ABSTRACT

Oral dosage forms and granulations with a high loading of a methyl hydrogen fumarate prodrug are disclosed.
FIG. 1
Before granulation:

- X(10%) = 2.2 µm
- X(50%) = 22.19 µm
- X(90%) = 71.05 µm

After granulation:

- X(10%) = 2.0 µm
- X(50%) = 4.0 µm
- X(90%) = 10.0 µm

FIG. 2
Before granulation

After granulation

FIG. 3
FIG. 5

A bar chart showing the relationship between % SiO2 and F (mm). The chart indicates that as the % SiO2 increases, F (mm) decreases. There is a marked decrease at % SiO2 of 0.5 with a notation of *<5mm.
FIG. 6

% R

T (hrs)

0 4 8 12 16 20 24
FIG. 10

Time (hr)

MMF Concentration (µg/mL)

0 2 4 6 8 10 12

0 2 4 6 8

FIG. 10
ORAL DOSAGE FORMS HAVING A HIGH LOADING OF A METHYL HYDROGEN FUMARATE PRODRUG


TECHNICAL FIELD

[0002] The present disclosure relates to oral dosage forms with a high loading of a methyl hydrogen fumarate prodrug.

BACKGROUND

[0003] The compound methyl hydrogen fumarate (MHF), which is alternatively called monomethyl fumarate (MMF), has the following chemical structure:

\[
\text{HO} \quad \text{O} \quad \text{O} \quad \text{Cl}
\]

[0004] Fumaric acid esters, i.e., dimethylfumarate (DMF) in combination with salts of ethylhydrogenfumarate, have been used in the treatment of psoriasis for many years. The combination product, marketed under the tradename Fumaderm®, is in the form of oral tablets and is available in two different dosage strengths (Fumaderm® initial and Fumaderm®):

<table>
<thead>
<tr>
<th>Fumarate Compound</th>
<th>Fumaderm® Initial (mg)</th>
<th>Fumaderm® (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethylfumarate</td>
<td>30</td>
<td>120</td>
</tr>
<tr>
<td>Ethyl hydrogen fumarate, calcium salt</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>Ethyl hydrogen fumarate, magnesium salt</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ethyl hydrogen fumarate, zinc salt</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

[0005] The two strengths are intended to be applied in an individually based dosing 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.

[0006] Another marketed composition is Fumaratin 120® containing 120 mg of DMF and 95 mg of calcium monomethyl fumarate (Tiofarma, Oud-Beijerland, Netherlands). The pharmacokinetic profile of Fumaratin 120® in healthy subjects is described in Litjens et al., Br. J. Clin. Pharmacol., 2004, vol. 58-4, pp. 429-432. The results show that a single oral dose of Fumaratin 120® is followed by a rise in serum MHF concentration and only negligible concentrations of DMF and fumaric acid is observed. Thus, DMF is thought to be a precursor or prodrg of MHF.

[0007] U.S. Pat. Nos. 6,277,882 and 6,355,676 disclose respectively the use of alkyl hydrogen fumarates and the use of certain fumaric acid monoalkyl ester salts for preparing microtablets for preparing 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 microtablets or microgellets. U.S. Pat. No. 4,959,389 discloses compositions containing different salts of fumaric acid monoalkyl esters alone or in combination with a dialkyl fumarate. GB 1,153,927 relates to medical compositions comprising dimethyl maleic anhydride, dimethyl maleate and/or DMF.

[0008] Biogen Idec’s BG12, an oral dosage form of DMF that is an enteric coated capsule containing DMF in microgellet form, has been used in human clinical testing for the treatment of MS and has shown promising results in reducing MS relapses and MS disability progression, at daily doses of 480 mg DMF, which translates to 435 mg of MHF assuming complete conversion of DMF to MHF in vivo. Unfortunately, DMF is highly irritating to the skin and mucosal membranes with the result that oral administration of DMF tends to cause serious digestive tract irritation with attendant nausea, vomiting, abdominal pain and diarrhea. This irritation problem is particularly problematic with the mucosal tissue lining the stomach. For this reason, products such as Fumaderm® and BG12 are made with enteric coatings that prevent the DMF from being released from the dosage form until after the dosage form passes out of the stomach and into the small intestine.

[0009] More recently, Gangakheetkar et al. U.S. Pat. Nos. 8,148,414 discloses the MHF prodrug (N,N-Diethylcarbamoyl)methylmethyl (2E)-buta-2-enedioate (1) having the following chemical structure:

\[
\text{HO} \quad \text{O} \quad \text{O} \quad \text{Cl}
\]


SUMMARY

[0012] One issue with prodrgs is that the weight of the active metabolite portion of the prodrg molecule comprises only a portion of the total weight of the prodrg. In the case of (N,N-Diethylcarbamoyl)methylmethyl (2E)-buta-2-enedioate, the prodrg portion comprises about 47 wt % of the total weight of the prodrg while the MHF portion comprises about 53 wt % of the total weight of the prodrg. This means that almost one-half of the prodrg loading in a dosage form is taken up by the non-pharmacologically active prodrg.
For example, to achieve an equivalent daily dose of 435 mg of MHF as Biogen's BG12 product, it would be necessary to administer daily 821 mg of (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate, assuming complete breakdown of compound (1) to MHF in vivo. Conventional pharmaceutical tablet formulations typically contain high loadings of tableting excipients such as binders, fillers, flow promoters, lubricants, etc. In cases where the drug is not exceptionally potent, and therefore the tablets contain only a very small amount of the drug, these excipients typically comprise at least 30 to 50 wt % of the total weight of the tablet. In the case of prodrugs such as (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate, the use of such conventional tablet formulations would result in either very large tablet or capsule sizes, or the need for a patient to take multiple tablets or capsules for each dosing of prodrug, neither of which is desirable.

Thus, oral dosage forms comprising a high loading of (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate and that are amenable to high throughput commercial tableting manufacture are disclosed.

Oral dosage forms prepared from granulations having a high loading of (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate are disclosed.

In one aspect, oral tablet dosage forms are disclosed comprising about 70 wt % to about 98 wt % (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate. In certain embodiments, the oral tablet dosage forms comprise about 80 wt % to about 97 wt % (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate.

In another aspect, solid granulations comprising greater than about 95 wt % (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate are disclosed. In certain embodiments, the solid granulations comprise greater than about 97 wt % (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate.

In yet another aspect, mixtures comprising the above-described solid granulations and one or more pharmaceutically acceptable excipients are disclosed.

In another aspect, mixtures comprising a small amount of glidant markedly improve the flowability of the mixture including high loading granules. In certain embodiments, the mixtures may contain up to 3 wt % of a glidant, e.g., silicon dioxide as a flow aid. In other embodiments, the mixtures contain up to 1 wt %, e.g., silicon dioxide.

In yet other aspects, methods of treating a disease in a subject are disclosed comprising orally administering to a subject in need of such treatment at least one oral dosage form provided by the present disclosure. In certain embodiments, the dosage forms can be used to treat multiple sclerosis and/or psoriasis.

**DEFINITIONS**

“Compound (1)” means the MHF prodrug (1), (N,N-Diethylcarbamoyl)methylmethyl (2E)-but-2-ene-1,4-dioate, alternatively named 1-[2-(diethylamino)-2-oxoethyl]-4-methyl (2E)-but-2-ene-1,4-dioate, pharmaceutically acceptable solvates thereof, and crystalline forms of any of the foregoing.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Those skilled in the art will understand that the drawings, described herein, are for illustration purposes only. The drawings are not intended to limit the scope of the present disclosure.

FIG. 1 is a graph showing the particle size distribution of blends and granulations made in Example 3.

FIG. 2 is a graph showing the particle size distribution of blends and granulations made in Example 4.

FIG. 3 is a graph showing the particle size distribution of blends and granulations made in Example 5.

FIG. 4 is a graph showing the in vitro MHF prodrug release profile (percent MHF prodrug released over time) for the tablets of Example 7.

FIG. 5 is a plot illustrating flow characterization of dry powder blends and granulations of Example 9.

FIG. 6 is a graph showing the in vitro MHF prodrug release profile (percent MHF prodrug released over time) for the tablets of Example 10, tested in accordance with Example 13.

FIG. 7 is a graph showing the in vitro MHF prodrug release profile (percent MHF prodrug released over time) for the tablets of Example 11, tested in accordance with Example 13.

FIG. 8 is a graph showing the in vitro MHF prodrug release profile (percent MHF prodrug released over time) for the tablets of Example 12, tested in accordance with Example 13.

FIG. 9 is a graph showing the concentration of MHF in the blood of fasted monkeys following administration of the tablets of Examples 10 and 11.

FIG. 10 is a graph showing the concentration of MHF in the blood of fed monkeys following administration of the tablets of Examples 10 and 11.

FIG. 11 is a graph showing the in vitro MHF prodrug release profile (percent MHF prodrug released over time) for the dosage forms of Example 15, tested in accordance with Example 17; and

FIG. 12 is a graph showing the in vitro MHF prodrug release profile (percent MHF prodrug released over time) for the dosage forms of Example 16, tested in accordance with Example 17.

![Chemical Structure](image-url)
cally pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures may be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well-known to those skilled in the art. Compounds include, for example, optical isomers, racemates thereof, and other mixtures thereof. In such embodiments, a single enantiomer or diastereomer, i.e., optically active form, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates may be accomplished, for example, by methods such as crystallization in the presence of a resolving agent, or chromatography using, for example, chiral stationary phases. Notwithstanding the foregoing, the configuration of the illustrated double bond is only in the E configuration (i.e., trans configuration).

Compound (1) also includes isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds disclosed herein include, but are not limited to, 2H, 3H, 13C, 15C, 14N, 18O, 17O, etc. Compound (1) may exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In general, compound (1) may be the free acid, hydrated, solvated, N-oxides, or combinations of any of the foregoing. Compound (1) may exist in multiple crystalline, co-crystalline, or amorphous forms. Compound (1) includes pharmaceutically acceptable solvates thereof, as well as crystalline forms of any of the foregoing. Compound (1) also includes solvates. A solvate refers to a molecular complex of a compound with one or more solvent molecules in a stoichiometric or non-stoichiometric amount. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to a subject, e.g., water, ethanol, and the like. A molecular complex of a compound or moiety of a compound and a solvent can be stabilized by non-covalent intra-molecular forces such as, for example, electrostatic forces, van der Waals forces, or hydrogen bonds. The term "hydrate" refers to a solvate in which the one or more solvent molecules is water.

Controlled-release refers to release of a drug from a dosage form in which the drug release is controlled or modified over a period of time. Controlled can mean, for example, sustained, delayed, or pulsated-release at a particular time. Controlled can also mean that release of the drug from the dosage form is extended for longer than it would be in an immediate-release dosage form, i.e., at least over several hours. In some embodiments, in vivo release of the compound occurs over a period of at least 2 hours, in some embodiments, over a period of at least 4 hours, in some embodiments, over a period of at least 8 hours, in some embodiments over a period of at least 12 hours, in some embodiments, over a period of at least 16 hours, in some embodiments, over a period of at least 20 hours, and in some embodiments, over a period of at least 24 hours.

A composition or material that is "substantially free of carboxylic acid moieties" is a composition or material that has less than 2% w/w of carboxylic acid moieties. In some embodiments, a composition or material that is "substantially free of carboxylic acid moieties" is a composition or material that has less than 1% w/w of carboxylic acid moieties. In other embodiments, a composition or material that is "substantially free of carboxylic acid moieties" is a composition or material that has less than 0.01% w/w of carboxylic acid moieties.

Dosage form refers to a form of a formulation that contains an amount of active agent or prodrug of an active agent, i.e., MHF prodrug compound (1), which can be administered to a subject to achieve a therapeutic effect. An oral dosage form is intended to be administered to a subject via the mouth and swallowed. A dose of a drug may include one or more dosage forms administered simultaneously or over a period of time.

Immediate release refers to formulations or dosage forms that rapidly dissolve in vitro and in vivo and are intended to be completely dissolved and absorbed in the stomach or upper gastrointestinal tract. Immediate release formulations can release at least 90% of the active ingredient or precursor thereof within about 15 minutes, within about 30 minutes, within about one hour, or within about two hours of administering an immediate release dosage form.

Subject includes mammals, such as for example, humans.

Pharmaceutically acceptable refers to approved or approvable by a regulatory agency of a federal or a state government, listed in a U.S. Pharmacopoeia, or listed in other generally recognized pharmacopeia for use in mammals, including humans.

Pharmaceutically acceptable salt refers to a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanopropanoic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalensulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxyglutathione acid, salicylic acid, stearic acid, mucic acid, and the like; and (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth metal ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethylamine, triethanolamine, N-methylglucamine, and the like.

Pharmaceutically acceptable vehicle or pharmaceutically acceptable excipient refers to a pharmaceutically acceptable diluent, a pharmaceutically acceptable adjuvant, a pharmaceutically acceptable excipient, a pharmaceutically acceptable carrier, or a combination of any of the foregoing with which a compound such as the MHF prodrug, (N,N-Diethylcarbamoylmethyl)methyl (2E)-but-2-ene-1,4-dioate compound (1), may be administered to a subject, which does not substantially compromise the pharmacological activity thereof, and which is nontoxic when administered in doses sufficient to provide a therapeutically effective amount of the MHF prodrug or MHF metabolite.

Prodrug refers to a derivative of an active compound (drug) that undergoes a transformation under the conditions of use, such as within the body, to release an active
drug. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug. Prodrugs may be obtained by bonding a promoiety (defined herein), typically via a functional group, to a drug. For example, MHF prodrug compound (1) is metabolized within a subject’s body to form the parent drug MHF.

“Promoiety” refers to a group bonded to a drug, typically to a functional group of the drug, via a bond(s) that is cleavable under specified conditions of use. The bond(s) between the drug and promoiety may be cleaved by enzymatic or non-enzymatic means. Under the conditions of use, for example following administration to a subject, the bond(s) between the drug and promoiety may be cleaved to release the parent drug. The cleavage of the promoiety may proceed spontaneously, such as via a hydrolysis reaction, or it may be catalyzed or induced by another agent, such as by an enzyme, by light, by acid, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature, pH, etc. The agent may be endogenous to the conditions of use, such as an enzyme present in the systemic circulation of a subject to which the prodrug is administered or the pH conditions of the gastrointestinal tract or the agent may be supplied exogenously. For example, for MHF prodrug compound (1), the drug is MHF and the promoiety has the structure:

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\end{align*}
\]

Consistent with “Dissolution Testing of Immediate Release Solid Oral Dosage Forms—Guidance for Industry”, FDA-CDER, August 1997, dissolution profiles may be considered similar based on a difference factor (f₁) and a similarity factor (f₂). For dissolution profiles to be considered similar, f₁ values should be close to 0, and f₂ values should be close to 100. Generally, f₁ values up to 15 (0-15) and f₂ values greater than 50 (50-100) ensure sameness or equivalence of two dissolution profiles. Procedures for calculating f₁ and f₂ are set forth in the foregoing reference.

“Sustained release” refers to release of a compound from a dosage form at a rate effective to achieve a therapeutic amount of a compound, e.g., MHF in the systemic blood circulation over a prolonged period of time relative to that achieved by oral administration of an immediate release formulation, e.g., of MHF. In some embodiments, in vivo release of MHF, from a high prodrug load tablet disclosed herein, occurs over a period of at least about 4 hours, in some embodiments, over a period of at least about 8 hours, in some embodiments, over a period of at least about 12 hours, in some embodiments, over a period of at least about 16 hours, in some embodiments, over a period of at least about 20 hours, and in some embodiments, over a period of at least about 24 hours.

“Therapeutically effective amount” refers to the amount of (N,N-Diethylcarbamoyl)methylmethyl (2E)but-2-ene-1,4-dioate that, when administered to a subject for treating a disease, is sufficient to reduce the severity of, eliminate, or prevent the disease, or a symptom of the disease, in the subject. The therapeutically effective amount may vary depending, for example, on the form of the compound (1), the cause of disease, the severity of the disease, the age, weight, and/or health of the subject to be treated, and the judgment of the prescribing physician. A therapeutically effective amount may be ascertained by those skilled in the art and/or capable of determination by routine experimentation.

“Treating” or “treatment” of any disease refers to reversing, alleviating, arresting, or ameliorating a disease or at least one of the clinical symptoms of a disease, reducing the risk of acquiring at least one of the clinical symptoms of a disease, inhibiting the progress of a disease or at least one of the clinical symptoms of the disease or reducing the risk of developing at least one of the clinical symptoms of a disease. “Treating” or “treatment” also refers to inhibiting the disease, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both, and to inhibiting at least one physical parameter that may or may not be discernible to the patient. In certain embodiments, “treating” or “treatment” refers to protecting against or delaying the onset of at least one or more symptoms of a disease in a patient.

DETAILED DESCRIPTION

Reference is now made in detail to certain embodiments of dosage forms and methods. The disclosed embodiments are not intended to be limiting of the claims. To the contrary, the claims are intended to cover all alternatives, modifications, and equivalents.

(N,N-Diethylcarbamoyl)methylmethyl (2E)but-2-ene-1,4-dioate, has the following chemical structure:

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\end{align*}
\]

Compound (1) may be prepared using the methods described in Gangakhedkar et al. U.S. Pat. No. 8,148,414, which is herein incorporated by reference.

Compound (1) may be prepared using the methods described in Gangakhedkar et al. U.S. Pat. No. 8,148,414, which is herein incorporated by reference.

Oral dosage forms disclosed herein comprise a tablet or capsule containing (N,N-Diethylcarbamoyl)methylmethyl (2E)but-2-ene-1,4-dioate and one or more pharmaceutically acceptable excipients. In certain aspects, the oral dosage forms comprise granules having a high loading of (N,N-Diethylcarbamoyl)methylmethyl (2E)but-2-ene-1,4-dioate.

High Drug Loading Granulations and Mixture Blends

In certain embodiments, high drug loading solid granulations comprise at least about 95 wt % compound (1), and in certain embodiments, at least about 97% compound (1).

The high drug loading granulations may also comprise one or more pharmaceutically acceptable excipients. In an embodiment, the pharmaceutically acceptable excipient may comprise a pharmaceutically acceptable binder. In certain embodiments, granulations, or granules as used interchangeably herein, may comprise from about 0.5 wt % to about 5.0 wt %, and in certain embodiments about 1 wt % to about 3.0 wt % of a pharmaceutically acceptable binding agent. Binding agents may be included in granules to facili-
tate adhesion of the constituents. Examples of binding agents useful in tablet dosage forms provided by the present disclosure include polyvinyl acetate phthalate, molasses, starch, methylcellulose, hydroxypropyl cellulose (HPC), hydroxypetyl methyl cellulose (HPMC), sodium carboxymethyl cellulose, microcrystalline cellulose, polyvinyl pyrrolidone, and other polymers including vinyl pyrrolidone as a sub-unit, and combinations thereof. In certain embodiments provided by the present disclosure, a binder may be a polymer selected from hydroxypropyl cellulose, hydroxypetyl methyl cellulose, polyvinyl pyrrolidone and combinations thereof. In a particular embodiment, the binder may be hydroxypropyl cellulose (Klucel EXF, Ashland).

[0056] Granules having a high loading of compound (1) may be prepared using high shear wet granulation. At least in part, the amount of binder and other pharmaceutically acceptable excipients are chosen to provide a wide processing window for the amount of water used during granulation. For manufacturing, it is generally desirable to be able to vary process parameters without significantly negatively impacting the properties of the granules and to produce granules having optimal physical and mechanical properties to facilitate subsequent processes for manufacture of oral dosage forms.

[0057] In certain embodiments, a mixture comprising the high drug load granules of compound (1) may be formed. The mixture may comprise a blend of one or more pharmaceutically acceptable excipients and high drug load granules. If desired, the mixture may be used in preparation of oral dosage forms, as described herein. In certain embodiments it was unexpectedly found that the additional of a small amount of glidant markedly improved the flowability of the mixture including high loading granules, as described in further detail herein. Glidants may be included in blends provided by the present disclosure to reduce sticking effects during processing, film formation, and/or drying. Examples of useful glidants include talc, magnesium stearate, glycerol monostearate, colloidal silicon dioxide, precipitated silicon dioxide, fumed silicon dioxide, and combinations of any of the foregoing. In certain embodiments, the blends may contain up to 3 wt % of a glidant as a flow aid. In other embodiments, the mixtures may contain up to 1 wt % glidant as a flow aid. In other embodiments, the mixtures may contain 0.1 to about 0.5 wt % glidant as a flow aid. In certain embodiments, a glidant is colloidal silicon dioxide.

Oral Dosage Forms

[0058] The high drug loading granulations and mixtures of the disclosure may be used to prepare any suitable pharmaceutical formulations, including oral dosage forms. In certain embodiments, the oral dosage forms may provide immediate release, sustained release, delayed release or any combination thereof.

[0059] In certain embodiments, an oral dosage form comprising a high drug load granulation may be compressed into a tablet dosage form. In certain embodiments, a mixture comprising a high drug load granulation may be inserted into and contained in a capsule dosage form. In certain embodiments, an oral dosage form comprising a high drug load granulation may be a liquid oral dosage from such as an emulsion or suspension.

[0060] In certain embodiments, the amount of compound (1) in a dosage form provided by the present disclosure is from about 50 mg to about 2,000 mg, in certain embodiments, from about 100 mg to about 1,200 mg, and in certain embodiments is about 200 mg to about 800 mg. For dosage forms comprising a pharmaceutically acceptable solvate of compound (1), the amount of compound (1) in a dosage form refers to the mass equivalent weight of compound (1) comprising the solvate. For reference, one (1) mg compound (1) corresponds to 0.53 mg-equivalents of MIF.

[0061] In certain embodiments, dosage forms may be in the form of tablets comprising compound (1). Tablet dosage forms may be of any shape suitable for oral administration of a drug such as spheroidal, cube-shaped, oval, or elliptoidal. In certain embodiments, tablet dosage forms, e.g., an oral dosage form in the form of a tablet, provided by the present disclosure are matrix systems in which the compound (1) is dispersed in a matrix comprising at least one release-rate modifying compound. Matrix systems are well-known in the art as described, for example, in “Handbook of Pharmaceutical Controlled Release Technology,” ed. Wise, Marcel Dekker, Inc. (2000) and “Treatise on Controlled Drug Delivery, Fundamentals, Optimization, and Applications,” ed. Kydones, Marcel Dekker, Inc. (1992).

[0062] Oral dosage forms may comprise a tablet core with greater than about 70 wt % compound (1), greater than about 80 wt % compound (1), greater than about 90 wt % compound (1), greater than about 95 wt % compound (1), greater than about 97 wt % compound (1), where wt % is based on the weight of an uncoated tablet core of a dosage form. In certain embodiments, the oral dosage form may comprise at least one additional pharmaceutically acceptable excipient where the pharmaceutical excipient is selected from fillers, diluents, binders, lubricants, disintegrants, glidants, sustained release agents, surfactants, plasticizers, anti-adherents, buffers, dyes, wetting agents, emulsifying agents, pH buffering agents, thickening agents, coloring agents, enteric agents, and combinations thereof.

[0063] Diluents, or fillers, may be added to increase the bulk to make dosage forms a practical size for compression. Fillers may be added to increase the bulk to make dosage forms. Examples of fillers useful in the present disclosure include dibasic calcium phosphate, dibasic calcium phosphate diphosphate, calcium sulfate, dicalcium phosphate, tricalcium phosphate, lactose, cellulose including microcrystalline cellulose, mannnitol, sodium chloride, dry starch, pregelatinized starch, compressible sugar, mannitol, and combinations of any of the foregoing. In certain embodiments, a filler is lactose monohydrate. Fillers may be water insoluble, water soluble, or combinations thereof. Examples of useful water insoluble fillers include starch, dibasic calcium phosphate diphosphate, calcium sulfate, dicalcium phosphate, tricalcium phosphate, powdered cellulose, microcrystalline cellulose, and combinations of any of the foregoing. Examples of water-soluble fillers include water soluble sugars and sugar alcohols, such as lactose, glucose, fructose, sucrose, mannose, dextrose, galactose, the corresponding sugar alcohols and other sugar alcohols, such as mannitol, sorbitol, xylitol, and combinations of any of the foregoing.

[0064] Lubricants and anti-static agents may be included in a pharmaceutically acceptable coating to aid in processing. Examples of lubricants useful in coatings provided by the present disclosure include calcium stearate, glycerol behenate, glycercyl monostearate, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, sodium lauryl sulfate, stearic acid, talc, vegetable oil, zinc stearate, and
combinations of any of the foregoing. In certain embodiments, the lubricant is magnesium stearate. In certain embodiments, coatings may comprise an amount of lubricant ranging from about 0.5 wt % to about 3 wt %, from about 1 wt % to about 3 wt %, and in certain embodiments is about 1 to about 2 wt %, based on the total solids weight of the coating.

Disintegrants may be included in the tablet core to cause a tablet core to break apart, for example, by expansion of a disintegrant when exposed to water. Examples of useful disintegrants include water swellable substances such as croscarmellose sodium, sodium starch glycolate, cross-linked polyvinyl pyrrolidone, and combinations of any of the foregoing. In various embodiments, the disintegrants can be selected to be substantially free of carboxylic acid moieties.

Examples of surfactants useful in tablet dosage forms provided by the present disclosure include pharmaceutically acceptable anionic surfactants, cationic surfactants, zwitterionic, amphoteritic (amphiphilic/amphiphilic) surfactants, non-ionic surfactants, polyethyleneglycol esters or ethers, and combinations of any of the foregoing. Examples of useful pharmaceutically acceptable anionic surfactants include monovalent alkyl carboxylates, alkyl lactates, alkyl ether carboxylates, N-acyl sarcosinates, polyvalent alkyl carbonates, N-acyl glutamates, fatty acid-polypeptide condensates, sulfuric acid esters, alkyl sulfates such as sodium lauryl sulfate and sodium dodecyl sulfate, ethoxylated alkyl sulfates, ester linked sulfonates such as docusate sodium and dioctyl sodium sulfosuccinate, alpha olein sulfonates, or phosphated ethoxylated alcohols. Examples of useful pharmaceutically acceptable cationic surfactants include monooctyl quaternary ammonium salts, dihexyl quaternary ammonium compounds, amidoamines, and aminimides. Examples of useful pharmaceutically acceptable amphoteric surfactants include N-substituted alkyl amides, N-alkyl betaines, sulfobetaines, and N-alkyl-6-amino propionates. Examples of useful pharmaceutically acceptable nonionic surfactants include diblock and triblock copolymers of polyethylene oxide, polypropylene oxide, polyoxethylene (20) sorbitan monooleate, and polyethyleneglycol esters or ethers such as polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, and hydrogenated castor oil. In certain embodiments, a surfactant is chosen from sodium lauryl sulfate and sodium dodecyl sulfate.

Tablet dosage forms provided by the present disclosure may further comprise one or more coatings, which may partially or fully cover the tablets. While certain coatings may be applied to modify or affect the release of compound (1) from a tablet dosage form in the gastrointestinal tract, others may have no such effect. For example, one or more additional coatings may be for physical protection, chemical protection, aesthetics, ease in swallowing, identification, and/or to facilitate further processing of the tablets. Coatings may be impermeable to moisture or may be moisture permeable. Moisture impermeable exterior tablet coatings may be useful for maintaining low moisture content in a dosage form that is packaged in the presence of a desiccant and may thereby enhance, for example, the storage stability of a tablet dosage form. Examples of materials useful in coatings for physical protection include permeable or soluble materials such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, lactose, hydroxypropyl ethylcellulose, hydroxyethyl cellulose, and xanthan gum. Examples of materials useful in external tablet coatings to facilitate further processing include talc; colloidal silica, polyvinyl alcohol, titanium dioxide, micronized silica, fumed silica, glycerol monostearate, magnesium trisilicate, and magnesium stearate. An external tablet coating may further include one or more vehicles such as plasticizers, binders, fillers, lubricants, compression aids, and combinations of any of the foregoing. The one or more additional coatings may comprise a single material or a combination of more than one material including any of those disclosed herein. These additional coatings may be applied to tablet dosage forms by methods known to those skilled in the art.

Plasticizers may also be included in tablet dosage forms, e.g., in coatings, provided by the present disclosure. Examples of plasticizers useful in tablet dosage forms provided by the present disclosure include alkyl citrates such as triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl triethyl citrate, and acetyl tributyl citrate; alkyl acetates such as triethyl acetate, acetyl triethyl acetate, tributyl acetate, acetyl triethyl acetate, and acetyl tributyl acetate; sucrose fatty acid esters; glycerin mono-, di- and tri-fatty acid esters such as tricetin, glycerin mono-fatty acid esters, glycerin monostearate and acetylated monoglyceride; polyglycerin fatty acid esters; polyethylene glycols such as macrool 400, macrool 600, macrool 1500, macrool 4000, macrool 6000, macrool 20,000, and macrool 35,000; dibutyl sebacate; tributyl sebacate; vinyl pyrrolidione; propylene glycol; sesame oil; castor oil; glycerin; silicone resins; D-sorbitol; phytosterol; alkyl phthalates such as diethyl phthalate, dibutyl phthalate and dioctyl phthalate; adipate polyesters; isopropyl myristate; medium chain triglyceride; butyl phthalyl butyl glycolate; polyoxyethylene polyoxypropylene glycol; and combinations of any of the foregoing.

In certain embodiments, the tablet core may be coated with a compression coating to provide, e.g., a desired release profile. In certain aspects the compression coating layers typically release no more than 20% of compound (1) over a period of 2 hours after the oral dosage form is placed in an aqueous solution free of compound (1). In certain aspects, the compression coating may comprise a compression coating layer comprises (i) a non-ionic polymer that is (a) a proton-donating acid having a pKa of greater than 8 or (b) a proton-accepting basic material having a pKa of less than 2, (ii) a natural gum or polysaccharide, (iii) a neutral polymer salt, (iv) a sugar, or (v) a lipid.

In certain embodiments, the tablet core may be coated with a barrier layer, e.g., physical or chemical protection. In certain aspects, the barrier layer may comprise a (i) non-ionic polymer material that is (a) a weakly acid (proton-donating) material having a pKa of greater than 8 or (b) a weakly basic (proton-accepting) material having a pKa of less than 2, (ii) a natural gum or polysaccharide, (iii) a neutral polymer salt, (iv) a sugar, or (v) a lipid.

Examples of suitable non-ionic polymers include non-ionic cellulose polymers, non-ionic vinyl and polyvinyl alcohol polymers, and/or non-ionic polymers that are not cellulose or vinyl-based. In various embodiments, non-ionic polymers are substantially free of carboxylic acid moieties.

Specific examples of non-ionic cellulose polymers include methylcellulose, ethylcellulose, propylcellulose, butylcellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose acetate butyrate, cellulose acetate propionate, methyl cellulose, methyl cellulose acetate, methyl cellulose propionate, methyl cellulose butyrate, ethyl cellulose acetate, ethyl cellulose propionate, ethyl cellulose butyrate, hydroxymethyl cellulose, hydroxy-
ethyl cellulose, hydroxyethyl methyl cellulose, hydroxypropyl cellulose, hydroxybutyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, low-substituted hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate, hydroxypropyl methylcellulose propionate, hydroxypropyl methylcellulose butyrate, and corresponding salts and esters.

[0073] Exemplary vinyl-based polymers include polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, and crospovidone (polymers of N-vinyl-2-pyrrolidone). Exemplary vinyl-containing polymers further include vinyl polymers and copolymers having hydroxy-containing repeat units, alkylacrylic-containing repeat units, or cycloamido-containing repeat units. Further exemplary vinyl-containing polymers also include polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinylhydroxyethyl ether, polyvinyl alcohol polyvinyl acetate copolymers, polyvinylpyrrolidone-polyvinylacetate copolymers, polyethylene vinyl alcohol copolymers, and polyoxyethylene-polyoxypropylene copolymers. In alternate embodiments, vinyl copolymers can include a second polymer can having (1) substantially carboxy-free hydroxy-containing repeat units and (2) hydrophobic repeat units.

[0074] In certain embodiments, the non-ionizable polyvinyl materials show no degradation as an excipient. Non-limiting examples of such materials include polyvinylpyrrolidone and crospovidone.

[0075] Examples of non-cellulosic non-vinyl based non-ionizing polymers include poly(lactide) poly(glycolide), poly(e-caprolactone), poly(lactide-co-glycolide), poly(lactide-co-ε-caprolactone), poly(ε-caprolactone), poly(ε-caprolactone), poly(ε-caprolactone), poly(isobutylcyanoacrylate, and poly(hexylcryanoacrylate, polylethylene glycol, polyethylene glycol, polypropylene glycol copolymers, polylethylene-polypropylene block copolymers, polylethylene glycol, poly(ε-caprolactone-co-methyl methacrylate) 2:1 (Eudragit NE), polylethylene glycol, polyethylene glycol propylene glycol copolymers, and polyethylene-polypropylene block copolymers (i.e. poloxamers). In some variations, non-ionizable polymers such as polylethylene-polyoxymethylene block copolymers show no degradation as an excipient. In certain variations, the non-cellulosic non-vinyl based non-ionizable polymers do not contain carboxylic acid moieties, or are substantially free of carboxylic acid moieties.

[0076] Suitable examples of such natural gums and polysaccharides include starch, chitin, guar gum, tara gum, locust bean gum, carrageenan, gellan gum, alginates, and xanthan gum.

[0077] In certain embodiments, the natural gums and polysaccharides contain carboxylic acid moieties, including salts thereof. Non-limiting examples of such materials include gellan gum, Alginates, and xanthan gum.

[0078] In various embodiments, natural gums or polysaccharides are substantially free of carboxylic acid moieties. Non-limiting examples of such materials include starch, chitin, guar gum, tara gum, locust bean gum, carrageenan.

[0079] Non-limiting examples of such neutral polymer salts include poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1, Poly (ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2, crosslinked sodium carboxymethyl cellulose (crosscarmellose sodium), crosslinked sodium carboxymethyl cellulose (sodium starch glycollate), salts of carboxymethyl cellulose, salts of carboxyethyl cellulose, salts of carboxylpropyl cellulose, salts of carboxybutyl cellulose, salts of carboxymethyl starch, and salts of carboxyethyl starch. In certain embodiments, the neutral polymer salts do not include a carboxylate group.

[0080] In certain embodiments, the neutral polymer salts do not degrade as excipients. Non-limiting examples of such materials include poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1, poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2, and croscarmellose sodium.

[0081] In certain embodiments, certain neutral polymer salts do not include a carboxyl group. These materials include poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1 and poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2.

[0082] In certain embodiments, certain neutral polymer salts include a carboxyl group that is neutralized with a counterion. Such compounds include crosslinked croscarmellose, crosslinked sodium carboxymethyl cellulose (sodium starch glycollate), salts of carboxymethyl cellulose, salts of carboxyethyl cellulose, salts of carboxypropyl cellulose, salts of carboxybutyl cellulose, salts of carboxymethyl starch, and salts of carboxyethyl starch.

[0083] In certain other embodiments, the ionizable polymers do not contain carboxylic acid groups. Such materials include poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1 (Eudragit E), chitosan, and methyl methacrylate diethylaminoethyl methacrylate copolymer. Eudragit E has polymer free amino groups, and is neutral at pH 3-5 and protonated at pH <5.

[0084] Examples of suitable sugars include lactose, mannitol, sorbitol, sucrose, and trehalose.

[0085] Examples of suitable lipids are glycerol behenate, castor oil, hydrogenated vegetable oil, hydrogenated carnauba wax, and microcrystalline wax. In certain variations, the lipids are substantially free of carboxylic acid moieties.

[0086] In certain embodiments, the barrier layer may be disposed between the tablet core and an enteric coating layer. In various aspects, the barrier layer is sufficiently thick and sufficiently continuous to prevent direct contact between the enteric coating and the core. Typically this can be accomplished by coating the cores to a target weight percent range. For cores having a size (e.g., diameter) of 2 mm or less, the barrier layer can comprise at least 5 wt % of the coated core. For cores having a size (e.g., diameter) greater than 6 mm, the barrier layer comprises at least 0.5 wt % of the coated core.

[0087] Alternatively, the barrier layer can be applied to a specified average thickness. For example, the barrier layer can have an average thickness of at least 5 μm. In other embodiments, the barrier layer has an average thickness of at least 15 μm.

[0088] Once the cores have been coated with the barrier layer, an enteric coating may then be applied. In various embodiments, the enteric coating comprises an enteric polymer that is substantially insoluble in aqueous solutions having a pH level below 4.5 but which starts to become soluble at a pH between 4.5 and 7.5 and is soluble in aqueous solutions having a pH above 7.5. The enteric coating remains intact while the oral dosage form is in the low pH environment of the stomach,
which means that the fumarate compound remains in the core while the dosage form is in the stomach.

Suitable enteric polymers include methacrylic acid polymers, cellulose acetate phthalate polymers, hydroxypropylmethyl cellulose acetate succinate polymers, hydroxypropylmethyl cellulose phthalate polymers and polyvinyl acetate phthalate polymers. Other examples of pH-sensitive polymers that can be used in the enteric coating include methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate (hypermelllose acetate succinate), polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers and shellac. Specific examples of enteric polymers include hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate phthalate, carboxymethyl cellulose, carboxymethyl cellulose, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate.

The oral dosage forms can be either immediate release, sustained release, delayed release or combinations thereof. For example, in order to minimize contact between the compound (1) and the tissues lining the stomach and to prevent exposure of the compound (1) to the low pH environments of the stomach, the dosage form may be a delayed release dosage form, and following the delay in prodrug release, thereafter provide either immediate release of the compound (1) or sustained release of the compound (1). As described herein, in certain embodiments, the oral dosage forms may be formulated to include compression coating layers to provide, e.g., delayed release, and the tablet cores may be prepared as immediate release formulations or sustained release formulations, depending on the desired release profile. In other embodiments, the oral dosage forms may be formulated to include a sustained release tablet core, an enteric coating, and a protective barrier layer intermediate the tablet core and the enteric coating.

Exemplary oral dosage forms are disclosed in co-owned applications, filed concurrently herein, entitled “ORAL DOSAGE FORMS OF METHYL HYDROGEN FUMARATE AND PRODRUGS THEREOF”, under Attorney Docket Number P234942.US.01 (X-0184 P1), and “ORAL DOSAGE FORMS OF METHYL HYDROGEN FUMARATE AND PRODRUGS THEREOF” under Attorney Docket Number P234941.US.01 (X-0183 P1), the contents of which are both herein incorporated by reference.

In certain embodiments in which tablet dosage forms comprise less than a therapeutically effective amount of compound (1), multiple tablet dosage forms may be administered to a subject simultaneously or over a period of time to provide a therapeutically effective dose of compound (1). For instance, the oral dosage form may be formulated to comprise an amount of compound (1) suitable for twice a day administration (BID), three times a day administration (TID), etc.

The release characteristics of dosage forms provided by the present disclosure comprising compound (1) may be characterized, in part, by the in vitro dissolution profile. Methods for determining dissolution profiles of dosage forms are well known to those skilled in the pharmaceutical arts. Standard methodologies set forth in the U.S. Pharmacopeia may be used. For example, a dissolution profile may be determined using either a U.S. Pharmacopeia Type I Apparatus (baskets) or a U.S. Pharmacopeia Type II Apparatus (paddles).

Using the latter method, dissolution, or release, profiles of dosage forms provided by the present disclosure may be determined by immersing the dosage forms into a dissolution vessel (USP Type I, basket) containing 750 mL of 0.1 N hydrochloric acid (pH 1.2). After 2 hours, 250 mL of 200 mM tribasic sodium phosphate was added to the vessel resulting in a pH adjustment from 1.2 to 6.8. The dissolution medium was kept at 37° C. and was agitated at 100 rpm.

Samples are withdrawn from the dissolution medium at intervals and the content of compound (1) in the dissolution medium determined using reverse phase high pressure liquid chromatography (HPLC).

In certain embodiments, release of compound (1) from tablet dosage forms provided by the present disclosure exhibits an in vitro dissolution profile wherein about 20% to about 45% of the (N,N-Diethylcarbamoyl)methylmethyl (2E)but-2-ene-1,4-dioate in the dosage form is released within about 4 hours; about 40% to about 70% of the (N,N-Diethylcarbamoyl)methylmethyl (2E)but-2-ene-1,4-dioate is released within about 8 hours; about 60% to about 85% of the (N,N-Diethylcarbamoyl)methylmethyl (2E)but-2-ene-1,4-dioate is released within about 12 hours; and about 80% to about 100% of the (N,N-Diethylcarbamoyl)methylmethyl (2E)but-2-ene-1,4-dioate is released within about 20 hours.

In certain embodiments, a tablet exhibits a dissolution profile that is similar to the foregoing profile as determined using the f1 difference factor and the f2 similarity factor according to FDA guidelines.

In certain of such embodiments, a tablet dosage form exhibiting the foregoing release profiles comprises about 700 mg to about 1,600 mg compound (1).

It is generally recognized that commercially acceptable tablets have a friability of less than about 1 wt % determined according to USP Test No. 1216. In certain embodiments, tablets provided by the present disclosure have a friability of less than about 0.1 wt %, in certain embodiments, less than about 0.5 wt %, in certain embodiments, less than about 0.3 wt %, and in certain embodiments, less than about 0.1 wt %.
Therapeutic Uses

[0099] The dosage forms disclosed herein may be administered to a patient suffering from any disease including a disorder, condition, or symptom for which MHF is known or hereafter discovered to be therapeutically effective. Indications for which MHF has been prescribed, and hence for which a dosage form disclosed herein is also expected to be effective, include psoriasis. Other indications for which the disclosed dosage forms may be therapeutically effective include multiple sclerosis, an inflammatory bowel disease, asthma, chronic obstructive pulmonary disease, and arthritis.

[0100] Methods of treating a disease in a patient provided by the present disclosure comprise administering to a patient in need of such treatment a dosage form disclosed herein. The dosage forms disclosed herein may provide therapeutic or prophylactic plasma and/or blood concentrations of MHF following administration to a patient.

[0101] The dosage forms disclosed herein may be administered in an amount and using a dosing schedule as appropriate for treatment of a particular disease. For example, daily doses of compound (1) may range from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 50 mg/kg, from about 1 mg/kg to about 50 mg/kg, and in certain embodiments, from about 5 mg/kg to about 25 mg/kg. In certain embodiments, the compound (1) may be administered at a dose per day from about 10 mg to about 4 g per day, and in certain embodiments from about 20 mg to about 2 g per day. An appropriate dose of compound (1) may be determined based on several factors, including, for example, the body weight and/or condition of the patient being treated, the severity of the disease being treated, the incidence and/or severity of side effects, the manner of administration, and the judgment of the prescribing physician. Appropriate dose ranges may be determined by methods known to those skilled in the art.

[0102] MHF may be assayed in vitro and in vivo for the desired therapeutic or prophylactic activity prior to use in humans. In vivo assays, for example using appropriate animal models, may also be used to determine whether administration of compound (1) is therapeutically effective.

[0103] In certain embodiments, a therapeutically effective dose of compound (1) may provide therapeutic benefit without causing substantial toxicity including adverse side effects. Toxicity of compound (1) and/or metabolites thereof may be determined using standard pharmaceutical procedures and may be ascertained by those skilled in the art. The dose ratio between toxic and therapeutic effect is the therapeutic index. A dose of compound (1) may be within a range capable of establishing and maintaining a therapeutically effective circulating plasma and/or blood concentration of MHF that exhibits little or no toxicity.

[0104] The dosage forms disclosed herein may be used to treat diseases, disorders, conditions, and symptoms of any of the foregoing for which MHF is known to provide or is later found to provide therapeutic benefit. MHF is known to be effective in treating psoriasis, multiple sclerosis, an inflammatory bowel disease, asthma, chronic obstructive pulmonary disease, and arthritis. Hence, the dosage forms disclosed herein may be used to treat any of the foregoing diseases and disorders. The underlying etiology of any of the foregoing diseases being treated may have a multiplicity of origins. Further, in certain embodiments, a therapeutically effective amount of compound (1) may be administered to a patient, such as a human, as a preventative measure against various diseases or disorders. Thus, a therapeutically effective amount of compound (1) may be administered as a preventative measure to a patient having a predisposition for and/or history of immunological, autoimmune, and/or inflammatory diseases including psoriasis, asthma and chronic obstructive pulmonary diseases, cardiac insufficiency including left ventricular insufficiency, myocardial infarction and angina pectoris, mitochondrial and neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, retinopathy pigmentosa and mitochondrial encephalopathy, transplantation rejection, autoimmune diseases including multiple sclerosis, ischemia and reperfusion injury, AGE-induced genome damage, inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis; and NF-κB mediated diseases.

Psoriasis

[0105] Psoriasis is characterized by hyperkeratosis and thickening of the epidermis as well as by increased vascularity and infiltration of inflammatory cells in the dermis. Psoriasis vulgaris manifests as silvery, scaly, erythematous plaques on typically the scalp, elbows, knees, and buttocks. Guttate psoriasis occurs as tear-drop size lesions.


[0107] Efficacy of compound (1) for treating psoriasis can be determined using animal models and in clinical trials.

Inflammatory Arthritis

[0108] Inflammatory arthritis includes diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis (juvenile idiopathic arthritis), psoriatic arthritis, and ankylosing spondylitis, each of which produces joint inflammation. The pathogenesis of immune-mediated inflammatory diseases including inflammatory arthritis is believed to involve TNF and NK-κB signaling pathways (Tracey et al., Pharmacology & Therapeutics 2008, 117, 244-279). Dimethyl fumarate has been shown to inhibit TNF and inflammatory diseases including inflammatory arthritis, which are believed to involve TNF and NK-κB signaling and therefore may be useful in treating inflammatory arthritis (Lowewe et al., J Immunology 2002, 168, 4781-4787).

[0109] The efficacy of compound (1) for treating inflammatory arthritis can be determined using animal models and in clinical trials.

Multiple Sclerosis

[0110] Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system caused by an autoimmune attack against the isolating axonal myelin sheets of the central nervous system. Demyelination leads to the breakdown of conduction and to severe disease with destruction of local axons and irreversible neuronal cell death. The symptoms of MS are highly varied with each individual patient exhibiting a particular pattern of motor, sensible, and sensory disturbances. MS is typified pathologically by multiple inflammatory foci, plaques of demyelination, gliosis, and axonal pathology within the brain and spinal cord, all of which contribute to the clinical manifestations of neurological disability (see e.g., Wingerchuk, Lab Invest 2001, 81,
Although the causal events that precipitate MS are not fully understood, evidence implicates an autoimmune etiology together with environmental factors, as well as specific genetic predispositions. Functional impairment, disability, and handicap are expressed as paralysis, sensory and ophthalmic disturbances, spasticity, tremor, a lack of coordination, and visual impairment, which impact on the quality of life of the individual. The clinical course of MS can vary from individual to individual, but invariably the disease can be categorized in three forms: relapsing-remitting, secondary progressive, and primary progressive.

Studies support the efficacy of FAEs for treating MS and are undergoing phase II clinical testing (Schimrigk et al., Eur J Neurology 2006, 13, 604-610; and Wallace and Thio, Current Opinion Investigational Drugs 2007, 8(11), 955-962).

Assessment of MS treatment efficacy in clinical trials can be accomplished using tools such as the Expanded Disability Status Scale and the MS Functional as well as magnetic resonance imaging lesion load, biomarkers, and self-reported quality of life. Animal models of MS shown to be useful to identify and validate potential therapeutics include experimental autoimmune/allergic encephalomyelitis (EAE) rodent models that simulate the clinical and pathological manifestations of MS and nonhuman primate EAE models.

Inflammatory Bowel Disease (Crohn's Disease, Ulcerative Colitis)

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the large intestine and in some cases, the small intestine that includes Crohn's disease and ulcerative colitis. Crohn's disease, which is characterized by areas of inflammation with areas of normal lining in between, can affect any part of the gastrointestinal tract from the mouth to the anus. The main gastrointestinal symptoms are abdominal pain, diarrhea, constipation, vomiting, weight loss, and/or weight gain. Crohn's disease can also cause skin rashes, arthritis, and inflammation of the eye. Ulcerative colitis is characterized by ulcers or open sores in the large intestine or colon. The main symptom of ulcerative colitis is typically constant diarrhea with mixed blood of gradual onset. Other types of intestinal bowel disease include collagenous colitis, lymphocytic colitis, ischemic colitis, diversion colitis, Behcet's colitis, and indeterminate colitis.

FAEs are inhibitors of NF-kB activation and therefore may be useful in treating inflammatory diseases such as Crohn's disease and ulcerative colitis (Atreya et al., J Intern Med 2008, 263(6), 59106).

The efficacy of compound (1) for treating inflammatory bowel disease can be evaluated using animal models and in clinical trials. Useful animal models of inflammatory bowel disease are known.

Asthma

Asthma is reversible airway obstruction in which the airway occasionally constricts, becomes inflamed, and is lined with an excessive amount of mucus. Symptoms of asthma include dyspnea, wheezing, chest tightness, and cough. Asthma episodes may be induced by airborne allergens, food allergies, medications, inhaled irritants, physical exercise, respiratory infection, psychological stress, hormonal changes, cold weather, or other factors.

As an inhibitor of NF-kB activation and as shown in animal studies (Joshi et al., US 2007/0027076) FAEs may be useful in treating pulmonary diseases such as asthma and chronic obstructive pulmonary disorder.

The efficacy of compound (1) for treating asthma can be assessed using animal models and in clinical trials.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), also known as chronic obstructive airway disease, is a group of diseases characterized by the pathological limitation of airflow in the airway that is not fully reversible, and includes conditions such as chronic bronchitis, emphysema, as well as other lung disorders such as asbestosis, pneumoconiosis, and pulmonary neoplasms (see, e.g., Barnes, Pharmacological Reviews 2004, 56(4), 515-548). The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. COPD is characterized by a shortness of breath that can last for months or years, possibly accompanied by wheezing, and a persistent cough with sputum production. COPD is most often caused by tobacco smoking, although it can also be caused by other airborne irritants such as coal dust, asbestos, urban pollution, or solvents. COPD encompasses chronic obstructive bronchiolitis with fibrosis and obstruction of small airways, and emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways.

The efficacy of administering compound (1) for treating chronic obstructive pulmonary disease may be assessed using animal models of chronic obstructive pulmonary disease and in clinical studies. For example, murine models of chronic obstructive pulmonary disease are known.

Neurodegenerative Disorders

Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis are characterized by progressive dysfunction and neuronal death. NF-kB inhibition has been proposed as a therapeutic target for neurodegenerative diseases (Camandola and Mattson, Expert Opin Ther Targets 2007, 11(2), 123-32).

Parkinson's Disease

Parkinson's disease is a slowly progressive degenerative disorder of the nervous system characterized by tremor when muscles are at rest (resting tremor), slowness of voluntary movements, and increased muscle tone (rigidity). In Parkinson's disease, nerve cells in the basal ganglia, e.g., substantia nigra, degenerate, and thereby reduce the production of dopamine and the number of connections between nerve cells in the basal ganglia. As a result, the basal ganglia are unable to properly control smooth muscle movements and coordinate movements in posture as normal, leading to tremor, incoordination, and slowed, reduced movement (bradykinesia) (Blandini et al., Mol. Neurobiol. 1996, 12, 73-94).

The efficacy of compound (1) for treating Parkinson's disease may be assessed using animal and human models of Parkinson's disease and in clinical studies.
Alzheimer’s Disease

[0124] Alzheimer’s disease is a progressive loss of mental function characterized by degeneration of brain tissue, including loss of nerve cells and the development of senile plaques and neurofibrillary tangles. In Alzheimer’s disease, parts of the brain degenerate, destroying nerve cells and reducing the responsiveness of the maintaining neurons to neurotransmitters. Abnormalities in brain tissue consist of senile or neuritic plaques, e.g., clumps of dead nerve cells containing an abnormal, insoluble protein called amyloid, and neurofibrillary tangles, twisted strands of insoluble proteins in the nerve cell.

[0125] The efficacy of compound (1) for treating Alzheimer’s disease may be assessed using animal and human models of Alzheimer’s disease and in clinical studies.

Huntington’s Disease

[0126] Huntington’s disease is an autosomal dominant neurodegenerative disorder in which specific cell death occurs in the neostriatum and cortex (Martin, N Engl J Med 1999, 340, 1970-80). Onset usually occurs during the fourth or fifth decade of life, with a mean survival at age of onset of 14 to 20 years. Huntington’s disease is universally fatal, and there is no effective treatment. Symptoms include a characteristic movement disorder (Huntington’s chorea), cognitive dysfunction, and psychiatric symptoms. The disease is caused by a mutation encoding an abnormal expansion of CAG-encoded polyglutamine repeats in the protein, huntingtin.

[0127] The efficacy of compound (1) for treating Huntington’s disease may be assessed using animal and human models of Huntington’s disease and in clinical studies.

Amyotrophic Lateral Sclerosis

[0128] Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the progressive and specific loss of motor neurons in the brain, brain stem, and spinal cord (Rowland and Schneider, N Engl J Med 2001, 344, 1688-1700). ALS begins with weakness, often in the hands and less frequently in the feet that generally progresses up an arm or leg. Over time, weakness increases and spasticity develops characterized by muscle twitching and tightening, followed by muscle spasms and possibly tremors. The average age of onset is 55 years, and the average life expectancy after the clinical onset is 4 years. The only recognized treatment for ALS is riluzole, which can extend survival by only about three months.

[0129] The efficacy compound (1) for treating ALS may be assessed using animal and human models of ALS and in clinical studies.

Other Diseases

[0130] Other diseases and conditions for which compound (1) can be useful in treating include rheumatica, granuloma annulare, lupus, autoimmune carditis, eczema, sarcoidosis, and autoimmune diseases including acute disseminated encephalomyelitis, Addison’s disease, alopecia areata, unkylosing spondylitis, antiphospholipid antibody syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, bullous pemphigoid, Behcet’s disease, celiac disease, Chagas disease, chronic obstructive pulmonary disease, Crohn’s disease, dermatomyositis, diabetes mellitus type 1, endometriosis, Goodpasture’s syndrome, Graves’ disease, Guillain-Barre syndrome, Hashimoto’s disease, hidradenitis suppurativa, Kawasaki disease, IgA neuropathy, idiopathic thrombocytopenic purpura, interstitial cystitis, lupus erythematosus, mixed connective tissue disease, morphea, multiple sclerosis, myasthenia gravis, narcolepsy, neumyotonia, nephritis vulgaris, pernicious anemia, psoriasis, psoriatic arthritis, polyoma virus, primary biliary cirrhosis, rheumatoid arthritis, schizophrana, scleroderma, Sjogren’s syndrome, stiff person syndrome, temporal arteritis, ulcerative colitis, vasculitis, vitiligo. Wegener’s granulomatosis, optic neuritis, neuromyelitis optica, subacute necrotizing myelopathy, bolo concentric sclerosis, transverse myelitis, susac syndrome, central nervous system vasculitis, neurosyphilis, Charcot-Marie-Tooth Disease, progressive supranuclear palsy, neurodegeneration with brain iron accumulation, paracaspoid syndromes, primary lateral sclerosis, Alper’s Disease, mononuclear myelopathy, adrenal leukodystrophy, Alexander’s Disease, Canavan disease, childhood ataxia with central nervous system hypomyelination, Krabbe Disease, Pelizaeus-Merzbacher disease, Schilder Disease, Zellweger’s syndrome, Sjogren’s Syndrome, human immunodeficiency viral infection, hepatitis C viral infection, herpes simplex viral infection and a tumor.

Dosing

[0131] The dosage forms disclosed herein, and their use for therapeutic treatment, are not limited to any particular oral dosing regimen as long as the dosing regimen achieves therapeutic plasma concentration levels and AUC levels. Compound (1) may be administered at dosage levels of about 0.001 mg/kg to about 50 mg/kg, from about 0.01 mg/kg to about 25 mg/kg, or from about 0.1 mg/kg to about 10 mg/kg of subject body weight per day, one, two, three, four or more times a day, to obtain the desired concentrations and AUC for MIF in the blood plasma.

[0132] The amount of MIF or a MIF prodrug that will be effective in the treatment of a disease in a patient will depend, in part, on the nature of the condition and can be determined by standard clinical techniques known in the art. In addition, in vitro or in vivo assays may be employed to help identify optimal dosage ranges. A therapeutically effective amount of compound (1) to be administered may also depend on, among other factors, the subject being treated, the weight of the subject, the severity of the disease, the manner of administration, and the judgment of the prescribing physician.

[0133] For systemic administration, a therapeutically effective dose may be estimated initially from in vitro assays. For example, a dose may be formulated in animal models to achieve a beneficial circulating composition concentration range. Initial doses may also be estimated from in vivo data, e.g., animal models, using techniques that are known in the art. Such information may be used to more accurately determine useful doses in humans. One having ordinary skill in the art may optimize administration to humans based on animal data.

[0134] A dose may be administered in a single dosage form or in multiple dosage forms. When multiple dosage forms are used the amount of compound (1) contained within each dosage form may be the same or different. The amount of compound (1) contained in a dose may depend on whether the disease in a patient is effectively treated by acute, chronic, or a combination of acute and chronic administration.
In certain embodiments an administered dose is less than a toxic dose. Toxicity of the compositions described herein may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD50 (the dose lethal to 50% of the population) or the LD100 (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. In certain embodiments, compound (1) may exhibit a high therapeutic index. The data obtained from these cell culture assays and animal studies may be used in formulating a dosage range that is not toxic for use in humans.

A dose of compound (1) provided by the present disclosure may be within a range of circulating concentrations for example the blood, plasma, or central nervous system, that include the effective dose and that exhibits little or no toxicity. A dose may vary within this range depending upon the dosage form employed. In certain embodiments, an escalating dose may be administered.

Since compound (1) is a prodrug of MIF, dosage forms containing compound (1) provide MIF to a subject. The proomity of compound (1) may be cleaved either chemically and/or enzymatically. One or more enzymes present in the stomach, intestinal lumen, intestinal tissue, blood, liver, brain or any other tissue suitable of a mammal can enzymatically cleave the proomity of compound (1). If the proomity is cleaved after absorption by the gastrointestinal tract, compound (1) can be absorbed into the systemic circulation from the large intestine. In certain embodiments, the proomity is cleaved after absorption by the gastrointestinal tract. In certain embodiments, the proomity is cleaved in the gastrointestinal tract and MIF is absorbed into the systemic circulation from the large intestine. In certain embodiments, compound (1) is absorbed into the systemic circulation from the gastrointestinal tract, and the proomity is cleaved in the systemic circulation, after absorption of compound (1) from the gastrointestinal tract.

In certain embodiments, dosage forms comprising compound (1) may be administered concurrently with the administration of another therapeutic agent, which may be part of the same dosage form as, or in a different dosage form than that comprising compound (1). Compound (1) may be administered prior or subsequent to administration of another therapeutic agent. In certain embodiments of combination therapy, the combination therapy may comprise alternating between administering compound (1) and a composition comprising another therapeutic agent, e.g., to minimize adverse drug effects associated with a particular drug. When compound (1) is administered concurrently with another therapeutic agent that potentially may produce an adverse drug effect including, but not limited to, toxicity, the other therapeutic agent may advantageously be administered at a dose that falls below the threshold at which the adverse drug reaction is elicited.

In certain embodiments, in the treatment of a subject suffering from multiple sclerosis, a dosage form comprising compound (1) may be administered in conjunction with an agent known or believed to be effective in treating multiple sclerosis, including Gilenya (lingolimod), Avonex (interferon β1a), Rebif (interferon-β1a), Betaseron/Extavia (interferon β1b), Copaxone (Copolymer1), Tysabri (natalizumab), Aubagio (teriflunomide), dimethyl fumarate, laquinimid, modafinil, azathioprine, mycophenolate mofetil, mitoxantrone, corticosteroids such as prednisolone, methylprednisolone, glatiramer, glatiramer acetate, monoclonal antibodies that bind to the very late antigen-4 (VLA-4) integrin such as natalizumab; immunomodulatory agents such as FTY 720 sphingosine-1 phosphate modulator and COX-2 inhibitors such as BW755c, piroxicam, and phenidone; and neuroprotective treatments including inhibitors of glutamate excitotoxicity and iNOS, free-radical scavengers, and cationic channel blockers; memantine; AMPA antagonists such as topiramate; and glycine-site NMDA antagonists and Lmitrada (lentuzumab).

In certain embodiments, in the treatment of a subject suffering from psoriasis, a dosage form comprising compound (1) may be administered in conjunction with an agent known or believed to be effective in treating psoriasis, including steroids such as fluarandrenolide, flucononide, alclometasone, amcinonide, desonide, halcinonide, triamcinolone, clobetasol, clocortolone, mometasone, desoximetasone, and halobetasol; anti-rheumatics such as Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab); immunosuppressive agents such as cyclosporine, alefacept, and efalizumab; psorlens such as methoxsalen; and other such as calcipotriene, methotrexate, hydrocortisone/pranoxine, Soriatane (acetretin), betamethasone/calcipotriene, tazarotene, benzoate/pyrrolamine/zinc oxide, Fumaderm (dimethyl fumarate and ethyl hydrogen fumarate), dimethyl fumarate, apropilast, tafocitini, LY2439821 (Eli Lilly), sccukinumab, and Stelera (ustekinumab).

**EXAMPLES**

The following examples describe in detail the preparation and properties of tablet dosage forms comprising compound (1). It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the disclosure.

Synthesis of (N,N-Diethylcarnamoyl)methyl methylenediamine (2E)-but-2-ene-1,4-dione by General Procedure A: Nucleophilic substitution of 1-haloacetamides or 1-halo acetic acid derivatives with monomethyl fumarate

(2E)-3-(Methoxycarbonyl)prop-2-enoic acid (methylenediamine fumarate, MIF), (2E)-3-(tert-butoxycarbonyl)prop-2-enoic acid (tert-butyl hydrogen fumarate), or fumaric acid (FA) (1.0 equivalents) is dissolved in 5-10 mL/3.0 mmol of an inert solvent such as N-methylpyrroldione (NMP), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA, DMAc), acetone (MeCN), dimethylsulfoxide (DMSO), tetrahydrofuran (THF), toluene, or mixtures thereof. To the solution, 0.8 to 1.2 equivalents of an appropriate inorganic base such as cesium hydrogen carbonate (CsHCO3), cesium carbonate (Cs2CO3), or potassium carbonate (K2CO3) is added. Alternatively, 0.8 b is 1.2 equivalents of a silver salt such silver(I) oxide (Ag2O) or silver(I) carbonate (Ag2CO3); an organic secondary or tertiary base such as dicyclohexylamine (DCHA), triethylamine (TEA), disopropylethylamine (DEA), tetraubutylammonium hydroxide (TBAOH), amidine; or a guanidine-based base such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or 1,1,3,3-tetramethylguanidine (TMG) may be employed. The corresponding alkali, silver, di-, tri- and tetraklylammonium, amidine, or guanide salt of monomethyl fumarate can also be preformed. The solution is stirred for 10-60 min at room temperature followed by addition of 0.8-1.2 equivalents of an appropri-
ately functionalized 1-haloacetamide, 1-halo acetic acid derivative, acyloxyalkyl halide, or alky- or aryloxycarbonyloxyalkyl halide. The reaction mixture is stirred overnight at a temperature between 40 to 100°C. After cooling to room temperature, insolubles can optionally be filtered off and the reaction mixture diluted with one molar (1.0 M) hydrochloric acid (HCl) and an appropriate organic solvent such as methyl tert-butyl ether (MTBE), diethyl ether (Et₂O), ethylacetate (EtOAc), or mixtures thereof. After phase separation, the aqueous phase is extracted several times with the same solvent. The combined organic extracts are washed with water, brine, and dried over anhydrous magnesium sulfate (MgSO₄). After filtration, the organic solvents are removed under reduced pressure using a rotary evaporator. If required, the crude reaction products are further purified by well known purification techniques such as silica gel flash column chromatography (i.e., Biotage), mass-guided reversed-phase preparative HPLC/flyophilization, precipitation, or crystallization.

Example 1
Synthesis of (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate (1)

Following General Procedure A above, methyl hydrogen fumarate (MHIF, 9 kg) and toluene (48.3 kg) were added to a 100 L glass-lined stainless steel conical reactor. The reactor was agitated at 125 rpm and charged with N,N-diethylchloroacetamide (10.4 kg). The reaction mixture was heated to 52°C and disisopropylmethane (9.8 kg) was added over 31 minutes, with a final internal temperature of 57°C. The reaction mixture was then heated to 85-90°C for 4 hours. The reaction volume was cooled to 50-55°C, a sample was removed for in-process analysis and then further cooled to 30°C. Water (13.5 kg) was added to the mixture and agitated for 30 minutes. The reaction mixture was filtered through a pressure plate with a polypropylene cloth and a bed of diatomaceous earth (9.0 kg) into a 100 L glass-lined reactor. The filter bed was rinsed forward into the reactor with toluene (15.6 kg). The layers were allowed to separate and the lower aqueous layer was removed into a USP water drum. Water (6.8 kg) was charged to the reactor and agitated for 10 minutes. Maturation was stopped and the layers were allowed to separate for 30 minutes. The lower aqueous layer was removed into a USP water drum. Toluene (116.8 kg) was added to the upper organic phase, the resulting solution was then passed through a previously prepared plug of silica gel (23.4 kg). The filtrate was collected through a 1 μM in-line filter into a 100 L glass-lined stainless steel reactor. The silica gel plug was rinsed with toluene (116.8 kg) into a clean GMP drum. In process check for residual Di(N,N-diethylcarbamoyl)methyl (2E)but-2-ene-1,4-dioate was taken on both the reactor contents and the drum. The reaction solution from the drum and reactor was concentrated under reduced pressure to an approximate volume of 20 L, with an internal temperature of 51°C. To a separate 100 L glass lined conical reactor was added n-heptane (43.1 kg) which was cooled to 2°C. The prodrug solution in toluene at 51°C was transferred via a transfer pump into the n-heptane containing reagent with agitation over 19 minutes, with a final internal temperature of 4°C. The mixture was stirred at 156 rpm for 3 hours at 2-4°C. The product was collected on a filter press plate with a polypropylene cloth and rinsed with n-heptane (8.6 kg). The product was dried under nitrogen on the pressure plate for 2 hours and then transferred to a drying tray and died in a tray dryer at 43°C for 16 hours to afford 7.028 kg of (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate.

Example 2
Alternate Synthesis of (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate (1)

Following General Procedure A above, a 5-L, three-neck, round-bottom flask was equipped with a mechanical stirrer, an internal thermometer, a 500 mL addition funnel and a nitrogen inlet and was charged with methyl hydrogen fumarate (MHIF) (1.30 kg, 10 mol) and N,N-diethylchloroacetamide (1.34 kg, 9 mol). The resulting slurry was slowly heated to 50°C and disisopropylamine (1.75 L; 1.295 kg, 10 mol) was added slowly over a period of two hours with a final internal temperature of 75°C. The reaction mixture was heated to 70°C for three hours. A sample was taken from the reaction mixture for in process analysis by HPLC. The reaction mixture was then cooled to 50°C and diluted with ethyl acetate (10 L). The mixture was filtered through a 30 μM in-line filter into a 20 L separatory funnel and washed with water (3×2 L). The organic phase was separated, dried over sodium sulfate and then evaporated under vacuum to give the product as a viscous oil. This crude product was dissolved in disisopropyl ether (8 L) and warmed to 50°C. The resulting warm milky slurry was filtered through celite. The clear filtrate was slowly cooled to room temperature and then to 0°C over a period of four hours. During this period the compound crystallized out as a white-solid. It was filtered and dried in a vacuum oven at 40°C for 48 hrs to afford 1.5 kg of (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate (68.8% yield).

Example 3
Granulations, containing 97 wt% loading of the (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate made in accordance with Example 2, were made having the ingredients shown in Table 1:
**TABLE 1**

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>Role</th>
<th>Quantity (%) w/w</th>
<th>Batch Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N,N-Diethylcarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate (Compound (1))</td>
<td>XenoPort (Santa Clara, CA)</td>
<td>Drug substance</td>
<td>97.0</td>
<td>659.6</td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose</td>
<td>Aquacoll (Hopewell, VA)</td>
<td>Binder</td>
<td>3.0</td>
<td>20.4</td>
</tr>
<tr>
<td>Purified water</td>
<td>NA</td>
<td>Granulation agent</td>
<td>NA</td>
<td>43.5*</td>
</tr>
</tbody>
</table>

Total: 100.00 680.0 g*

*Water is dried off during process and does not contribute to the final granulation weight.

**Example 4**

Granulations, containing 97 wt % loading of (N,N-Diethylcarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate made in Example 1 were made having the ingredients shown in Table 2.

**TABLE 2**

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>Role</th>
<th>Quantity (%) w/w</th>
<th>Batch Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N,N-Diethylcarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate (Compound (1))</td>
<td>Cambridge Major (Germantown, WI)</td>
<td>Drug substance</td>
<td>97.0</td>
<td>480.00</td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose</td>
<td>Aquacoll (Hopewell, VA)</td>
<td>Binder</td>
<td>3.0</td>
<td>14.88</td>
</tr>
<tr>
<td>Purified water</td>
<td>NA</td>
<td>Granulation agent</td>
<td>NA</td>
<td>55</td>
</tr>
</tbody>
</table>

Total: 100.00 404.88 g*

*Water is dried off during process and does not contribute to the final granulation weight.

**Example 5**

Granulations, containing 97 wt % of (N,N-Diethylcarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate made in Example 2, were made having the ingredients shown in Table 3.
TABLE 3

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>Role</th>
<th>Quantity (%)</th>
<th>Batch Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XenoPort (Santa Clara, CA)</td>
<td>Drug substance</td>
<td>97.0</td>
<td>164.9</td>
<td></td>
</tr>
<tr>
<td>(N,N-Diethylcarbamoyl)methyl (2E)but-2-ene-1,4-dioate (Compound (1))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose</td>
<td>Aqualon (Hopewell, VA)</td>
<td>Binder</td>
<td>3.0</td>
<td>51</td>
</tr>
<tr>
<td>Purified water</td>
<td>NA</td>
<td>Granulation agent</td>
<td>NA</td>
<td>172*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100.00</td>
<td>170.0 g*</td>
</tr>
</tbody>
</table>

*Water is dried off during process and does not contribute to the final granulation weight.

[0153] The granules were prepared using a high shear wet granulation process. The granulation batch size was 170.0 g. Compound (1) was passed through the Quadro Comil U5 with an 813 micron screen at 2000 rpm. Hydroxypropyl cellulose was passed through a 500 micron mesh screen. Compound (1) and hydroxypropyl cellulose were combined in a Diosna P1/6 equipped with a 1 L bowl and mixed for 2 minutes with the impeller speed of approximately 770 rpm (~6.0 m/s) and chopper set to 2000 rpm. After 2 minutes of dry mixing, the purified water (17.2 g) was added to the granulator using a peristaltic pump at a rate of approximately 4.9 g/min. The wet granules were screened through an 1180 micron mesh screen and dried on trays in an oven at 30°C for 3 hours and 35 minutes. The dried granules were passed through a 600 micron mesh screen.

[0154] The particle size distributions of the blend before granulation and the granules after granulation were determined using a Symptec QICPIC particle size analyzer with a lens capable of detecting particles from 5-1705 microns and a RODOS dry powder dispersion system at 1.0 bar of pressure. FIG. 3 shows the particle size distribution both before (▼▼▼) and after (■■■) granulation. FIG. 3 clearly shows the increase in particle size due to the formation of granules.

Example 6

[0155] Four different tablets (6a through 6d), containing differing levels of (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate (compound (1)) ranging from from 86 to 96 wt%, were made from the granules made in Example 3. The compositions of the four tablets are summarized in Table 4. The dried granules (97% (N,N-Diethylcarbamoyl) methyl methyl (2E)but-2-ene-1,4-dioate and 3% hydroxypropyl cellulose), hypromellose 2208 (100000 mPa·s viscosity), and the silicon dioxide were then passed through a 600 micron mesh screen, combined in a glass jar and blended on a Turbula mixer for 5 minutes (except for blend 6a which was not blended until addition of magnesium stearate). Magnesium stearate was passed through a 250 micron screen and added to the blend and blended for 1.5 minutes. Tablets were compressed using a Carver Press with 1/4 inch (6.4 mm) round standard concave tooling at 0.4 metric ton (MT) force. The tablets had a final hardness of approximately 7.4 to 8.4 kp (72 to 82 Newtons).

| Example 7 |

[0156] A two-stage dissolution method was used to determine the in vitro dissolution profile of dosage forms prepared according to Example 6. The two-stage dissolution test was used to better approximate the pH conditions experienced by a dosage form after swallowing by a patient, i.e., low pH of the stomach followed by near neutral pH of the intestines. The dosage forms were first placed into a dissolution vessel (USP, Type I, basket) containing 750 mL of 0.1 N hydrochloric acid (pH 1.2). After 2 hours, 250 mL of 200 mM tribasic sodium phosphate was added to the vessel resulting in a pH adjustment from 1.2 to 6.8. The dissolution medium was kept at 37°C, and was agitated at 100 rpm.

[0157] Samples of the dissolution medium were withdrawn after 1 and 2 hours in the low pH stage, and at 0.5, 2, 4, 7, 10 and 14 hours following addition. The released amount of compound (1) in the samples was determined by reverse phase HPLC using a C18 column and a 7 minute gradient method according to Table 5 where Mobile Phase A is water/0.1% H3PO4 and Mobile Phase B is water/acetonitrile/H3PO4 (10/50/0.1 by volume) with UV detection at 210 nm.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>% Mobile Phase A</th>
<th>Mobile Phase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>5.5</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

[0158] FIG. 4 shows that the rate at which (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate is
released from the tablets slows with increasing percentage of hydroxypropylmethyl cellulose (hypromellose 2208 (100000 mPa.s viscosity)) in the tablets. Tablet 6a (0% HPMC K100M, •• symbols in FIG. 4) is an immediate release tablet. Tablets 6b (5% HPMC K100M, •• symbols in FIG. 4), 6c (8% HPMC K100M, △△ symbols in FIG. 4), and 6d (10% HPMC K100M, □□ symbols in FIG. 4) are sustained release tablets with the amount of released drug reaching 90% at approximately 5, 7, and 9 hours, respectively.

Example 8

Flow Characterization of Dry Powders

The flow of dry powders was characterized using a FLODEX™ Powder Flowability Index Test Instrument (Hanson Research Corporation, Chatsworth, Calif.). The instrument was equipped with a cylindrical metal reservoir, which holds the test powder prior to flow testing. The cylindrical reservoir has an inside diameter of 5.7 cm and a length of 7.4 mm. The bottom end of the reservoir can be closed with removable metal discs. Each disc has a round orifice centered in the disc. Orifice diameters range from 4 mm to 10 mm in 1 mm increments, and from 10 mm to 34 mm in 2 mm increments. Prior to flow testing, the orifice is blocked. Powder is then placed over the blocked orifice. When the orifice is unblocked, powder can flow through the orifice under the force of gravity if the orifice diameter is sufficiently large. Powder that flows through small orifices is considered to have flow properties useful for tabletting. For example, a FLODEX measurement (FLODEX) of less than about 24 mm is typically used for high-speed tabletting operations at commercial scale. A FLODEX less than about 20 mm is useful for high-speed tabletting operations. A FLODEX of 18 mm or less is considered especially useful for high speed tabletting operations.

Example 9

Granulation blends of (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate containing varying amounts of colloidal silicon dioxide were prepared in order to assess the impact of silicon dioxide on flow. The granules of Example 5 containing no silicon dioxide (blend 9a) were used as a control. To prepare blends 9b through 9f (at 30 g scale), (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-

dioate granules (from Example 3), hypromellose 2208, lactose, and the silicon dioxide were combined in a glass jar and blended on the Turbulac mixer for 2 min, passed through a 600 micron mesh screen, and then blended for another 2 min. Blend 9g was prepared at 109.2 g scale. The hypromellose 2208 (100000 mPa.s viscosity) and the silicon dioxide were combined, passed through a 600 micron mesh screen, and added to the dry (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate granules in a 5 L cube blender and blended for 10 minutes. Magnesium stearate was passed through a 600 micron screen and added to the blend before blending an additional 4 minutes.

Example 10

Compression coated tablets containing (N,N-Diethylcarbamoyl)methyl methyl (2E)but-2-ene-1,4-dioate were made having the ingredients shown in Table 7:

<table>
<thead>
<tr>
<th>Component</th>
<th>Blend 9a</th>
<th>Blend 9b</th>
<th>Blend 9c</th>
<th>Blend 9d</th>
<th>Blend 9e</th>
<th>Blend 9f</th>
<th>Blend 9g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 3 granules</td>
<td>0.0</td>
<td>69.4</td>
<td>69.4</td>
<td>69.4</td>
<td>66.04</td>
<td>66.04</td>
<td></td>
</tr>
<tr>
<td>(wt %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example 4 granules</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>96.1</td>
<td></td>
</tr>
<tr>
<td>(wt %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example 5 granules</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>(wt %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>0.0</td>
<td>15.3</td>
<td>15.2</td>
<td>15.17</td>
<td>15.15</td>
<td>15.23</td>
<td></td>
</tr>
<tr>
<td>(wt %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypermellose 2208 (wt %)</td>
<td>0.0</td>
<td>15.3</td>
<td>15.2</td>
<td>15.17</td>
<td>15.15</td>
<td>15.23</td>
<td></td>
</tr>
<tr>
<td>(wt %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicon</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
<td>0.2</td>
<td>0.30</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>(wt %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dioxide (wt %)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Total (wt %) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
Flodex (mm)  | 34    | 24    | 12    | 9     | 7     | <5     | 12     |
The tablets were made according to the following steps. The core tablets were prepared from the high drug load granules (97% N,N-Diethylcarbamoylmethyl methyl (2E) but-2-ene-1,4-dioate and 3% hydroxypropyl cellulose) described in Example 3. The core blend batch size was 5 g. The dried granules, hydroxypropylmethylcellulose (i.e., hypromellose 2208 having 100000 mPa·s viscosity), and the silicon dioxide were then passed through a 600 micron mesh screen, combined in a glass jar and blended on a Turbula mixer for 5 minutes. Magnesium stearate was passed through a 250 micron screen and added to the blend before blending an additional 1.5 minutes. Core tablets (114.2 mg total weight; 87.6% wt/wt N,N-Diethylcarbamoylmethyl methyl (2E)but-2-ene-1,4-dioate) were compressed using a Carver Press with ½ inch (6.35 mm) round standard concave tooling at 0.4 metric ton (MT) force. The core tablets had a final hardness of approximately 7.6 kp (–74 Newtons).

The mantle blend was prepared using a direct compression process and a batch size of 10 g. The hypromellose 2208 (100 MPa·s viscosity) and lactose hydrate were passed through a 600 micron mesh screen, combined in a glass jar and blended on a Turbula mixer for 5 minutes. Magnesium stearate was passed through a 250 micron screen and added to the blend and blended an additional 1.5 minutes. The mantle blend was then applied to the core tablets using the Carver Press with ½ inch (9.53 mm) round standard concave tooling. Half the mantle blend (114.2 mg) was weighed out, added to the die, and tamped slightly to flatten. Then, the core tablet was placed into the die and pressed down gently into the mantle blend. The second half of the mantle blend (114.2 mg) was then added on top of the core tablet and the mantle was compressed using 1.5 MT force. The final compression coated tablets had a total weight of 342.6 mg with a (N,N-Diethylcarbamoylmethyl methyl (2E)but-2-ene-1,4-dioate loading of 100 mg (29.19%). The tablets had a final hardness around 14.7 kp (–144 Newtons).

Example 11

Compression coated tablets containing (N,N-Diethylcarbamoylmethyl methyl (2E)but-2-ene-1,4-dioate were made having the ingredients shown in Table 8:
The tablets were made according to the following steps. The core tablets were prepared from the high drug load granules (97% N,N-Diethylcarbamoylmethyl methyl (2E)but-2-ene-1,4-dioate and 3% hydroxypropyl cellulose) described in Example 3. The core blend batch size was 5 g. The dried granules and the silicon dioxide were then passed through a 600 micron mesh screen, combined in a glass jar and blended on a Turbula mixer for 5 minutes. Magnesium stearate was passed through a 250 micron screen and added to the blend before blending an additional 1.5 minutes. Core tablets (104.9 mg total weight; 95.3% N,N-Diethylcarbamoylmethyl methyl (2E)but-2-ene-1,4-dioate) were compressed using a Carver Press with ¼ inch (6.35 mm) round standard concave tooling at 0.4 metric ton (MT) force. The core tablets had a final hardness of approximately 6.1 kip (~60 Newtons).

The mantle blend was prepared using a direct compression process and a batch size of 100 g. The hydroxypropylmethylcellulose (i.e., hypromellose 2208 having 100000 MPa-s viscosity) and lactose hydrate were passed through a 600 micron mesh screen, combined in a 1 quart (0.95 l) V-blender and blended for 10 minutes. Magnesium stearate was passed through a 250 micron screen and added to the blend and blended an additional 4 minutes. The mantle blend was then applied to the core tablets using the Carver Press with ½ inch (9.53 mm) round standard concave tooling. Half the mantle blend (104.9 mg) was weighed out, added to the die, and tamped slightly to flatten. Then, the core tablet was placed into the die and pressed down gently into the mantle blend. The second half of the mantle blend (104.9 mg) was then added on top of the core tablet and the mantle was compressed using 1.5 MT force. The final compression coated tablets had a total weight of 314.7 mg with a (N,N-Diethylcarbamoylmethyl methyl (2E)but-2-ene-1,4-dioate) loading of 100 mg (31.78%). The tablets had a final hardness around 13.1 kip (~128 Newtons).

Example 12

Compression coated tablets containing (N,N-Diethylcarbamoylmethyl methyl (2E)but-2-ene-1,4-dioate were made having the ingredients shown in Table 9:

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>Role</th>
<th>Quantity (mg/tablet)</th>
<th>Quantity (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N,N-Diethylcarbamoylmethyl (2E)but-2-ene-1,4-dioate) Hydroxypropyl Cellulose</td>
<td>Cambridge Major (Germantown, WI)</td>
<td>Drug substance</td>
<td>100.0</td>
<td>27.59</td>
</tr>
<tr>
<td>Hypermellose 2208 (100000 mPa-s)</td>
<td>Aquafine (Hopewell, VA)</td>
<td>Binder</td>
<td>3.1</td>
<td>0.86</td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>Evonik (Rehlingen, Germany)</td>
<td>Sustained Release Polymer</td>
<td>9.1</td>
<td>2.51</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Mallinckrodt (St. Louis, MO)</td>
<td>Lubricant</td>
<td>1.7</td>
<td>0.47</td>
</tr>
<tr>
<td>Lactose Hydrate</td>
<td>Foremost (Rothschild, WI)</td>
<td>Total Core Filler</td>
<td>114.5</td>
<td>31.59</td>
</tr>
<tr>
<td>Hypermellose 2208 (100 mPa-s)</td>
<td>Dow Chemical (Midland, MI)</td>
<td>Sustained Release Polymer</td>
<td>80.6</td>
<td>22.44</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Mallinckrodt (St. Louis, MO)</td>
<td>Lubricant</td>
<td>2.5</td>
<td>0.69</td>
</tr>
<tr>
<td>Total Mante</td>
<td></td>
<td></td>
<td>247.9</td>
<td>68.41</td>
</tr>
<tr>
<td>Total Tablet</td>
<td></td>
<td></td>
<td>362.4</td>
<td>100.00</td>
</tr>
</tbody>
</table>
The tablets were made according to the following steps. The core tablets were prepared from the high drug load granules (97% N,N-Diethylcarbamoylmethyl methyl (2E)-but-2-ene-1,4-dioate and 3% hydroxypropyl cellulose) described in Example 4. The core blend batch size was 1099.2 g. The hydroxypropylmethylcellulose (i.e., Hypermellose 2208 having 100000 mPas viscosity) and the silicon dioxide were combined, passed through a 600 micron mesh screen, and added to the dry granules in a 5 L cube blender and blended for 10 minutes at 25 rpm. Magnesium stearate was passed through a 600 micron screen and added to the blend before blending an additional 4 minutes at 25 rpm. Core tablets (114.5 mg total weight; 87.3% wt/wt N,N-Diethylcarbamoylmethyl methyl (2E)-but-2-ene-1,4-dioate) were compressed using a Manesty F3 tablet press with 6.0 mm round concave tooling. The core tablets had a final mean hardness between 8.1 to 10.2 kp (79-100 Newtons).

The mantle blend was prepared using a direct compression process and a batch size of 5.0 kg. The hypermellose 2208 (100 MPa s viscosity) and lactose hydrate were combined and passed through a 600 micron mesh screen, placed in and blended on the Tumblemix 18 L Bin Blender for 8.5 minutes at 30 rpm. Magnesium stearate was passed through a 600 micron screen and added to the blend and blended an additional 3.5 minutes. The mantle blend was then applied to the core tablets using a Kikusui tablet press (Kikusui Seisakusho Ltd., Kyoto, Japan) specially designed for the manufacture of compression coated tablets. Compression was completed using 9.5 mm round concave tooling and approximately 1000 kp force. The final compression coated tablets had a total weight of 362.4 mg with a (N,N-Diethylcarbamoylmethyl methyl (2E)-but-2-ene-1,4-dioate loading of 100 mg (27.5%). The compression coated tablets had a final mean hardness between 10.9 to 14.0 kp (107-137 Newtons).

Example 13

A two-stage dissolution method was used to determine the in vitro dissolution profile of dosage forms prepared according to Examples 10, 11 and 12 in order to mimic the conditions of a dosage form as it transits the gastrointestinal tract. Thus, the dosage forms were first placed into a dissolution medium having a pH of 1.2, to mimic the conditions of the stomach, and then placed into a dissolution medium of pH 6.8, to mimic the conditions of the intestines. The dissolution vessel (USP Type I, basket) initially contained 750 mL of 0.1 N hydrochloric acid (pH 1.2). After 2 hours of dissolution, 250 mL of 200 mM tribasic sodium phosphate was added to the vessel resulting in a pH adjustment from 1.2 to 6.8. The dissolution medium was kept at 37° C. and was agitated at 100 rpm.

For the Example 10 dosage forms, samples of the dissolution medium were withdrawn at 1 and 2 hours following the start of the low pH stage, and at 0.5, 2, 4, 7, 10 and 14 hours following the start of the neutral pH/buffered stage. For the Example 11 dosage forms, samples were withdrawn at 1 and 2 hours following the start of the low pH stage, and at 0.5, 2, 4, 7, 10, 16 and 22 hours following the start of the neutral pH/buffered stage. For the Example 12 dosage forms, samples were withdrawn at 1 and 2 hours following the start of the low pH stage, and at 0.5, 2, 4, 7, 10, 14 and 20 hours following the start of the neutral pH/buffered stage. The amount of (N,N-Diethylcarbamoylmethyl methyl (2E)-but-2-ene-1,4-dioate in the dissolution medium samples was determined by reverse phase HPLC using a C18 column and a 7 minute gradient method according to Table 10 where Mobile Phase A is water/0.1% H3PO4 and Mobile Phase B is water/acetonitrile:H3PO4 (10:90:0.1 by volume) with UV detection at 210 nm.

<table>
<thead>
<tr>
<th>Time (minute)</th>
<th>% Mobile Phase A</th>
<th>% Mobile Phase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>5.5</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

As shown in FIG. 6, for dosage forms prepared according to Example 10, drug release is delayed for approximately 2 hours, and thereafter the drug is released gradually, reaching more than 90% released at 16 hours.

As shown in FIG. 7, for dosage forms prepared according to Example 11, drug release is delayed for approximately 2 hours, followed by near zero order release, reaching more than 90% released at 24 hours.

As shown in FIG. 8, for dosage forms prepared according to Example 3, drug release is delayed for approximately 2 hours, and thereafter the drug is released gradually, reaching more than 90% released at 16 hours.

Example 14

The concentration ±1 SD of monomethyl fumarate (MMF) in the blood of Cynomolgous monkeys following oral dosing of delayed release enteric coated tablets prepared according to Examples 10 and 11 is shown in FIGS. 9 and 10. In these Figures, the MMF concentrations following dosing with the Example 10 tablets are shown with ○○ symbols and the MMF concentrations following dosing with the Example 11 tablets are shown with ●● symbols. The data in FIG. 9 is from animals dosed in a fasted state and the data in FIG. 10 is from animals dosed in a fed state.

Administration Protocol

Tablets prepared according to Examples 10 and 11 (100 mg N,N-Diethylcarbamoylmethyl methyl (2E)-but-2-ene-1,4-dioate per tablet) were administered by oral dosing to groups of four adult male Cynomolgous (Macaca fascicularis) monkeys (each monkey weighed about 4 to 5 kg). Each monkey was administered two tablets in either a fasted state or a fed state. All animals were fasted overnight before the study. For the fed leg, animals were administered blended food via oral gavage in the morning 30 minutes prior to administration of each test formulation. For the fasted leg, the animals remained fasted for 4 hours post-dosing. Blood samples (1.0 mL) were obtained from all animals via the femoral vein at pre-dose and intervals over 24 hours after oral dosing. Blood was collected in pre-chilled K3EDTA, quenched with acetonitrile and stored at −50° C. to −90° C. until analyzed. There was a minimum 7 day wash out period between dosing sessions.

Sample Preparation for Absorbed Drug

300 μL of acetonitrile was added to 1.5 mL Eppendorf tubes for the preparation of samples and standards.

Sample Preparation: Blood was collected at different time points and immediately 100 μL of blood was added into Eppendorf tubes containing 300 μL of methanol and mixed by vortexing.

Standard Preparation: One hundred μL of blood was added to 290 μL of acetonitrile in Eppendorf tubes. 10 μL of MMF standard solution (0.2, 0.5, 1, 2.5, 5, 10, 25, 50 and 100 μg/mL) was added to each tube to make up the final calibration standards (0.02, 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5 and 10 μg/mL).

A 150 μL aliquot of supernatant from quenched blood standards, QCs and samples was transferred to a
96-well plate and 20 µL of the internal standard solution was added to each well. The plate was capped and vortexed well. The supernatant was injected onto the API 4000 LC/MS/MS system for analysis.

**LC/MS/MS Analysis**

[0183] The concentration of MMF in monkey blood was determined using an API 4000 LC/MS/MS instrument equipped with Agilent Binary pump and autosampler. The column was a Luna C8 (2) 4.6x150 mm, 5 µm column operating at 2 to 8°C temperature. The mobile phases were (A) 0.1% formic acid in water, and (B) 0.1% formic acid in acetonitrile. The gradient condition was: 2% B for 1 min, increasing to 95% B in 3.5 min and maintained for 2 min, then decreasing to 2% B in 5.6 min and maintained for 2.3 min. 30 µL of sample was injected into the column. A Turbo-Ion Spray source was used, and was detected in negative ion mode for the MRM transition of 128.95/84.8. Peaks were integrated using Analyst 1.5 quantitation software.

Example 15

[0184] Delayed release tablets containing compound (1) were made having the ingredients shown in Table 11:

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>Role</th>
<th>Quantity (mg/tablet)</th>
<th>Quantity (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N,N-</td>
<td>Xenopol (Santa</td>
<td>Drug substance</td>
<td>200.00</td>
<td>78.38</td>
</tr>
<tr>
<td>Diethylcarbamoylmethyl</td>
<td>Clara, CA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methyl (2E)-2-ene-1,4-dicarboxylic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose</td>
<td>Ashland (Hopewell, VA)</td>
<td>Binder</td>
<td>6.19</td>
<td>2.42</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>Foremost (Rotfachsdorf, WI)</td>
<td>Filler</td>
<td>38.28</td>
<td>15.00</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>FMC BioPolymer (Philadelphia, PA)</td>
<td>Disintegrant</td>
<td>7.66</td>
<td>3.00</td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>Cabot (Tuscola, IL)</td>
<td>Glidant</td>
<td>0.51</td>
<td>0.20</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Mallinckrodt (St. Louis, MO)</td>
<td>Lubricant</td>
<td>2.55</td>
<td>1.00</td>
</tr>
<tr>
<td>Opadry O3019184</td>
<td>Colorcon (West Point, PA)</td>
<td>Total Core Barrier coat</td>
<td>255.19</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**TABLE 11**

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>Role</th>
<th>Quantity (mg/tablet)</th>
<th>Quantity (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methacrylic Acid Copolymer Dispersion</td>
<td>Evonik Industries (Eisen, Germany)</td>
<td>Coating</td>
<td>6.80</td>
<td>2.66</td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td>Vertelus (Greenboro, NC)</td>
<td>Enteric polymer</td>
<td>21.10</td>
<td>8.27</td>
</tr>
<tr>
<td>PlasCRYL™ T20</td>
<td>Emerson Resources (Norristown, PA)</td>
<td>Plasticizer</td>
<td>1.10</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-tacking agent</td>
<td>2.10</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total Enteric Coating</td>
<td>24.30</td>
<td>9.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total Tablet</td>
<td>286.29</td>
<td>112.19</td>
</tr>
</tbody>
</table>

[0185] The tablets were made according to the following steps. The core tablets were prepared using a high drug load wet granulation process. The granulation was performed in two batches at 463.9 g per batch. Compound (1) and hydroxypropyl cellulose were first passed through a conical mill with a 610 micron round holed screen. The granulation was then performed by combining 97% of compound (1) and 3% of hydroxypropyl cellulose in a Key KG-5 granulator bowl followed by mixing with water addition for approximately 9 minutes. The wet granules were dried in a Glatt GPCG-1 fluid bed dryer at 40°C. The two portions of dried granules were combined and blended with the silicon dioxide in an 8 quart V-blender for 5 minutes and then sized by passing through a conical mill with an approximately 1300 micron grater type screen. The milling granule was then combined with the croscarmellose sodium and lactose monohydrate for 10 minutes in an 8 quart V-blender. The magnesium stearate was passed through a 600 micron mesh screen and blended with the additional core materials in the V-blender for 5 minutes. Core tablets (254.87 mg) were compressed using a GlobePharma Minipress II rotary tablet press with 11/32 inch (8.7 mm) round concave tooling. The core tablets had a final mean hardness of approximately 15.5 kp. An aqueous suspension was prepared by mixing with an impeller 68.85 g Opadry O3019184 with 792.0 g of purified water. The water contained in the suspension is removed during the film coating process and therefore not included in the final formulation in Table 1. The tablets were coated with the aqueous suspension in an O'Hara Technologies Labeoat M coater with a 12" (30.5 cm) diameter perforated pan until the desired weight gain of barrier coat was achieved. The coating process occurred at an inlet temperature of approximately 52°C and an outlet temperature of 37°C. After coating, the tablets were dried for 2 hours at 40°C. An aqueous suspension was prepared by mixing with a binder 578.7 g methacrylic acid copolymer dispersion, 9.0 g triethyl citrate, 86.5 g Pla-
Example 16

Delayed sustained release tablets containing compound (1) were made having the ingredients shown in Table 12:

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>Role</th>
<th>Quantity (mg/tablet)</th>
<th>Quantity (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N,N-Dietylcarbamoyl)methyl methyl (2R,3S)n-2-ene-1,4-dioate</td>
<td>XcelaPort (Santa Clar, CA)</td>
<td>Drug substance</td>
<td>200.00</td>
<td>66.74</td>
</tr>
<tr>
<td>Hydroxypropyl Cellulose</td>
<td>Ashland (Hopewell, VA)</td>
<td>Binder</td>
<td>6.19</td>
<td>0.06</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>Formosa (Rothschild, WI)</td>
<td>Filler</td>
<td>44.95</td>
<td>15.00</td>
</tr>
<tr>
<td>Hyprinollose 2208</td>
<td>Dow Chemical (Midland, MI)</td>
<td>Sustained release agent</td>
<td>44.95</td>
<td>15.00</td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>Cabot (Tuscola, IL)</td>
<td>Lubricant</td>
<td>0.60</td>
<td>0.20</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Mallinckrodt (St. Louis, MO)</td>
<td>Lubricant</td>
<td>3.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Opadry 03019184</strong></td>
<td><strong>Coloreon (West Point, PA)</strong></td>
<td>Total Core</td>
<td><strong>299.69</strong></td>
<td><strong>100.00</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barrier coat</td>
<td>7.13</td>
<td>2.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total Barrier Coating</td>
<td>7.13</td>
<td>2.38</td>
</tr>
<tr>
<td><strong>Methacrylic Acid Copolymer Dispersion Triethyl Citrate</strong></td>
<td><strong>Evonik Industries (Eisen, Germany)</strong></td>
<td>Enteric polymer</td>
<td>24.20</td>
<td>8.08</td>
</tr>
<tr>
<td></td>
<td><strong>Vertellus (Greensboro, NC)</strong></td>
<td>Plasticizer</td>
<td>1.25</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>PlasACRYL™ T20</strong></td>
<td><strong>Emerson Resources (Norristown, PA)</strong></td>
<td>Anti-tacking agent</td>
<td>2.41</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total Enteric Coating</td>
<td>27.87</td>
<td>9.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total Tablet</td>
<td>334.69</td>
<td>111.68</td>
</tr>
</tbody>
</table>

The tablets were made according to the following steps. The core tablets were prepared using a high drug load wet granulation process. The granulation was performed in two batches at 456 g per bath. Compound (1) and hydroxypropyl cellulose were first passed through a conical mill with a 610 micron round hole screen. The granulation was then performed by combining 97% of compound (1) and 3% of hydroxypropyl cellulose in a Key KG-5 granulator bowl followed by mixing with water addition for approximately 7 minutes. The wet granules were dried in a Glatt GPCG-1 fluid bed dryer at 40°C. The two portions of dried granules were sized by passing through a conical mill with an approximately 1300 micron grater type screen. The milled granules were blended with the hyprinollose 2208, silicon dioxide, and lactose monohydrate for 10 minutes in an 8 quart (7.6 l) V-blender. This blend was passed through an 850 micron mesh screen. The magnesium stearate was passed through a 600 micron mesh screen and blended with the additional core materials in the V-blender for 5 minutes. Core tablets (299.69 mg) were compressed using a GlobePharma Minipress II rotary tablet press with 8.6 mm round concave tooling. The core tablets had a final mean hardness of approximately 12 kp. An aqueous suspension was prepared by mixing with an impeller 63.8 g Opadry 03019184 with 770.7 g of purified water. The water contained in the suspension is removed during the film coating process and therefore not included in the final formulation in Table 2. The tablets were coated with the aqueous suspension in an O'Hara Technologies Labcoat M coater with a 12" (30.5 cm) diameter perforated pan until the desired weight gain of barrier coat was achieved. The coating process occurred at an inlet temperature of approximately 52°C, and an outlet temperature of 36° C. After coating, the tablets were dried for 2 hours at 40°C. An aqueous suspension was prepared by mixing with an impeller 405.1 g methacrylic acid copolymer dispersion, 6.3 g triethyl citrate, 60.6 g PlasACRYL™ T20 with 228.1 g water. The water contained in the methacrylic acid copolymer dispersion and the PlasACRYL™ T20 is removed during the film coating process and therefore not included in the final formulation in Table 1. The tablets were coated with the aqueous suspension in the O'Hara Technologies Labcoat M coater until the desired weight gain of enteric film was achieved. The coating process occurred at an inlet temperature of approximately 40°C, and an outlet temperature of 30° C. After coating, the tablets were dried for 2 hours at 40°C.

Example 17

A two-stage dissolution method was used to determine the in vitro dissolution profile of dosage forms prepared according to Examples 15 and 16. The 2-stage dissolution test was used to better approximate the pH conditions experienced by a dosage form after swallowing by a patient, i.e., low pH of the stomach followed by near neutral pH of the intestines. The dosage forms were first placed into a dissolution vessel (USP, Type I, basket) containing 750 mL of 0.1 N hydrochloric acid (pH 1.2). After 2 hours, 250 mL of 200 mM
tribasic sodium phosphate was added to the vessel resulting in a pH adjustment from 1.2 to 6.8. The dissolution medium was kept at 37°C and was agitated at 100 rpm.

[0189] For the Example 15 dosage forms, samples of the dissolution medium were withdrawn after 1 and 2 hours in the low pH stage, and at 0.25, 0.5, 0.75, and 1 hours following buffer addition. For the Example 16 dosage forms, samples of the dissolution medium were withdrawn after 1 and 2 hours in the low pH stage, and at 0.5, 2, 4, 7, 10, and 14 hours following buffer addition. The released amount of compound (1) in the samples was determined by reverse phase HPLC using a C18 column and a 7 minute gradient method according to Table 3 where Mobile Phase A is water/0.1% H₃PO₄ and Mobile Phase B is water/acetone/triethylamine/H₃PO₄ (10/90/0.1 by volume) with UV detection at 210 nm.

<table>
<thead>
<tr>
<th>Time (minute)</th>
<th>% Mobile Phase A</th>
<th>% Mobile Phase B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>5.5</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

[0190] As shown in FIG. 11, for dosage forms prepared according to Example 15, drug release is delayed for approximately 2 hours, followed with near immediate release with >90% released between 2 and 3 hours. As shown in FIG. 12, for dosage forms prepared according to Example 16, drug release is delayed for approximately 2 hours, followed by sustained release reaching >90% at 12 hours.

[0191] Finally, it should be noted that there are alternative ways of implementing the embodiments disclosed herein. Accordingly, the present embodiments are to be considered as illustrative and not restrictive. Furthermore, the claims are not to be limited to the details given herein, and are entitled their full scope and equivalents thereof.

1. A solid pharmaceutical granulation comprising at least about 95 wt % (N,N-Diethylecarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate and one or more pharmaceutically acceptable excipients.
2. The granulation of claim 1, comprising at least about 97 wt % (N,N-Diethylecarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate.
3. The granulation of claim 1, wherein the pharmaceutically acceptable excipient comprises a binder.
4. The granulation of claim 3, wherein the binder comprises a polymer selected from hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone and combinations thereof.
5. A mixture comprising the solid granulation of claim 1, and at least one additional pharmaceutically acceptable excipient.
6. The mixture of claim 5, wherein the at least one additional excipient is selected from fillers, diluents, binders, lubricants, disintegrants, glidants, sustained release agents and combinations thereof.
7. The mixture of claim 5, comprising a glidant, so as to improve flowability of said mixture.
8. The mixture of claim 7, comprising up to about 3 wt % silicon dioxide glidant.
9. The mixture of claim 7, comprising up to about 1 wt % silicon dioxide glidant.
10. The mixture of claim 7, comprising about 0.1 to about 0.5 wt % silicon dioxide glidant.
11. The mixture of claim 8, wherein the silicon dioxide glidant has an average particle size of less than 200 nm.
12. An oral dosage form comprising the mixture of claim 5.
13. The dosage form of claim 12, wherein the dosage form comprises a capsule containing the mixture.
14. The dosage form of claim 12, wherein the dosage form comprises a tablet.
15. The dosage form of claim 13, comprising from about 100 mg to about 1,200 mg (N,N-Diethylecarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate.
16. The dosage form of claim 13, comprising from about 200 mg to about 800 mg (N,N-Diethylecarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate.
17. The tablet of claim 14, comprising a sustained release agent.
18. The tablet of claim 17, wherein the sustained release agent comprises hydroxypropylmethyl cellulose.
19. A pharmaceutical tablet dosage form, the tablet having a core and one or more coatings surrounding the core, the core comprising from about 70 wt % to about 98 wt % (N,N-Diethylecarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate.
20. The pharmaceutical tablet dosage form of claim 19, wherein the core comprises from about 80 wt % to about 97 wt % (N,N-Diethylecarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate.
21. The pharmaceutical tablet dosage form of claim 19, including at least one pharmaceutically acceptable excipient.
22. The pharmaceutical tablet dosage form of claim 21, wherein the excipient is selected from fillers, diluents, binders, lubricants, disintegrants, glidants, sustained release agents and combinations thereof.
23. The pharmaceutical tablet dosage form of claim 19, comprising about 5 wt % to about 15 wt % of hydroxypropylmethyl cellulose.
24. The pharmaceutical tablet dosage form of claim 23, wherein the dosage form is a sustained release dosage formulation.
25. The dosage form of claim 12, wherein the dosage form has an enteric coating.
26. The dosage form of claim 12, wherein in a sodium phosphate dissolution medium buffered to pH 6.8, maintained at 37°C and stirred at 100 rpm, the dosage form releases 90 wt % of the (N,N-Diethylecarbamoyl)methyl methyl (2E)-but-2-ene-1,4-dioate within 0.5 to 24 hours.
27. A method of treating a disease in a subject comprising orally administering to a subject in need of such treatment at least one dosage form of claim 12.
28. The method of claim 27, wherein the disease is multiple sclerosis.
29. The method of claim 27, wherein the disease is psoriasis.
30. The method of claim 27, wherein the disease is selected from Parkinson’s disease, amyotrophic lateral sclerosis (ALS), Huntington’s disease, Alzheimer’s disease, lupus, Crohn’s disease, psoriatic arthritis and ankylosing spondylitis.
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