.

The term "Dimethylfumarate" encompasses any particulate form of dimethyl fumarate. It may be a crystalline or an amorphous particle and may be produced by any conventional method such as crystallization, precipitation, spray drying, etc.

The term "enteric polymer" and "gastro resistant polymer" are used interchangeably within the specification and cover polymers that allow majority release of dimethyl fumarate active substance in the intestines; and the release is minimized in stomach environment. The desired release rate in the intestines may be modulated by choosing the right combination of enteric polymer(s), amount of the enteric polymer, relative thickness of the coating layer and optionally, by the inclusion of other excipients.

The formulation of the present invention is intended to have the following release characteristics:

Not more than 10% released in 120 minutes in 0.1N HCl:

Not less than 85% (Q) released after 10 minutes, when the acid medium exposed formulations are subsequently tested for dissolution in pH 6.8 buffer medium

The granule compositions of Dimethylfumarate of the present invention comprise:

- (i) Dimethyl fumarate

- (ii) One or more enteric polymers, and optionally
- (iii) Other excipients

The invention further comprises one or more excipients selected from the group consisting of a filler (or a binder), glidants, flow control agents, disintegrants, lubricants, surfactants, anti-oxidants, preservatives, pH adjusting agents, solubilizers, emulsifiers, plasticizers, pH sensitive polymers or any combination thereof. The number of excipients that can be included in a composition is not limited.

One embodiment of the invention relates to a Dimethylfumarate granule composition comprising:

- (i) Dimethyl fumarate
- (ii) One or more enteric polymers, and any of the excipients selected from
 - (a) Fillers
 - (b) Binders and
 - (c) Lubricants

Another embodiment of the invention relates to a Dimethylfumarate granule composition comprising:

- (i) Dimethyl fumarate
- (ii) One or more enteric polymers selected from the group consisting of methacrylate copolymers, hypromellose phthalate, cellulose acetate phthalate, hypromellose acetate succinate.
- (iii) Fillers selected from microcrystalline cellulose, silicified microcrystalline cellulose, sugars, polysaccharides or mixtures thereof
- (iv) Disintegrants selected from crospovidone, sodium starch glycolate, croscarmellose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch.
- (v) Lubricants and glidants selected from colloidal silicon dioxide, maize starch, talc, magnesium stearate, calcium stearate, sodium stearyl fumarate.

Another embodiment of the invention comprises Dimethylfumarate blend composition comprising:

- (i) Dimethyl fumarate
- (ii) fillers selected from microcrystalline cellulose, silicified microcrystalline cellulose, sugars, polysaccharides or mixtures thereof
- (iii) lubricants and glidants selected from colloidal silicon dioxide, maize starch, talc, magnesium stearate, calcium stearate, sodium stearyl fumarate and
- (iv) optionally other pharmaceutically acceptable excipients such as disintegrants and the like.

In one of the preferred embodiments, the granulates or the blend composition may be compressed to form tablets. These tablets may further be enteric coated using any of the known enteric polymers.

In another embodiment, the granulates or the blend composition may be filled into hard gelatin or HPMC capsules. These capsules may further be provided with enteric coating. Alternately, the granulates or the blend composition may be filled into commercially available acid resistant capsules and optionally capsules may further be provided with enteric coating(s).

The enteric polymer for purposes of the present invention is a polymer, which dissolves at a pH of 5 or above.

Non-limiting examples of suitable pH-dependent entero-resistant polymers useful in the present invention include, polymethacrylates (for instance a copolymer of methacrylic acid and methyl methacrylate or a copolymer of methacrylic acid and ethylacrylate), hydroxypropyl methyl cellulose acetate succinate (HPMC-AS), hydroxypropyl methyl cellulose phthalate (HPMC- P), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), shellac and mixtures thereof. Examples of suitable commercially available polymers of this kind are Eudragit(R) L, Eudragit(R) S and Eudragit(R) FS and other brand-name equivalents thereof such as Eastacryl(R) 30D and Kollicoat(R)

30. Suitable commercially available hydroxypropyl methyl cellulose phthalate polymers are hypromellose phthalate HP-55, hypromellose phthalate HP-55S, hypromellose phthalate HP-50 and the like.

Examples of fillers include, but are not limited to sucrose, glucose, lactose, mannitol, xylitol, dextrates, dextrin, dextrose, trehalose, erythritol, ethylcellulose, fructose, glyceryl palmitostearate, hydrogenated vegetable oil type I, isomalt, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltodextrin, polydextrose, cellulose, cellulose acetate, microcrystalline cellulose, coprocessed microcrystalline celluloses (such as various grades of Avicel), silicified microcrystalline cellulose, maltose, sorbitol, calcium phosphate, calcium sulphate, carrageenan, chitosan, pectinic acid, sodium alginate, magnesium aluminium silicate, calcium carbonate, calcium phosphate, calcium sulfate and the like.

Examples of binders include, but are not limited to, celluloses such as microcrystalline cellulose, modified celluloses (such as low substituted hydroxypropyl cellulose, hydroxypropyl cellulose (or HPC), hydroxypropyl methylcellulose (or HPMC or hypromellose), hydroxyethylcellulose, hydroxyethyl methylcellulose, ethyl cellulose, cellulose gum, xanthan gum, sugars (such as sucrose, glucose, amilose, maltodextrin, dextrose and the like), starches such as corn or potato starch partially pregelatinized starches (such as Starch 1500), copovidone, cross-linked polyvinylpyrrolidone, acrylic acid polymer (Carbopol), poloxamer, polycarbophil, polyethylene glycol or a combination thereof.

Examples of disintegrants include, but are not limited to starches, hydroxypropyl starch, partially pregelatinized starches, sodium starch glycolate, pregelatinized starch, alginic acid, calcium alginate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, powdered cellulose, chitosan, croscarmellose sodium, polyvinylpyrrolidones, including modified polyvinylpyrrolidones such as crospovidone, docusate sodium, guar gum, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, magnesium aluminum silicate, methylcellulose, polacrilin potassium, povidone, sodium alginate or a combination thereof.

Examples of glidants include, but are not limited to, calcium phosphate, calcium silicate, powdered cellulose, magnesium stearate, magnesium trisilicate, silicon dioxide, talcum and colloidal silica, and colloidal silica anhydrous.

Examples of lubricants include, but are not limited to, canola oil, hydroxyethyl cellulose, lauric acid, leucine, mineral oil, poloxamers, polyvinyl alcohol, oxyldodecanol, sodium hyaluronate, sterilizable maize starch, triethanolamine, calcium stearate, magnesium stearate, glycerin monostearate, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type I, light mineral oil, magnesium lauryl sulfate, medium-chain triglycerides, mineral oil, myristic acid, palmitic acid, poloxamer, polyethylene glycol, potassium benzoate, sodium benzoate, sodium lauryl sulfate, stearic acid, talc and zinc stearate.

Solvents for applying the coating materials include, but not limited to, water, acetone, hexane, ethanol, methanol, propanol, isopropanol, butanol, isobutanol, sec-butanol, tert-butanol, dichloromethane, trichloromethane, chloroform, and the like.

The manufacturing process for making the granulates comprises of the following steps:

- (i) Admixing Dimethylfumarate with excipients such as fillers, disintegrants
- (ii) Granulating using a solvent in which enteric polymer is dissolved
- (iii) Subsequently processing the wet mass into granulates using any known granulation technique

The granulates may also be made by dry compaction or slugging process. The granulates, thus obtained can be filled into capsules or compressed into tablets.

The manufacturing process for making the blend composition comprises

- (i) Co-sifting Dimethylfumarate with other excipients
- (ii) Admixing Dimethylfumarate with excipients such as fillers and other excipients.

The blend, thus obtained can be filled into HPMC capsules or acid resistant capsules or compressed into tablets. These tablets/capsules may further be enteric coated using any of the known enteric polymers.

Coatings can be applied by any known means, including spraying. In some embodiments, the compositions are coated or partially coated with one or more seal coatings, for example one, two, three or more seal coatings. In some embodiments, the compositions are coated or partially coated with one or more enteric coatings, for example one, two, three or more enteric coatings. In some embodiments, the compositions are coated with one or more seal coatings and one or more enteric coatings. In some embodiments, the compositions are coated with one seal coating and one enteric coating. Alternatively dry coating can also be used.

The present invention also provides a process for the preparation of highly pure Dimethyl fumarate with a particle less than 1000 μ m. The process of the invention provides Dimethyl fumarate having a particle size wherein at least 90% of the particles have a particle size of less than 1000 μ m. Suitable conventional methods such as jet milling or any suitable techniques are employed to get desired particle size.

The following examples further describe certain specific aspects and embodiments of the present invention and demonstrate the practice and advantages thereof. It is to be understood that the examples are given by way of illustration only and are not intended to limit the scope of the invention in any manner.

Examples

Example 1

S.No	Ingredient	Formula 1	Formula 2	Formula 3	Formula 4	Formula 5
		Qty/Capsule (mg)	Qty/Capsule (mg)	Qty/Capsule (mg)	Qty/Capsule (mg)	Qty/Capsule (mg)
1	Dimethyl fumarate	240	240	240	240	240
2	Microcrystalline Cellulose	q.s. 455	q.s. 455	q.s. 455	q.s. 455	q.s. 455
3	Sodium starch	40	40	40	40	40

	glycolate					
4	Hypromellose	15	15	15	15	15
5	Talc	3.0	3.0	3.0	3.0	3.0
6	Colloidal silicon dioxide	3.0	3.0	3.0	3.0	3.0
7	Magnesium stearate	2	2	2	2	2
Granulating agent						
1	Triethyl citrate	0.836	0.836	0.836	0.836	0.836
2	Cellulose acetate Pthalate	40	-	-	-	-
3	Hypromellose phthalate	-	40	-	-	-
4	Hypromellose acetate succinate	-	-	40	-	-
5	Methacrylate copolymer A	-	-	-	40	-
6	Methacrylate copolymer B	-	-	-	-	40
7	Solvent mixture	q.s. to prepare 8% (w/w)	q.s. to prepare 8% (w/w)	q.s. to prepare 8% (w/w)	q.s. to prepare 8% (w/w)	q.s. to prepare 8% (w/w)

Manufacturing process:

1. All Intragranular Excipients (Microcrystalline Cellulose, sodium starch glycolate, colloidal silicon dioxide, hypromellose) and Dimethyl Fumarate were cosifted through the sieve #40.
2. Granulating solution was prepared by dissolving enteric polymer (separately for each formula) and triethyl citrate in solvent mixture.
3. The cosifted Mixture in step 1 was granulated using granulating mixture prepared in step 2 and the wet mass was passed from sieve #10.
4. The granules of step 3 were dried at 40°C till desired moisture content is achieved
5. Magnesium stearate and talc were cosifted through sieve #40 and added to the above dried granules and blended for 3 minutes.
6. Final blended granules were then filled into acid resistant capsules.

Example 2

S.No	Ingredient	Qty/Cap (mg)	Qty/Cap (mg)	Qty/Cap (mg)	Qty/Cap (mg)
1	Dimethyl fumarate	240	120	360	480
2	Microcrystalline cellulose	92.7	212.7	74	44
3	Silicified Microcrystalline cellulose	107.0	107.0	110.5	40.5
4	Talc	5.3	5.3	8.0	8.0
5	Colloidal silicon dioxide	3	3	4.5	4.5
6	Magnesium stearate	2	2	3.0	3.0
Total weight		450	450	560	580
Coating composition for capsules					
1	Triethyl citrate	0.836	0.836	0.836	0.836
2	Methacrylate copolymer A	35	35	35	35
3	Solvent mixture	q.s to 12% (w/w)	q.s to 12% (w/w)	q.s to 12% (w/w)	q.s to 12% (w/w)

Manufacturing process:

1. Dimethyl Fumarate of desired particle size and microcrystalline cellulose were cosifted from sieve 60#.
2. The cosifted material was added to silicified microcrystalline cellulose, talc, colloidal silicon dioxide and magnesium stearate and blended for 3 minutes in an octagonal blender.
3. The blend obtained in step 2 was filled in HPMC capsules.
4. Coating solution of 12% w/w was prepared by dissolving methacrylate copolymer A and triethyl citrate in solvent mixture.
5. The filled capsules were coated with the above prepared 12% w/w coating solution till 5% weight gain was obtained.

Example 3

S.No.	Ingredient	Qty/Capsule(mg)
1	Dimethyl fumarate	240

2	Microcrystalline cellulose	q.s. 450
3	Silicified microcrystalline cellulose	107
4	Talc	5.3
5	Colloidal silicon dioxide	3.0
6	Magnesium stearate	2
Coating composition for Capsules		
1	Triethyl citrate	0.836
2	Cellulose acetate Pthalate	40
3	Solvent mixture	qs to prepare 8% (w/w)

Manufacturing process:

1. Dimethyl Fumarate and microcrystalline cellulose were cosifted from sieve 60#.
2. The cosifted material was added to silicified microcrystalline cellulose, talc, colloidal silicon dioxide and magnesium stearate and blended for 3 minutes in an octagonal blender.
3. The blend obtained in step 2 was filled in HPMC capsules.
4. Coating solution of 8% w/w was prepared by dissolving cellulose acetate pthalate and triethyl citrate in solvent mixture.
5. The filled capsules were coated with the prepared 8% w/w coating solution till 6% weight gain was obtained.

Example 4

S.No	Ingredient	Qty /Capsule (mg)
Capsule composition		
1	Dimethyl fumarate	240
2	Microcrystalline cellulose	24
3	Croscarmellose sodium	15
4	Crospovidone	25
5	Magnesium stearate	2
6	Colloidal silicon dioxide	2
7	Talc	2

Total weight		310
Primary Coating Composition		
8	Eudragit L100 (Methacrylate Copolymer A)	qs
Secondary coating composition		
9	Eudragit L30D55 (Methacrylate copolymer B dispersion)	qs

Manufacturing process

1. Dimethyl fumarate, microcrystalline cellulose, croscarmellose sodium and crospovidone were cosifted from sieve 60#.
2. The cosifted material was added to talc, colloidal silicon dioxide and magnesium stearate and blended for 3 minutes.
3. The obtained blend was filled in acid resistant capsules.
4. The obtained capsules were coated with primary and secondary coatings as mentioned in composition.

Dimethyl fumarate formulation prepared according to the invention (Example 4) was tested for stability under accelerated conditions. Tecfidera (Reference listed drug) capsules were (Batch No. P12020) considered as the reference product for comparative stability study. Comparative stability data of the invention formulation with the reference product is summarized in table 1. Percentage of total impurities present in the invention formulation was comparable with that of the reference product.

Table 1: Comparative stability data of invention formulation with Reference product

Comparison of stability data of Invention formulation with Reference Product					
Product	Stability conditions		Related Substances		
			Fumaric Acid	Mono methyl fumarate	Total Impurities
Invention formulation	25°C	1M	ND	0.03	0.03
		3M	ND	0.08	0.08
		6M	ND	0.09	0.09
	40°C	1M	ND	0.04	0.04
		3M	ND	0.12	0.2

		6M	0.12	0.13	0.3
Tecfidera	25°C	1M	0.01	0.1	0.11
		3M	ND	0.15	0.15
		6M	ND	0.14	0.14
		1M	0.02	0.15	0.17
	40°C	3M	ND	0.22	0.23
		6M	ND	0.21	0.22

ND: Not detectable

Example 5

S.No	Ingredient	Qty/Capsule (mg)
Capsule Composition		
1	Dimethyl fumarate	240
2	Microcrystalline Cellulose	74
3	Croscarmellose sodium	15
4	Crospovidone	25
5	Magnesium Stearate	2
6	Colloidal Silicon dioxide	2
7	Talc	2
Total weight		360
Primary Coating Composition		
8	Eudragit L100	qs
Secondary Coating Composition		
9	Eudragit L 100 D 55 (Acryl Eze ®)	qs

Manufacturing process

1. Dimethyl fumarate, microcrystalline cellulose, croscarmellose sodium and crospovidone were cosifted from sieve 60#.
2. The cosifted material was added to talc, colloidal silicon dioxide and magnesium stearate and blended for 3 minutes in an octagonal blender.
3. The blend obtained in step 2 was filled in acid resistant capsules.
4. The obtained capsules were coated with the coating material as mentioned.

Example 6

S.No	Ingredient	Qty /Capsule (mg)
Capsule Composition		
1	Dimethyl fumarate	240
2	Microcrystalline Cellulose	74
3	Croscarmellose sodium	15
4	Crospovidone	25
5	Magnesium Stearate	2
6	Colloidal Silicon dioxide	2
7	Talc	2
Total weight		360
Primary Coating Composition		
8	Eudragit L30D55 (Methacrylate Copolymer B dispersion)	qs
Secondary Coating Composition		
9	Eudragit L100 (Methacrylate Copolymer A)	qs
Tertiary Coating Composition		
10	Opadry Green	qs

Manufacturing process

1. Dimethyl fumarate, microcrystalline cellulose, croscarmellose sodium and crospovidone were cosifted from sieve 60#.
2. The cosifted material was added to talc, colloidal silicon dioxide and magnesium stearate and blended for 3 minutes.
3. The blend obtained in step 2 was filled in acid resistant capsules.
4. The obtained capsules were coated with primary, secondary and tertiary coatings as mentioned.

Example 7

S.No	Ingredient	Qty /Capsule (mg)
Capsule Composition		
1	Dimethyl fumarate	240

2	Microcrystalline cellulose	74
3	Croscarmellose sodium	15
4	Crospovidone	25
5	Magnesium stearate	2
6	Colloidal silicon dioxide	2
7	Talc	2
Total weight		360
Primary Coating Composition		
8	Eudragit L 100 D 55 (Acryl Eze ®)	qs
Secondary coating composition		
9	Eudragit L100 (Methacrylate Copolymer A)	qs
Tertiary coating composition		
10	Opadry Green	qs

Manufacturing process

1. Dimethyl fumarate, microcrystalline cellulose, croscarmellose sodium and crospovidone were cosifted from sieve 60#.
2. The cosifted material was added to talc, colloidal silicon dioxide and magnesium stearate and blended for 3 minutes.
3. The blend obtained in step 2 was filled in acid resistant capsules.
4. The obtained capsules were coated with primary, secondary and tertiary coatings as mentioned.

We Claim:

1. A pharmaceutical composition in the form of granules comprising:
 - (i) Dimethylfumarate
 - (ii) Enteric polymers, and optionally
 - (iii) One or more excipients
2. The composition of claim 1 comprising
 - (i) Dimethyl fumarate
 - (ii) One or more enteric polymers selected from the group consisting of methacrylate copolymers, hypromellose phthalate, cellulose acetate phthalate, hypromellose acetate succinate;
 - (iii) Fillers selected from microcrystalline cellulose, silicified microcrystalline cellulose, sugars, polysaccharides or mixtures thereof;
 - (iv) Disintegrants selected from crospovidone, sodium starch glycolate, croscarmellose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch;
 - (v) Lubricants and glidants selected from colloidal silicon dioxide, maize starch, talc, magnesium stearate, calcium stearate, sodium stearyl fumarate.
3. The pharmaceutical composition of claims 1 or 2, wherein the granules are compressed into tablets or filled into capsules.
4. The pharmaceutical composition of claim 3, wherein the tablets or capsules are enteric coated.
5. The pharmaceutical composition of claims 1 or 2, wherein the granules are filled into gastro resistant capsules.
6. A pharmaceutical composition in the form of a blend comprising:
 - (i) Dimethylfumarate
 - (ii) One or more excipients

7. The blend composition of claim 6 comprising:
 - (i) Dimethyl fumarate
 - (ii) fillers selected from microcrystalline cellulose, silicified microcrystalline cellulose, sugars, polysaccharides or mixtures thereof
 - (iii) lubricants and glidants selected from colloidal silicon dioxide, maize starch, talc, magnesium stearate, calcium stearate, sodium stearyl fumarate and
 - (iv) optionally other pharmaceutically acceptable excipients such as disintegrants and the like
8. The pharmaceutical composition of claim 6 or 7, wherein the blend is compressed into tablets or filled into capsules.
9. The pharmaceutical composition of claim 8, wherein the tablets or capsules are enteric coated.
10. The pharmaceutical composition of claim 6 or 7, wherein the blend is filled into acid resistant capsules and further enteric coated.