PHARMACEUTICAL COMPOSITIONS CONTAINING DIMETHYL FUMARATE

BRIEF SUMMARY

[0001] Provided herein are compositions containing compounds, or pharmaceutically acceptable salts, that metabolize to monomethyl fumarate (MMF) and methods for treating, prophylaxis, or amelioration of neurodegenerative diseases including multiple sclerosis using such compositions in a subject. In one embodiment, the compound that metabolizes to MMF is dimethyl fumarate (DMF).

[0001a] In one aspect, there is provided a solid oral dosage form comprising dimethyl fumarate and one or more excipients, wherein the amount of dimethyl fumarate in the solid oral dosage form is about 65% w/w excluding the weight of any coating components, and wherein patients orally administered said oral dosage form exhibit a time to maximum plasma monomethyl fumarate concentration (T_{max}) of from about 1.5 hours to about 3.5 hours.

[0001b] In another aspect, there is provided a solid oral dosage form comprising about 65% w/w dimethyl fumarate excluding the weight of any coating components, a total amount of about 3.5% w/w to about 55% w/w of one or more fillers, a total amount of about 0.2% w/w to about 20% w/w of one or more disintegrants, a total amount of about 0.1% w/w to about 9.0% w/w of one or more glidants, and a total amount of about 0.1% w/w to about 3.0% w/w of one or more lubricants, and wherein patients orally administered said oral dosage form exhibit a time to maximum plasma monomethyl fumarate concentration (T_{max}) of from about 1.5 hours to about 3.5 hours.

[0001c] In another aspect, there is provided a capsule comprising microtablets comprising dimethyl fumarate, wherein the amount of dimethyl fumarate in each of the microtablets in an uncoated form is about 65% w/w, and wherein patients orally administered said capsule exhibit a time to maximum plasma monomethyl fumarate concentration (T_{max}) of from about 1.5 hours to about 3.5 hours.

~~[0001d] In another aspect, there is provided a solid oral dosage form as defined above~~ for use in treating or ameliorating multiple sclerosis by having said solid oral dosage form administered orally.

[0001e] In another aspect, there is provided a capsule as defined above for use in treating or ameliorating multiple sclerosis by having said capsule administered orally.

[0001f] In another aspect, there is provided a solid oral dosage form and one or more non-steroidal anti-inflammatory drugs for use in treating or ameliorating multiple sclerosis, by having the solid oral dosage form orally administered, and the one or more non-steroidal anti-inflammatory drugs orally administered in an amount that is effective to reduce flushing, wherein the solid oral dosage form comprises an amount of dimethyl fumarate, wherein the amount of dimethyl fumarate is about 65% w/w excluding the weight of any coating components, and wherein patients orally administered said oral dosage form exhibit a time to maximum plasma monomethyl fumarate concentration (T_{max}) of from about 1.5 hours to about 3.5 hours.

[0001g] In another aspect, there is provided a method of making a powder composition comprising combining about 43% w/w to about 95% w/w dimethyl fumarate, a total amount of about 3.5% w/w to about 55% w/w of one or more fillers, a total amount of about 0.2% w/w to about 20% w/w of one or more disintegrants, a total amount of about 0.1% w/w to about 9.0% w/w of one or more glidants, and a total amount of about 0.1% w/w to about 3.0% w/w of one or more lubricants to form the composition.

[0001h] In another aspect, there is provided a composition comprising dimethyl fumarate and one or more excipients, wherein about 80% or higher of the dimethyl fumarate has a particle size of 250 microns or less.

[0001i] In another aspect, there is provided the use of a solid oral dosage form as defined above for the manufacture of a medicament for treating or ameliorating multiple sclerosis by having the medicament administered orally.

[0001j] In another aspect, there is provided the use of a capsule as defined above for the manufacture of a medicament for treating or ameliorating multiple sclerosis by having the medicament administered orally.

WHAT IS CLAIMED IS:

1. A solid oral dosage form comprising dimethyl fumarate and one or more excipients, wherein the amount of dimethyl fumarate in the solid oral dosage form is about 65% w/w excluding the weight of any coating components, and wherein patients orally administered said oral dosage form exhibit a time to maximum plasma monomethyl fumarate concentration (T_{max}) of from about 1.5 hours to about 3.5 hours.

2. The solid oral dosage form of claim 1, wherein the one or more excipients is selected from the group consisting of one or more fillers, one or more disintegrants, one or more glidants, one or more lubricants, and combinations thereof.

3. The solid oral dosage form of claim 1, wherein the one or more excipients is selected from the group consisting of microcrystalline cellulose, croscarmellose sodium, colloidal silica anhydrous, magnesium stearate, talc, and combinations thereof.

4. The solid oral dosage form of claim 1, wherein the solid oral dosage form comprises a compact.

5. The solid oral dosage form of claim 4, wherein the compact has a tensile strength that is equal to or greater than about 1.5 MPa at an applied pressure of about 100 MPa.

6. The solid oral dosage form of claim 4, wherein the compact has a tensile strength that is equal to or greater than about 3.0 MPa at an applied pressure of about 100 MPa.

7. The solid oral dosage form of claim 4, wherein the compact is in the form of a microtablet.

8. The solid oral dosage form of claim 7, wherein dimethyl fumarate is the only active ingredient in the composition.

9. The solid oral dosage form of claim 7, wherein the microtablet in uncoated form has a mean diameter ranging from about 1 mm to about 3 mm.

10. The solid oral dosage form of claim 7, wherein the microtablet is coated with one or more of methacrylic acid-methyl acrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methacrylic acid-methylacrylate copolymer, ethyl cellulose, hydroxyl propyl cellulose, and methyl acrylate-methyl methacrylate-methacrylic acid copolymer.

11. A solid oral dosage form comprising about 65% w/w dimethyl fumarate excluding the weight of any coating components, a total amount of about 3.5% w/w to about 55% w/w of one or more fillers, a total amount of about 0.2% w/w to about 20% w/w of one or more disintegrants, a total amount of about 0.1% w/w to about 9.0% w/w of one or more glidants, and a total amount of about 0.1% w/w to about 3.0% w/w of one or more lubricants, and wherein patients orally administered said oral dosage form exhibit a time to maximum plasma monomethyl fumarate concentration (T_{max}) of from about 1.5 hours to about 3.5 hours.

12. The solid oral dosage form of claim 11, wherein the solid oral dosage form is in the form of a microtablet.

13. The solid oral dosage form of claim 1, wherein the amount of dimethyl fumarate is about 240 mg, and wherein patients administered the solid oral dosage form twice daily, exhibit one or more pharmacokinetic parameters selected from the group consisting of (a) a mean plasma monomethyl fumarate C_{max} ranging from about 1.03 mg/L to about 2.41 mg/L and (b) a mean plasma monomethyl fumarate $AUC_{overall}$ ranging from about 4.81 h.mg/L to about 11.2 h.mg/L.

14. The solid oral dosage form of claim 1, wherein the amount of dimethyl fumarate is about 240 mg, and wherein patients administered the dosage form exhibit one or more pharmacokinetic parameters selected from the group consisting of (a) a mean plasma monomethyl fumarate C_{max} ranging from about 1.5 mg/L to about 3.4 mg/L, (b) a mean plasma monomethyl fumarate AUC_{0-12} ranging from about 2.4 h.mg/L to about 5.5 h.mg/L, and (c) a mean $AUC_{0-infmity}$ ranging from about 2.4 h.mg/L to about 5.6 h.mg/L.

15. A capsule comprising microtablets comprising dimethyl fumarate, wherein the amount of dimethyl fumarate in each of the microtablets in an uncoated form is about 65% w/w, and wherein patients orally administered said capsule exhibit a time to maximum plasma monomethyl fumarate concentration (T_{max}) of from about 1.5 hours to about 3.5 hours.

16. The capsule of claim 15, wherein the microtablets are partially or fully enteric coated with at least one coating.

17. The capsule of any of claims 15 and 16, wherein the capsule contains about 35 to about 55 microtablets.

18. The capsule of claim 15, wherein the amount of dimethyl fumarate is about 240 mg, and wherein patients administered the capsule exhibit one or more pharmacokinetic parameters selected from the group consisting of (a) a mean plasma monomethyl fumarate T_{max} of from about 1.5 hours to about 3.5 hours; (b) (a) a mean plasma monomethyl fumarate C_{max} ranging from about 1.5 mg/L to about 3.4 mg/L, (b) a mean plasma monomethyl fumarate AUC_{0-12} ranging from about 2.4 h.mg/L to about 5.5 h.mg/L, and a mean $AUC_{0-infinity}$ ranging from about 2.4 h.mg/L to about 5.6 h.mg/L.

19. The solid oral dosage form of claim 1, wherein about 80% or higher of the dimethyl fumarate has a particle size of 250 microns or less.

20. The solid oral dosage form of any one of claims 1-12, and 19, wherein the amount of dimethyl fumarate is about 240 mg.

21. The capsule of any of claims 15 and 16, wherein the amountof dimethyl fumarate is about 240 mg.

22. A solid oral dosage form for any of claims 1-14, 19 and 20 for use in treating or ameliorating multiple sclerosis by having said solid oral dosage form administered orally.

23. A capsule of any of claims 15, 16, 18 and 21 for use in treating or ameliorating multiple sclerosis by having said capsule administered orally.

24. A solid oral dosage form and one or more non-steroidal anti-inflammatory drugs for use in treating or ameliorating multiple sclerosis, by having the solid oral dosage form orally administered, and the one or more non-steroidal anti-inflammatory drugs orally administered in an amount that is effective to reduce flushing, wherein the solid oral dosage form comprises an amount of dimethyl fumarate, wherein the amount of dimethyl fumarate is about 65% w/w excluding the weight of any coating components, and wherein patients orally administered said oral dosage form exhibit a time to maximum plasma monomethyl fumarate concentration (T_{max}) of from about 1.5 hours to about 3.5 hours.

25. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 24, wherein the treating or ameliorating is by having the one or more non-steroidal anti-inflammatory drugs administered before the solid oral dosage form.

26. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 25, wherein the treating or ameliorating is by having the one or more non-steroidal anti-inflammatory drugs administered in an amount of about 50 mg to about 500 mg.

27. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 26, wherein the treating or ameliorating is by having the one or more non-steroidal anti-inflammatory drugs selected from the group consisting of aspirin, ibuprofen, naproxen, ketoprofen, celecoxib, and combinations thereof.

28. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 27, wherein the treating or ameliorating is by having the one or more non-steroidal anti-inflammatory drugs be aspirin.

29. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 28, wherein the treating or ameliorating is by having the amount of dimethyl fumarate be about 60 mg to about 720 mg.

30. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 28, wherein the treating or ameliorating is by having said oral dosage form be administered twice daily in a dose of 240 mg dimethyl fumarate.

31. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 30, wherein the treating or ameliorating is by having said oral dosage form be administered twice daily in a dose of 120 mg dimethyl fumarate for 7 days prior to the administering of 240 mg dimethyl fumarate twice daily.

32. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 30, wherein the treating or ameliorating is by having said oral dosage form be administered twice daily in a dose of 120 mg dimethyl fumarate for one month prior to the administering of 240 mg dimethyl fumarate twice daily.

33. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of any of claims 31 and 32, wherein the treating or ameliorating is by having said amount of dimethyl fumarate be administered with food.

34. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 28, wherein the treating or ameliorating is by having the aspirin be non-enterically coated.

35. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 28, wherein the treating or ameliorating is by having the amount of dimethyl fumarate be about 240 mg.

36. The solid oral dosage form and one or more non-steroidal anti-inflammatory drugs of claim 28, wherein the treating or ameliorating is by having the solid oral dosage form comprise a therapeutically effective amount of dimethyl fumarate.

37. A method of making a powder composition comprising combining about 43% w/w to about 95% w/w dimethyl fumarate, a total amount of about 3.5% w/w to about 55% w/w of one or more fillers, a total amount of about 0.2% w/w to about 20% w/w of one or more disintegrants, a total amount of about 0.1% w/w to about 9.0% w/w of one or more glidants, and a total amount of about 0.1% w/w to about 3.0% w/w of one or more lubricants to form the composition.

38. A composition comprising dimethyl fumarate and one or more excipients, wherein about 80% or higher of the dimethyl fumarate has a particle size of 250 microns or less.

39. The composition of claim 38, wherein about 97% or higher of the dimethyl fumarate has a particle size of 250 microns or less.

40. Use of a solid oral dosage form of any of claims 1-14, 19 and 20 for the manufacture of a medicament for treating or ameliorating multiple sclerosis by having the medicament administered orally.

41. Use of a capsule of any of claims 15, 16, 18 and 21 for the manufacture of a medicament for treating or ameliorating multiple sclerosis by having the medicament administered orally.

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BRIEF SUMMARY

[0001] Provided herein are compositions containing compounds, or pharmaceutically acceptable salts, that metabolize to monomethyl fumarate (MMF) and methods for treating, prophylaxis, or amelioration of neurodegenerative diseases including multiple sclerosis using such compositions in a subject. In one embodiment, the compound that metabolizes to MMF is dimethyl fumarate (DMF).

[0001a] In one aspect, there is provided a solid oral dosage form comprising a pharmaceutical composition in the form of a compact comprising dimethyl fumarate and one or more excipients, wherein the amount of dimethyl fumarate in the compact is 65% w/w to 95% w/w excluding the weight of any coating components, and wherein said compact has a tensile strength that is equal to or greater than 1.5 MPa at an applied or compaction pressure of 100 MPa.

[0001b] In another aspect, there is provided a solid oral dosage form as defined above for use in treating or ameliorating multiple sclerosis.

[0001c] In another aspect, there is provided the solid oral dosage form as defined above, in combination with one or more non-steroidal anti-inflammatory drugs, for use in treating or ameliorating multiple sclerosis, wherein the amount of the one or more non-steroidal anti-inflammatory drugs is effective to reduce flushing.

[0001d] In another aspect, there is provided a method of making the solid oral dosage form as defined above, wherein the solid oral dosage form is a tablet, comprising combining dimethyl fumarate with solid excipients to obtain tablets.

[0001e] In another aspect, there is provided the use of a solid oral dosage form as defined above in the manufacture of a medicament for treating or ameliorating multiple sclerosis.

WHAT IS CLAIMED IS

1. A solid oral dosage form comprising a pharmaceutical composition in the form of a compact comprising dimethyl fumarate and one or more excipients, wherein the amount of dimethyl fumarate in the compact is 65% w/w to 95% w/w excluding the weight of any coating components, and wherein said compact has a tensile strength that is equal to or greater than 1.5 MPa at an applied or compaction pressure of 100 MPa.

2. The solid oral dosage form of claim 1, wherein the amount of dimethyl fumarate in the compact is 65% w/w excluding the weight of any coating components.

3. The solid oral dosage form of claim 1 or 2, wherein the compact has a tensile strength that is 2.0 to 5.0 MPa at an applied or compaction pressure of 100 MPa.

4. The solid oral dosage form of claim 1 or 2, wherein the compact has a tensile strength that is 2.5 to 4.5 MPa at an applied or compaction pressure of 100 MPa.

5. The solid oral dosage form of any of claims 1-4, wherein the compact is a tablet.

6. The solid oral dosage form of claim 5, wherein the tablet is a product of a process comprising (a) combining dimethyl fumarate with solid excipients; (b) grinding the resulting mixture to form granules; (c) adding suitable auxiliaries to the granules from step (b); and (d) processing the mixture of step (c) to obtain the tablet.

7. The solid oral dosage form of any of claims 1-4, wherein the compact is in the form of a microtablet.

8. The solid oral dosage form of any of claims 1-4 or 7, wherein the solid oral dosage form is in the form of a capsule comprising a plurality of microtablets.

9. The solid oral dosage form of claim 8, wherein dimethyl fumarate is the only active ingredient in the microtablets.

10. The solid oral dosage form of claim 9, wherein the microtablets in uncoated form have a mean diameter ranging from 1 mm to 3 mm.

11. The solid oral dosage form of claim 8 or 9, wherein the microtablets are partially or fully enteric coated.

12. The solid oral dosage form of any of claims 8-11, wherein the capsule contains 35 to 55 microtablets.

13. The solid oral dosage form of any of claims 7-12, wherein the microtablet is coated with one or more of methacrylic acid-methyl acrylate copolymer, methacrylic acid-ethyl acrylate copolymer, methacrylic acid-methylacrylate copolymer, ethyl cellulose, hydroxyl propyl cellulose, and methyl acrylate-methyl methacrylate-methacrylic acid copolymer.

14. The solid oral dosage form of any of claims 1-13, wherein the amount of dimethyl fumarate in the solid oral dosage form is 240 mg.

15. The solid oral dosage form of any of claims 1-14, wherein the one or more excipients are one or more selected from the group consisting of a filler, a disintegrant, a glidant, a lubricant, and any combination thereof.

16. The solid oral dosage form of any of claims 1-15, wherein the one or more excipients comprise a filler, wherein the filler is microcrystalline cellulose.

17. The solid oral dosage form of claim 16, wherein the microcrystalline cellulose is PROSOLV SMCC® HD90.

18. The solid oral dosage form of any of claims 1-14, wherein the one or more excipients are a filler that is microcrystalline cellulose, a disintegrant that is croscarmellose sodium, a glidant that is colloidal silica anhydrous, and a lubricant that is magnesium stearate.

19. The solid oral dosage form of any of claims 1-14 further comprising a total amount of 3.5% w/w to 55% w/w of one or more fillers, a total amount of 0.2% w/w to 20% w/w of one or more disintegrants, a total amount of 0.1% w/w to 9.0% w/w of one or more glidants, and a total amount of 0.1% w/w to 3.0% w/w of one or more lubricants.

20. The solid oral dosage form of any of claims 1-14, wherein the compact comprises (a) dimethyl fumarate in an amount of 65% w/w of the compact excluding the weight of any coating

components; (b) croscarmellose sodium in an amount of 5.0% w/w of the compact excluding the weight of any coating components; (c) PROSOLV SMCC® HD90 in an amount of 29% w/w of the compact excluding the weight of any coating components; (d) magnesium stearate in an amount of 0.5% w/w of the compact excluding the weight of any coating components; and (e) silica colloidal anhydrous in an amount of 0.6% w/w of the compact excluding the weight of any coating components.

21. The solid oral dosage form of claim 6, wherein at least 90% of the dimethyl fumarate that is combined in step (a) has a particle size of 250 microns or less.

22. The solid oral dosage form of claim 6, wherein at least 97% of the dimethyl fumarate that is combined in step (a) has a particle size of 250 microns or less.

23. The solid oral dosage form of any of claims 1-22 for use in treating or ameliorating multiple sclerosis.

24. The solid oral dosage form of any of claims 1-22, in combination with one or more non-steroidal anti-inflammatory drugs, for use in treating or ameliorating multiple sclerosis, wherein the amount of the one or more non-steroidal anti-inflammatory drugs is effective to reduce flushing.

25. The solid oral dosage form of claim 24, wherein the one or more non-steroidal anti-inflammatory drugs are administered before the solid oral dosage form.

26. The solid oral dosage form of claim 24 or 25, wherein the one or more non-steroidal anti-inflammatory drugs is aspirin.

27. The solid oral dosage form of any of claims 23-26, wherein said oral dosage form is administered twice daily in a dose of 240 mg dimethyl fumarate.

28. The solid oral dosage form of claim 27, wherein said oral dosage form is administered twice daily in a dose of 120 mg dimethyl fumarate for 7 days prior to the administering of 240 mg dimethyl fumarate twice daily.

29. The solid oral dosage form of claim 28, wherein said amount of dimethyl fumarate is administered with food.

30. The solid oral dosage form of claim 26, wherein the aspirin is non-enterically coated.

31. A method of making the solid oral dosage form of any of claims 1-22, wherein the solid oral dosage form is a tablet, comprising combining dimethyl fumarate with solid excipients to obtain tablets.

32. The method of claim 31 comprising (a) combining dimethyl fumarate with solid excipients; (b) grinding the resulting mixture to form granules; (c) adding suitable auxiliaries to the granules from step (b); and (d) processing the mixture of step (c) to obtain tablets.

33. The use of a solid oral dosage form of any of claims 1-22 in the manufacture of a medicament for treating or ameliorating multiple sclerosis.