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## (54) Title: PHARMACEUTICAL BEAD FORMULATIONS COMPRISING DIMETHYL FUMARATE

(57) Abstract: The present invention provides novel pharmaceutical compositions of dimethyl fumarate. The pharmaceutical compositions of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein the first pharmaceutical bead composition is an enterically coated immediate-release composition and the second pharmaceutical bead composition is an enterically coated controlled-release composition, wherein the first pharmaceutical bead composition and the second pharmaceutical bead composition both comprise dimethyl fumarate. Methods of using the pharmaceutical compositions of the present invention for treating multiple sclerosis are also included.



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## PHARMACEUTICAL BEAD FORMULATIONS COMPRISING DIMETHYL FUMARATE

### RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application No. 62/294,054, filed on February 11, 2016, the entire content of which is incorporated herein by reference.

### BACKGROUND OF THE INVENTION

Tecfidera<sup>®</sup> (dimethyl fumarate) was approved by FDA in March, 2013 to be used for treating adults with relapsing forms of multiple sclerosis (MS). The starting dose for the currently approved formulation of Tecfidera<sup>®</sup> is 120 mg twice a day orally. After 7 days, the dose is increased to the maintenance dose of 240 mg twice a day orally.

Dimethyl fumarate (DMF) quickly gets absorbed in vivo and converted to monomethyl fumarate (MMF). The half-life of MMF was shown to be approximately 1 hour (0.9 h in rat at 100 mg/Kg oral dose). Both DMF and MMF are metabolized by esterases which are ubiquitous in the GI tract, blood and tissues.

DMF has demonstrated an acceptable safety profile in phase 3 clinical trials. However, tolerability issues such as flushing and gastrointestinal events were observed. While these events are generally mild to moderate in severity, it is desirable to reduce these side effects. It is also desirable to develop a once a day dosing formulation as opposed to the current twice a day formulation to improve patient compliance and convenience.

As such, there is a need for new pharmaceutical formulations of dimethyl fumarate with improved pharmacokinetic profiles and/or dosing regimen and reduced side effects.

### SUMMARY OF THE INVENTION

The present invention provides novel pharmaceutical compositions of dimethyl fumarate that have pharmacokinetic profiles suitable for a once daily dosing regimen. In addition, the pharmaceutical compositions of the present invention have a desirable extended release profile that may reduce the GI side effects observed for the current formulation. Moreover, the pharmaceutical compositions of the present invention are believed to have maximized absorption of dimethyl fumarate *in vivo*.

One aspect of the present invention is directed to a pharmaceutical composition comprising a first pharmaceutical bead composition and a second pharmaceutical bead

composition. The first pharmaceutical bead composition is an enterically coated immediate-release composition and the second pharmaceutical bead composition is an enterically coated controlled-release composition, wherein the first pharmaceutical bead composition and the second pharmaceutical bead composition both comprise dimethyl fumarate as the active ingredient.

In yet another aspect, the present invention provides a method of treating a subject having multiple sclerosis. The method comprises administering to the subject an effective amount of a pharmaceutical composition of the present invention described herein.

The present invention also provides a pharmaceutical composition described herein for use in treating a subject having multiple sclerosis.

Use of a pharmaceutical composition described herein for the manufacture of a medicament in treating multiple sclerosis is also included in the present invention.

### BRIEF DESCRIPTION OF THE DRAWINGS

FIG 1. shows *in vitro* dissolution profiles for the pharmaceutical compositions comprising mixed beads of the present invention (Formulations 1 and 2) as compared to pharmaceutical composition comprising a single type of beads (Formulation 3) using dissolution test 1.

FIG 2. shows *in vitro* dissolution profiles for the pharmaceutical compositions comprising mixed beads of the present invention (Formulations 1 and 2) as compared to pharmaceutical composition comprising a single type of beads (Formulation 3) using dissolution test 2.

### DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term “**immediate-release**” refers to a pharmaceutical composition that releases substantially all (e.g., greater than 90%, 95%, 99% or 99.9%) of the active ingredient (e.g., dimethyl fumarate) in a body within a short period of time, such as less than 30 minutes.

As used herein, the term “**controlled-release**” and “**extended-release**” are used interchangeably herein. They refer to a pharmaceutical composition that releases the active ingredient (e.g., dimethyl fumarate) in a body over an extended period of time, such as within 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 16 hours or 24 hours. In one embodiment, the active substance dimethyl fumarate is released from the controlled-release

pharmaceutical bead compositions of the present invention in a prolonged manner compared to the immediate-release formulations. The term “prolonged” means that the active substance is released during a longer period of time than the current commercially available formulation of Tecfidera<sup>®</sup> (dimethyl fumarate), such as at least during a time period that is at least 1.2 times, at least 1.5 times, at least 2 times, at least 3 times, at least 4 times or at least 5 times greater than that of current commercial available formulation of Tecfidera<sup>®</sup>.

As used herein, the term “**enterically coated**” refers to a pharmaceutical composition having an enteric coating around the core or the layer that containing the active ingredient (*e.g.*, dimethyl fumarate).

In a first embodiment, the present invention is directed to a pharmaceutical composition comprising a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein the first pharmaceutical bead composition is an enterically coated immediate-release bead composition and the second pharmaceutical bead composition is an enterically coated controlled-release bead composition, wherein the first pharmaceutical bead composition and the second pharmaceutical bead composition both comprise dimethyl fumarate.

In a second embodiment, for the pharmaceutical composition described in the first embodiment, the first pharmaceutical bead composition comprises:

- an inert core;
  - a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder; and
  - an enteric coating surrounding the first layer; and
- the second pharmaceutical bead composition comprises:
- an inert core;
  - a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder;
  - an enteric coating surrounding the first layer; and
  - a functional coating surrounding the enteric coating.

In certain embodiments, the inert core, the first layer and/or the enteric coating for the first pharmaceutical bead composition are different from the inert core, the first layer and/or the enteric coating for the second pharmaceutical bead composition.

In certain embodiments, the inert core, the first layer and/or the enteric coating for the first pharmaceutical bead composition are the same as the inert core, the first layer and/or the enteric coating for the second pharmaceutical bead composition.

As used herein, the term “**inert core**” refers to a core comprising material(s) that are unreactive towards the active substance and any components of the bead and/or have no effect on the biological activity of the active substance, *i.e.*, dimethyl fumarate. In addition, the inert core does not contain any active substance. In certain embodiments, the inert core in the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention comprises a pharmaceutically acceptable inert material(s). Exemplary inert core materials include, but are not limited to, starch, dextrose, sucrose, lactose, maltose, and microcrystalline cellulose. In one embodiment, the inert core comprises lactose. In an alternative embodiment, the inert core comprises starch. In yet another alternative, the inert core comprises sucrose.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the weight percentage for the inert core is 10% -60% or 20-40% of the total weight of the inert core and the first layer. More specifically, the weight percentage for the inert core is 30%-40% or 20-30% of the total weight of the inert core and the first layer. Even more specifically, the weight percentage for the inert core is 20-24% of the total weight of the inert core and the first layer. Alternatively, the weight percentage for the inert core is 16-20% of the total weight of the inert core and the first layer. In another alternative, the weight percentage for the inert core is 16-22% of the total weight of the inert core and the first layer. In another embodiment, the weight percentage for the inert core is 15-30% of the total weight of the inert core and the first layer. In yet another embodiment, the weight percentage for the inert core is 16-26% of the total weight of the inert core and the first layer.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the inert core is a sphere having a diameter of 200-850  $\mu\text{m}$ . More specifically, the sphere has a diameter of 250-350  $\mu\text{m}$ , 300-400  $\mu\text{m}$ , 500-600  $\mu\text{m}$  or 700-850  $\mu\text{m}$ . Even more specifically, the sphere has a diameter of 350  $\mu\text{m}$ , 550  $\mu\text{m}$  or 750  $\mu\text{m}$ .

In certain embodiment, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the beads have a diameter of 0.5-2 mm, 0.5-1.5 mm,

0.8-2 mm, 0.8-1.5 mm, 1-2 mm or 1-1.5 mm. More specifically, the beads have a diameter of 0.9-1.5 mm, 0.9-1.4 mm, 0.9-1.3 mm, 0.9-1.2 mm, 1-1.4 mm, 1-1.3 mm or 1-1.2 mm.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the active substance dimethyl fumarate is layered on the inert core. More specifically, dimethyl fumarate is layered on the inert core by spraying a solution containing dimethyl fumarate onto the inert core in a fluidized bed system, such as a fluidized bed spray coating apparatus. A fluidized bed system can also be referred to as a fluid bed.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the weight percentage of dimethyl fumarate is 40%-80%, 50%-75%, 60-80%, 60%-70%, 65%-75%, or 70%-80% of the total weight of the inert core and the first layer. More specifically, the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer. In a specific embodiment, the weight percentage of dimethyl fumarate is 70% of the total weight of the inert core and the first layer. Alternatively, the weight percentage of dimethyl fumarate is 60%-63% of the total weight of the inert core and the first layer. In another embodiment, the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer. In yet another embodiment, the weight percentage of dimethyl fumarate is 74% of the total weight of the inert core and the first layer.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the first layer further comprises a binder. Exemplary binders include, but are not limited to, acacia, agar, alginic acid, amino methacrylate copolymer, ammonio methacrylate copolymer, ammonio methacrylate copolymer dispersion, calcium carbonate, calcium lactate, carbomer copolymer, carbomer homopolymer, carbomer interpolymers, carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, hydrogenated coconut oil, copovidone, corn syrup, corn syrup solids, dextrans, dextrin, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylene glycol and vinyl alcohol graft copolymer, gelatin, liquid glucose, glyceryl behenate, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hypromellose, hypromellose acetate succinate, inulin, alpha-lactalbumin, monohydrate lactose, maltodextrin, maltose, methacrylic acid copolymer,

methacrylic acid copolymer dispersion, methacrylic acid and ethyl acrylate copolymer dispersion, methylcellulose, hydrogenated palm oil, polycarbophil, hydrogenated polydextrose, polyethylene oxide, polyvinyl acetate, povidone, pullulan, sodium alginate, pregelatinized starch, pregelatinized modified starch, corn starch, hydroxypropyl corn starch, pregelatinized hydroxypropyl corn starch, pea starch, hydroxypropyl pea starch, pregelatinized hydroxypropyl pea starch, potato starch, hydroxypropyl potato starch, pregelatinized hydroxypropyl potato starch, tapioca starch, wheat starch, hydrogenated starch hydrolysate, sucrose, sunflower oil, syrup, trehalose, hydrogenated vegetable oil, vitamin E polyethylene glycol succinate, zein, hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), methyl cellulose, ethyl cellulose, sodium carboxy methyl cellulose, polyethylene glycol (PEG), polyvinyl alcohols, polymethacrylate, starch paste, sodium starch, tragacanth, gelatin, alginate, sodium alginate, alginic acid, cellulose, candelilla wax, carnuba wax, copolyvidone, and lactose hydrous. More specifically, the binder is HPMC.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the weight percentage for the binder is 1-25%, 1-20%, or 5-15% of the total weight of the inert core and the first layer. More specifically, the weight percentage for the binder is 5-10% (*e.g.*, 5%, 6%, 7%, 8%, 9% or 10%) of the total weight of the inert core and the first layer. In another specific embodiment, the weight percentage for the binder is 1-5% (*e.g.*, 1%, 2%, 3%, 4% or 5%) total weight of the inert core and the first layer. In a even more specific embodiment, the weight percentage for the binder is 7%.

In certain embodiment, the pharmaceutical bead compositions of the present invention have an enteric coating surrounding the first layer comprising dimethyl fumarate. As used herein, “**enteric coating**” refers to a coating that is stable at the highly acidic pH (*e.g.*, pH ~ 3) found in the stomach, but breaks down rapidly at a less acidic pH (*e.g.*, pH 7-9). Enteric coating materials known in the art can generally be used in the present invention. In one embodiment, for the pharmaceutical compositions described herein, the enteric coating is layered on the first layer comprising dimethyl fumarate. More specifically, the enteric coating is layered on the first layer by spraying a solution containing enteric coating materials onto the first layer in a fluid bed.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead



compositions of the present invention, the enteric coating is layered on the functional coating. More specifically, the enteric coating is layered on the functional coating by spraying a solution containing the enteric coating materials onto the functional coating in a fluid bed.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the enteric coating comprises an excipient selected from the group consisting of a copolymer of methacrylic acid and methyl methacrylate, a copolymer of methacrylic acid and ethyl acrylate, hypromellose phthalate (HPMCP), cellulose acetate phthalate. More specifically, the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate. Even more specifically, the ratio of methacrylic acid to methyl methacrylate in the copolymer is 0.8:1 to 1.2:1, (e.g., 1:1). In an even more specific embodiment, the enteric coating comprises EUDRAGIT<sup>®</sup> L 100 (poly(methacrylic acid-co-methyl methacrylate) 1:1).

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the enteric coating of the present invention further comprises one or more plasticizers. Exemplary plasticizers include, but are not limited to, acetyltriethyl citrate, benzyl benzoate, castor oil, chlorobutanol, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, mannitol, polyethylene glycol, polyethylene glycol monomethyl ether, propylene glycol, pullulan, sorbitol, sorbitol sorbitan solution, triacetin, tributyl citrate, triethyl citrate and Vitamin E. In a more specific embodiment, the plasticizer is triethyl citrate.

In one embodiment, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the enteric coating of the present invention comprises EUDRAGIT<sup>®</sup> L 100 and triethyl citrate. More specifically, the weight ratio of the triethyl citrate to EUDRAGIT<sup>®</sup> L 100 is from 1:1 to 1:20. Even more specifically, the weight ratio of the triethyl citrate to EUDRAGIT<sup>®</sup> L 100 is 1:5.

In certain embodiments, for the first pharmaceutical bead composition or the second pharmaceutical bead composition or both the first and the second pharmaceutical bead compositions of the present invention, the weight percentage for the enteric coating is 1-20% or 5-15% of the total weight of the inert core and the first layer. More specifically, the weight percentage for the enteric coating is 10-15% (e.g., 10%, 11%, 12%, 13% or 15%) of the total weight of the inert core and the first layer. In another more specific embodiment, the

weight percentage for the enteric coating is 11-13% of the total weight of the inert core and the first layer. Even more specifically, the weight percentage of the enteric coating is 12% of the total weight of the inert core and the first layer.

In certain embodiments, for the pharmaceutical bead compositions described herein, the functional coating is layered onto the enteric coating of the beads. More specifically, the functional coating is layered onto the enteric coating by spraying a solution containing functional coating materials onto the enteric coating in a fluid bed.

In certain embodiments, for the pharmaceutical bead compositions described herein, the functional coating is layered onto the first layer of the beads. More specifically, the functional coating is layered onto the first layer by spraying a solution containing functional coating materials onto the functional coating in a fluid bed.

As used herein, the “**functional coating**” refers to a coating that provides an extended release of the active substance (*i.e.*, dimethyl fumarate).

In certain embodiments, for the second pharmaceutical bead compositions of the present invention, the functional coating comprises a mixture of one or more water soluble polymers and one or more water insoluble polymers. In certain embodiments, the functional coating comprises one or more excipients selected from the group consisting of polyvinylpyrrolidone (PVP), polyethylene oxide (PEO), glyceryl monostearate, hydroxyl propyl methyl cellulose (HPMC), SoluPlus, polyvinyl alcohol (PVA), polyvinyl alcohol (PVA), hydroxypropylmethylcellulose, acetate succinate (HPMCAS), ethylene vinyl acetate (EVA), methacrylates (Eudragit™), cellulose acetate butyrate (CAB), cellulose acetate phthalate (CAP), poly(ethylene glycol), poly(vinyl acetate) (PVAc), polylactide (PLA), polyglycolide (PGA), copolymers of PLA/PGA and polycaprolactone (PCL), polyvinylpyrrolidone-co-vinyl acetate (Kollidon VA-64), polyurethanes, poly(lactic acid), poly(glycolic acid), poly(anhydride–imides), poly(anhydride–esters), poly(iminocarbonates), poly(phosphazenes), poly(phosphoesters), ethylcellulose (EC), hydroxypropyl cellulose (HPC), alginic acid, carbomer copolymer, carbomer homopolymer, carbomer interpolymer, carboxymethylcellulose sodium, carrageenan, cellaburate, ethylcellulose aqueous dispersion, ethylcellulose dispersion Type B, glyceryl monooleate, guar gum, hydroxypropyl betadex, polyvinyl acetate dispersion, shellac, sodium alginate, pregelatinized starch, pregelatinized modified starch and xanthan gum.

In one embodiment, for the second pharmaceutical bead compositions described herein, the functional coating comprises a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC). More specifically, the functional coating comprises a mixture of

ETHOCEL™ 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel® (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water). In one embodiment, the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) (*e.g.*, ETHOCEL™ 10 to JF Klucel®) is between 90:10 and 10:90, between 80:20 and 20:80, between 80:20 and 50:50, between 75:25 and 60:40, between 70:30 and 55:45, between 70:30 and 50:50, or between 65:35 and 55:45. More specifically, the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) (*e.g.*, ETHOCEL™ 10 to JF Klucel®) is 70:30. Alternatively, the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) (*e.g.*, ETHOCEL™ 10 to JF Klucel®) is 65:35. In another specific embodiment, the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) (*e.g.*, ETHOCEL™ 10 to JF Klucel®) is 60:40.

In another embodiment, for the second pharmaceutical bead compositions described herein, the functional coating of the present invention comprises a mixture of Eudragit® RS (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1) and Eudragit® RL (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2). The weight ratio of Eudragit® RS to Eudragit® RL is between 95:5 and 5:95, between 90:10 and 50:50, between 90:10 and 60:40, or between 85:15 and 70:30. More specifically, the weight ratio of Eudragit® RS to Eudragit® RL is 75:25. Alternatively, the weight ratio of Eudragit® RS to Eudragit® RL is 80:20.

In certain embodiments, for the second pharmaceutical bead compositions described herein, the weight percentage for the functional coating is 1-30%, 1-20%, 4-12%, 1-10%, 1-7% or 10-15% of the total weight of the inert core and the first layer. More specifically, the weight percentage for the functional coating is 2.0-3.0% of the total weight of the inert core and the first layer. In another more specific embodiment, the weight percentage for the functional coating is 4.0-5.0% of the total weight of the inert core and the first layer. In another more specific embodiment, the weight percentage for the functional coating is 4.5-5.5% of the total weight of the inert core and the first layer. In another more specific embodiment, the weight percentage for the functional coating is 5.0-6.0% of the total weight of the inert core and the first layer. In yet another more specific embodiment, the weight percentage for the functional coating is 11.5-12.5% of the total weight of the inert core and the first layer. Even more specifically, the weight percentage for the functional coating is 2.5% of the total weight of the inert core and the first layer. Alternatively, the weight percentage or

the functional coating is 4.5% of the total weight of the inert core and the first layer. In another alternative, the weight percentage of the functional coating is 5.0% of the total weight of the inert core and the first layer. In yet another alternative, the weight percentage of the functional coating is 5.5% of the total weight of the inert core and the first layer. In yet another alternative, the weight percentage of the functional coating is 12% of the total weight of the inert core and the first layer.

In a 1<sup>st</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 40%-80% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 1-25% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 1-20% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 10-60% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 40%-80% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 1-25% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition; and

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 1-20% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 1-30% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 10-60% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 2<sup>nd</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 50%-75% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 1-20% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 5-15% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 20-40% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 50%-75% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 1-20% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 5-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 1-20% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 20-40% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 3<sup>rd</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 65%-75% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-15% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 10-15% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 20-30% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 65%-75% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 10-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 1-10% or 10-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 20-30% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 4<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) a second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the second layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 2.0%-3.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 5<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer in the first pharmaceutical bead

composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.5%-5.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 6<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;



an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 5.0%-6.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 7<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 11.5%-12.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 8<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 2.0%-3.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 9<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the second pharmaceutical bead

composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.5%-5.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 10<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 5.0%-6.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 11<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 11.5%-12.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 12<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.0%-5.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition,

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 13<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 6-8% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 6-8% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.0%-5.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In a 14<sup>th</sup> specific embodiment, the pharmaceutical composition of the present invention comprises a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein:

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 74% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition and the weight percentage of the binder is 7% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 12% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition;

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 74% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition and the weight percentage of the binder is 7% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 12% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

More specifically, for the pharmaceutical bead composition in the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup> or 14<sup>th</sup> specific embodiment, the inert core comprises sucrose or starch; the binder is HPMC; the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate and the ratio of methacrylic acid to methyl methacrylate is 1:1; and the functional coating comprises of a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC) and weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) is 65:35. More specifically, the enteric coating further comprises triethyl citrate and the weight ratio of the copolymer of methacrylic acid and methyl methacrylate to triethyl citrate is 5:1; and the functional coating comprises a mixture of ETHOCEL<sup>TM</sup> 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel<sup>®</sup> (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water), wherein the weight ratio of ETHOCEL<sup>TM</sup> 10 to JF Klucel<sup>®</sup> is 65:35.



In another more specific embodiment, for the pharmaceutical bead composition in the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, 7<sup>th</sup>, 8<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, 12<sup>th</sup>, 13<sup>th</sup> or 14<sup>th</sup> specific embodiment, the inert core comprises sucrose or starch; the binder is HPMC; the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate and the ratio of methacrylic acid to methyl methacrylate is 1:1; and the functional coating comprises of a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC) and weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) is 60:40. More specifically, the enteric coating further comprises triethyl citrate and the weight ratio of the copolymer of methacrylic acid and methyl methacrylate to triethyl citrate is 5:1; and the functional coating comprises a mixture of ETHOCEL™ 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel® (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water), wherein the weight ratio of ETHOCEL™ 10 to JF Klucel® is 60:40.

In certain embodiments, the amount of dimethyl fumarate in the pharmaceutical compositions described herein is from 90 mg to 960 mg, more specifically from 120 mg to 480 mg. In one embodiment, the amount of dimethyl fumarate in a single capsule described herein is 240 mg. Alternatively, the amount of dimethyl fumarate in a single capsule described herein is 480 mg.

In one aspect, the present invention is described in the following embodiments:

In embodiment (1), for the pharmaceutical composition described in the first embodiment, the first pharmaceutical bead composition comprises an inert core; a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate; and an enteric coating surrounding the first layer.

In embodiment (2), for the pharmaceutical composition of embodiment (1), the inert core in the first pharmaceutical bead composition comprises one or more inert substance selected from the group consisting of starch, dextrose, sucrose, lactose, maltose, and microcrystalline cellulose.

In embodiment (3), for the pharmaceutical composition of embodiment (1), the inert core in the first pharmaceutical bead composition comprises lactose.

In embodiment (4), for the pharmaceutical composition of embodiment (1), the inert core in the first pharmaceutical bead composition comprises sucrose.

In embodiment (5), for the pharmaceutical composition of embodiment (1), the inert core in the first pharmaceutical bead composition comprises starch.

In embodiment (6), for the pharmaceutical composition of any one of embodiments (1)-(5), the weight percentage of the inert core in the first pharmaceutical bead composition is 10%-60% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (7), for the pharmaceutical composition of embodiment (6), the weight percentage of the inert core in the first pharmaceutical bead composition is 20%-40% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (8), for the pharmaceutical composition of embodiment (6), the weight percentage of the inert core in the first pharmaceutical bead composition is 20%-30% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (9), for the pharmaceutical composition of embodiment (6), the weight percentage of the inert core in the first pharmaceutical bead composition is 20%-24% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (10), for the pharmaceutical composition of embodiment (6), the weight percentage of the inert core in the first pharmaceutical bead composition is 16%-20% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (11), for the pharmaceutical composition of any one of embodiments (1)-(10), the inert core in the first pharmaceutical bead composition is a sphere having a diameter of 200-850  $\mu\text{m}$ .

In embodiment (12), for the pharmaceutical composition of embodiment (11), the sphere of the inert core in the first pharmaceutical bead composition has a diameter of 250-350  $\mu\text{m}$ , 500-600  $\mu\text{m}$  or 700-850  $\mu\text{m}$ .

In embodiment (13), for the pharmaceutical composition of embodiment (11), the sphere of the inert core in the first pharmaceutical bead composition has a diameter of 350  $\mu\text{m}$ , 550  $\mu\text{m}$ , or 750  $\mu\text{m}$ .

In embodiment (14), for the pharmaceutical composition of any one of embodiments (1)-(13), the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 40%-80% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (15), for the pharmaceutical composition of embodiment (14), wherein the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 50%-75% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (16), for the pharmaceutical composition of embodiment (14), the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 65%-75% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (17), for the pharmaceutical composition of embodiment (14), the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 68%-72% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (18), for the pharmaceutical composition of embodiment (14), the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 72%-76% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (19), for the pharmaceutical composition of any one of embodiments (1)-(18), the first layer in the first pharmaceutical bead composition further comprises a binder.

In embodiment (20), for the pharmaceutical composition of embodiment (19), the binder in the first layer of the first pharmaceutical bead composition is selected from the group consisting of acacia, agar, alginic acid, amino methacrylate copolymer, ammonio methacrylate copolymer, ammonio methacrylate copolymer dispersion, calcium carbonate, calcium lactate, carbomer copolymer, carbomer homopolymer, carbomer interpolymer, carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, hydrogenated coconut oil, copovidone, corn syrup, corn syrup solids, dextrans, dextrin, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylene glycol and vinyl alcohol graft copolymer, gelatin, liquid glucose, glyceryl behenate, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hypromellose, hypromellose acetate succinate, inulin, alpha-lactalbumin, monohydrate lactose, maltodextrin, maltose, methacrylic acid copolymer, methacrylic acid copolymer dispersion, methacrylic acid and ethyl acrylate copolymer dispersion, methylcellulose, hydrogenated palm oil, polycarbophil, hydrogenated polydextrose, polyethylene oxide, polyvinyl acetate, povidone, pullulan, sodium alginate, pregelatinized

starch, pregelatinized modified starch, corn starch, hydroxypropyl corn starch, pregelatinized hydroxypropyl corn starch, pea starch, hydroxypropyl pea starch, pregelatinized hydroxypropyl pea starch, potato starch, hydroxypropyl potato starch, pregelatinized hydroxypropyl potato starch, tapioca starch, wheat starch, hydrogenated starch hydrolysate, sucrose, sunflower oil, syrup, trehalose, hydrogenated vegetable oil, vitamin E polyethylene glycol succinate, zein, hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), methyl cellulose, ethyl cellulose, sodium carboxy methyl cellulose, polyethylene glycol (PEG), polyvinyl alcohols, polymethacrylate, starch paste, sodium starch, tragacanth, gelatin, alginate, sodium alginate, alginic acid, cellulose, candelilla wax, carnuba wax, copolyvidone, and lactose hydrous.

In embodiment (21), for the pharmaceutical composition of embodiment (20), the binder in the first layer of the first pharmaceutical bead composition is hydroxypropyl methylcellulose (HPMC).

In embodiment (22), for the pharmaceutical composition of any one of embodiments (19)-(21), the weight percentage of the binder in the first layer of the first pharmaceutical bead composition is 1%-25% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (23), for the pharmaceutical composition of embodiment (22), the weight percentage of the binder in the first layer of the first pharmaceutical bead composition is 1%-20% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (24), for the pharmaceutical composition of embodiment (22), the weight percentage of the binder in the first layer of the first pharmaceutical bead composition is 5%-15% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (25), for the pharmaceutical composition of embodiment (22), the weight percentage of the binder in the first layer of the first pharmaceutical bead composition is 5%-10% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (26), for the pharmaceutical composition of embodiment (22), the weight percentage of the binder in the first layer of the first pharmaceutical bead composition is 7% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (27), for the pharmaceutical composition of any one of embodiments (1)-(26), the weight percentage of the enteric coating in the first pharmaceutical bead composition is 1-20% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (28), for the pharmaceutical composition of embodiment (27), the weight percentage of the enteric coating in the first pharmaceutical bead composition is 5-15% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (29), for the pharmaceutical composition of embodiment (27), the weight percentage of the enteric coating in the first pharmaceutical bead composition is 10-15% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (30), for the pharmaceutical composition of embodiment (27), the weight percentage of the enteric coating in the first pharmaceutical bead composition is 11-13% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (31), for the pharmaceutical composition of embodiment (27), the weight percentage of the enteric coating in the first pharmaceutical bead composition is 12% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (32), for the pharmaceutical composition of the first embodiment, the first pharmaceutical bead composition comprises a core comprising dimethyl fumarate; and an enteric coating surrounding the core.

In embodiment (33), for the pharmaceutical composition of embodiment (32), the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 40%-80% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (34), for the pharmaceutical composition of embodiment (33), the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 60%-80%, 60-70% or 70-80% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (35), for the pharmaceutical composition of embodiment (34), the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 65% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (36), for the pharmaceutical composition of embodiment (34), the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 75% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (37), for the pharmaceutical composition of any one of embodiments (32)-(36), the core in the first pharmaceutical bead composition further comprises a binder.

In embodiment (38), for the pharmaceutical composition of embodiment (37), the binder in the core of the first pharmaceutical bead composition is selected from the group consisting of acacia, agar, alginic acid, amino methacrylate copolymer, ammonio methacrylate copolymer, ammonio methacrylate copolymer dispersion, calcium carbonate, calcium lactate, carbomer copolymer, carbomer homopolymer, carbomer interpolymers, carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, hydrogenated coconut oil, copovidone, corn syrup, corn syrup solids, dextrans, dextrin, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylene glycol and vinyl alcohol graft copolymer, gelatin, liquid glucose, glyceryl behenate, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hypromellose, hypromellose acetate succinate, inulin, alpha-lactalbumin, monohydrate lactose, maltodextrin, maltose, methacrylic acid copolymer, methacrylic acid copolymer dispersion, methacrylic acid and ethyl acrylate copolymer dispersion, methylcellulose, hydrogenated palm oil, polycarbophil, hydrogenated polydextrose, polyethylene oxide, polyvinyl acetate, povidone, pullulan, sodium alginate, pregelatinized starch, pregelatinized modified starch, corn starch, hydroxypropyl corn starch, pregelatinized hydroxypropyl corn starch, pea starch, hydroxypropyl pea starch, pregelatinized hydroxypropyl pea starch, potato starch, hydroxypropyl potato starch, pregelatinized hydroxypropyl potato starch, tapioca starch, wheat starch, hydrogenated starch hydrolysate, sucrose, sunflower oil, syrup, trehalose, hydrogenated vegetable oil, vitamin E polyethylene glycol succinate, zein, hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), methyl cellulose, ethyl cellulose, sodium carboxy methyl cellulose, polyethylene glycol (PEG), polyvinyl alcohols, polymethacrylate, starch paste, sodium starch, tragacanth, gelatin, alginate, sodium alginate, alginic acid, cellulose, candelilla wax, carnauba wax, copolyvidone, and lactose hydrous.

In embodiment (39), for the pharmaceutical composition of embodiment (38), the binder in the core of the first pharmaceutical bead composition is microcrystalline cellulose or starch.

In embodiment (40), for the pharmaceutical composition of embodiment (38) or (39), the weight percentage of the binder in the core of the first pharmaceutical bead composition is 1-50% of the weight of the core in the first pharmaceutical bead composition.

In embodiment (41), for the pharmaceutical composition of embodiment (38) or (39), the weight percentage of the binder in the core of the first pharmaceutical bead composition is 15-35% of the weight of the core in the first pharmaceutical bead composition.

In embodiment (42), for the pharmaceutical composition of any one of embodiments (32)-(41), the weight percentage of the enteric coating in the first pharmaceutical bead composition is 1-20% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (43), for the pharmaceutical composition of embodiment (42), wherein the weight percentage of the enteric in the first pharmaceutical bead composition coating is 5-15% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (44), for the pharmaceutical composition of embodiment (42), wherein the weight percentage of the enteric coating in the first pharmaceutical bead composition is 10-15% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (45), for the pharmaceutical composition of embodiment (42), the weight percentage of the enteric coating in the first pharmaceutical bead composition is 11-13% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (46), for the pharmaceutical composition of embodiment (42), the weight percentage of the enteric coating in the first pharmaceutical bead composition is 12% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (47), for the pharmaceutical composition of any one of embodiments (1)-(46), the enteric coating in the first pharmaceutical bead composition comprises an excipient selected from the group consisting of a copolymer of methacrylic acid and methyl methacrylate, a copolymer of methacrylic acid and ethyl acrylate, hypromellose phthalate (HPMCP), cellulose acetate phthalate.

In embodiment (48), for the pharmaceutical composition of embodiment (47), the enteric coating in the first pharmaceutical bead composition comprises a copolymer of methacrylic acid and methyl methacrylate.

In embodiment (49), for the pharmaceutical composition of embodiment (48), the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 0.8:1 to 1.2:1.

In embodiment (50), for the pharmaceutical composition of embodiment (49), the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 1:1 (Eudragit L100).

In embodiment (51), for the pharmaceutical composition of any one of embodiments (1)-(50), the enteric coating in the first pharmaceutical bead composition comprises a plasticizer.

In embodiment (52), for the pharmaceutical composition of embodiment (51), the plasticizer in the enteric coating of the first pharmaceutical bead composition is selected from the group consisting of acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, castor oil, chlorobutanol, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, mannitol, polyethylene glycol, polyethylene glycol monomethyl ether, propylene glycol, pullulan, sorbitol, sorbitol sorbitan solution, triacetin, tributyl citrate, triethyl citrate and vitamin E.

In embodiment (53), for the pharmaceutical composition of embodiment (52), the plasticizer is triethyl citrate.

In embodiment (54), for the pharmaceutical composition of embodiment (53), the weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is from 1: 1 to 1:20.

In embodiment (55), for the pharmaceutical composition of embodiment (54), the weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is 1:5.

In embodiment (56), for the pharmaceutical composition of any one of embodiments (1)-(31) and (47)-(55), the first pharmaceutical bead formulation further comprises a functional coating surround the enteric coating, wherein the weight percentage of the functional coating is 0.1-3.9% of the total weight of the inert core and the first layer of the first pharmaceutical bead formulation.

In embodiment (57), for the pharmaceutical composition of any one of embodiments (1)-(31) and (47)-(55), the first pharmaceutical bead formulation further comprises a functional coating, wherein the functional coating is in between the first layer and the enteric coating (*i.e.*, the functional coating surrounds the first layer and the enteric coating surrounds the functional coating) and the weight percentage of the functional coating is 0.1-3.9% of the total weight of the inert core and the first layer of the first pharmaceutical bead formulation.

In embodiment (58), for the pharmaceutical composition of embodiment (56) or (57), the weight percentage of the functional coating in the first pharmaceutical bead composition



is 2.0-3.0% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (59), for the pharmaceutical composition of embodiment (58), the weight percentage of the functional coating in the first pharmaceutical bead composition is 2.5% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition.

In embodiment (60), for the pharmaceutical composition of any one of embodiments (32)-(55), the first pharmaceutical bead formulation further comprises a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 0.1-3.9% of the total weight of the core of the first pharmaceutical bead formulation.

In embodiment (61), for the pharmaceutical composition of any one of embodiments (32)-(55), the first pharmaceutical bead formulation further comprises a functional coating, wherein the functional coating is in between the core and the enteric coating (*i.e.*, the functional coating surrounds the core and the enteric coating surrounds the functional coating) and the weight percentage of the functional coating is 0.1-3.9% of the total weight of the core of the first pharmaceutical bead formulation.

In embodiment (62), for the pharmaceutical composition of embodiment (60) or (61), the weight percentage of the functional coating in the first pharmaceutical bead composition is 2.0-3.0% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (63), for the pharmaceutical composition of embodiment (60) or (61), the weight percentage of the functional coating in the first pharmaceutical bead composition is 2.5% of the total weight of the core in the first pharmaceutical bead composition.

In embodiment (64), for pharmaceutical composition of any one of embodiments (56)-(63), the functional coating in the first pharmaceutical bead composition comprises a mixture of one or more water-insoluble polymer and one or more water-soluble polymer.

In embodiment (65), for the pharmaceutical composition of any one of embodiments (56)-(63), wherein the functional coating in the first pharmaceutical bead composition comprises one or more excipients selected from the group consisting of polyvinylpyrrolidone (PVP), polyethylene oxide (PEO), glyceryl monostearate, hydroxyl propyl methyl cellulose(HPMC), SoluPlus, polyvinyl alcohol (PVA), polyvinyl alcohol (PVA), hydroxypropylmethylcellulose, acetate succinate (HPMCAS), ethylene vinyl acetate (EVA), methacrylates (Eudragit™), cellulose acetate butyrate (CAB), cellulose acetate phthalate (CAP), poly(ethylene glycol), poly(vinyl acetate) (PVAc), polylactide (PLA), polyglycolide (PGA), copolymers of PLA/PGA and polycaprolactone (PCL), polyvinylpyrrolidone-co-vinyl

acetate (Kollidon VA-64), polyurethanes, poly(lactic acid), poly(glycolic acid), poly(anhydride–imides), poly(anhydride–esters), poly(iminocarbonates), poly(phosphazenes), poly(phosphoesters), ethylcellulose (EC), hydroxypropyl cellulose (HPC), alginic acid, carbomer copolymer, carbomer homopolymer, carbomer interpolymers, carboxymethylcellulose sodium, carrageenan, cellaburate, ethylcellulose aqueous dispersion, ethylcellulose dispersion Type B, glyceryl monooleate, guar gum, hydroxypropyl betadex, polyvinyl acetate dispersion, shellac, sodium alginate, pregelatinized starch, pregelatinized modified starch and xanthan gum.

In embodiment (66), for the pharmaceutical composition of embodiment (65), wherein the functional coating in the first pharmaceutical bead composition comprises a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC).

In embodiment (67), for the pharmaceutical composition of embodiment (65), the functional coating in the first pharmaceutical bead composition comprises a mixture of ETHOCEL™ 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel® (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water).

In embodiment (68), for the pharmaceutical composition of embodiment (66) or (67), the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 90:10 and 10:90.

In embodiment (69), for the pharmaceutical composition of embodiment (68), the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 20:80.

In embodiment (70), for the pharmaceutical composition of embodiment (68), the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 50:50.

In embodiment (71), for the pharmaceutical composition of embodiment (68), the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 75:25 and 60:40.

In embodiment (72), for the pharmaceutical composition of embodiment (68), the weight ratio of ethylcellulose to hydroxypropyl cellulose is 70:30.

In embodiment (73), for the pharmaceutical composition of embodiment (68), the weight ratio of ethylcellulose to hydroxypropyl cellulose is 65:35.

In embodiment (74), for the pharmaceutical composition of embodiment (68), the weight ratio of ethylcellulose to hydroxypropyl cellulose is 60:40.

In embodiment (75), for the pharmaceutical composition of embodiment (65), the functional coating in the first pharmaceutical bead composition comprises a mixture of Eudragit® RS (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl

methacrylate chloride) 1:2:0.1) and Eudragit<sup>®</sup> RL (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2).

In embodiment (76), for the pharmaceutical composition of embodiment (75), the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is between 95:5 to 5:95.

In embodiment (77), for the pharmaceutical composition of embodiment (75), the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is between 90:10 to 50:50.

In embodiment (78), for the pharmaceutical composition of embodiment (75), wherein the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is between 90:10 to 60:40.

In embodiment (79), for the pharmaceutical composition of embodiment (75), wherein the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is between 85:15 to 70:30.

In embodiment (80), for the pharmaceutical composition of embodiment (75), wherein the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is 75:25.

In embodiment (81), for the pharmaceutical composition of embodiment (75), wherein the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is 80:20.

In embodiment (82), for the pharmaceutical composition of any one of embodiments (1)-(81), the second pharmaceutical bead composition comprises:

- an inert core;

- a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate;

- an enteric coating surrounding the first layer; and

- a functional coating surrounding the enteric coating.

In embodiment (83), for the pharmaceutical composition of any one of embodiments (1)-(81), the second pharmaceutical bead composition comprises:

- an inert core;

- a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate;

- a functional coating surrounding the first layer; and

- an enteric coating surrounding the functional coating.

In embodiment (84), for the pharmaceutical composition of embodiment (82) or (83), the inert core in the second pharmaceutical bead composition comprises one or more inert substance selected from the group consisting of starch, dextrose, sucrose, lactose, maltose, and microcrystalline cellulose.

In embodiment (85), for the pharmaceutical composition of embodiment (82) or (83), the inert core in the second pharmaceutical bead composition comprises lactose.

In embodiment (86), for the pharmaceutical composition of embodiment (82) or (83), the inert core in the second pharmaceutical bead composition comprises sucrose.

In embodiment (87), for the pharmaceutical composition of embodiment (82) or (83), the inert core in the second pharmaceutical bead composition comprises starch.

In embodiment (88), for the pharmaceutical composition of any one of embodiments (82)-(87), the weight percentage of the inert core in the second pharmaceutical bead composition is 10%-60% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (89), for the pharmaceutical composition of embodiment (88), the weight percentage of the inert core in the second pharmaceutical bead composition is 20%-40% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (90), for the pharmaceutical composition of embodiment (88), the weight percentage of the inert core in the second pharmaceutical bead composition is 20%-30% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (91), for the pharmaceutical composition of embodiment (88), the weight percentage of the inert core in the second pharmaceutical bead composition is 20%-24% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (92), for the pharmaceutical composition of embodiment (88), the weight percentage of the inert core in the second pharmaceutical bead composition is 16%-20% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (93), for the pharmaceutical composition of any one of embodiments (82)-(92), the inert core in the second pharmaceutical bead composition is a sphere having a diameter of 200-850  $\mu\text{m}$ .

In embodiment (94), for the pharmaceutical composition of embodiment (93), the sphere of the inert core in the second pharmaceutical bead composition has a diameter of 250-350  $\mu\text{m}$ , 500-600  $\mu\text{m}$  or 700-850  $\mu\text{m}$ .

In embodiment (95), for the pharmaceutical composition of embodiment (93), the sphere of the inert core in the second pharmaceutical bead composition has a diameter of 350  $\mu\text{m}$ , 550  $\mu\text{m}$ , or 750  $\mu\text{m}$ .

In embodiment (96), for the pharmaceutical composition of any one of embodiments (82)-(95), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 40%-80% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (97), for the pharmaceutical composition of embodiment (96), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 50%-75% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (98), for the pharmaceutical composition of embodiment (96), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 65%-75% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (99), for the pharmaceutical composition of embodiment (96), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 68%-72% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (100), for the pharmaceutical composition of embodiment (96), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 72-76% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (101), for the pharmaceutical composition of any one of embodiments (82)-(100), the first layer in the second pharmaceutical bead composition further comprises a binder.

In embodiment (102), for the pharmaceutical composition of embodiment (101), the binder in the first layer of the second pharmaceutical bead composition is selected from the group consisting of acacia, agar, alginic acid, amino methacrylate copolymer, ammonio methacrylate copolymer, ammonio methacrylate copolymer dispersion, calcium carbonate, calcium lactate, carbomer copolymer, carbomer homopolymer, carbomer interpolymers, carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, hydrogenated coconut oil, copovidone, corn syrup, corn syrup solids, dextrans, dextrin, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylene glycol and vinyl alcohol graft copolymer, gelatin, liquid glucose, glyceryl behenate, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hypromellose, hypromellose acetate succinate, inulin, alpha-lactalbumin,

monohydrate lactose, maltodextrin, maltose, methacrylic acid copolymer, methacrylic acid copolymer dispersion, methacrylic acid and ethyl acrylate copolymer dispersion, methylcellulose, hydrogenated palm oil, polycarbophil, hydrogenated polydextrose, polyethylene oxide, polyvinyl acetate, povidone, pullulan, sodium alginate, pregelatinized starch, pregelatinized modified starch, corn starch, hydroxypropyl corn starch, pregelatinized hydroxypropyl corn starch, pea starch, hydroxypropyl pea starch, pregelatinized hydroxypropyl pea starch, potato starch, hydroxypropyl potato starch, pregelatinized hydroxypropyl potato starch, tapioca starch, wheat starch, hydrogenated starch hydrolysate, sucrose, sunflower oil, syrup, trehalose, hydrogenated vegetable oil, vitamin E polyethylene glycol succinate, zein, hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), methyl cellulose, ethyl cellulose, sodium carboxy methyl cellulose, polyethylene glycol (PEG), polyvinyl alcohols, polymethacrylate, starch paste, sodium starch, tragacanth, gelatin, alginate, sodium alginate, alginic acid, cellulose, candelilla wax, carnuba wax, copolyvidone, and lactose hydrous.

In embodiment (103), for the pharmaceutical composition of embodiment (102), the binder in the first layer of the second pharmaceutical bead composition is hydroxypropyl methylcellulose (HPMC).

In embodiment (104), for the pharmaceutical composition of any one of embodiments (101)-(103), the weight percentage of the binder in the first layer of the second pharmaceutical bead composition is 1%-25% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (105), for the pharmaceutical composition of embodiment (104), the weight percentage of the binder in the first layer of the second pharmaceutical bead composition is 1%-20% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (106), for the pharmaceutical composition of embodiment (104), the weight percentage of the binder in the first layer of the second pharmaceutical bead composition is 5%-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (107), for the pharmaceutical composition of embodiment (104), the weight percentage of the binder in the first layer of the second pharmaceutical bead composition is 5%-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (108), for the pharmaceutical composition of embodiment (104), the weight percentage of the binder in the first layer of the second pharmaceutical bead composition is 7% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (109), for the pharmaceutical composition of any one of embodiments (82)-(108), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 1-20% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (110), for the pharmaceutical composition of embodiment (109), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 5-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (111), for the pharmaceutical composition of embodiment (109), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 10-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (112), for the pharmaceutical composition of embodiment (109), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (113), for the pharmaceutical composition of embodiment (109), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 12% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (114), for the pharmaceutical composition of any one of embodiments (82)-(113), wherein the weight percentage of the functional coating in the second pharmaceutical bead composition is 1-30% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (115), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 1-20% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (116), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is

4-12% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (117), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 1-10% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (118), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 10-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (119), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 4.5-5.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (120), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 5.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (121), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 4.0-5.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (122), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 4.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (123), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 5.0-6.0% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (124), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 5.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.



In embodiment (125), for the pharmaceutical composition of embodiment (114), the weight percentage of the functional coating in the second pharmaceutical bead composition is 11.5-12.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (126), for the pharmaceutical composition of embodiment (114), wherein the weight percentage of the functional coating in the second pharmaceutical bead composition is 12% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (127), for the pharmaceutical composition of any one of embodiments (1)-(81), the second pharmaceutical bead composition comprises:

- an core comprising dimethyl fumarate;
- an enteric coating surrounding the core; and
- a functional coating surrounding the enteric coating.

In embodiment (128), for the pharmaceutical composition of any one of embodiments (1)-(81), the second pharmaceutical bead composition comprises:

- a core comprising dimethyl fumarate;
- a functional coating surrounding the core; and
- an enteric coating surrounding the functional coating.

In embodiment (129), for the pharmaceutical composition of embodiment (127) or (128), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 40%-80% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (130), for the pharmaceutical composition of embodiment (129), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 60%-80%, 60-70% or 70-80% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (131), for the pharmaceutical composition of embodiment (130), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 65% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (132), for the pharmaceutical composition of embodiment (130), the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 75% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (133), for the pharmaceutical composition of any one of embodiments (127)-(132), the core in the second pharmaceutical bead composition further comprises a binder.

In embodiment (134), for the pharmaceutical composition of embodiment (133), the binder in the core of the second pharmaceutical bead composition is selected from the group consisting of acacia, agar, alginic acid, amino methacrylate copolymer, ammonio methacrylate copolymer, ammonio methacrylate copolymer dispersion, calcium carbonate, calcium lactate, carbomer copolymer, carbomer homopolymer, carbomer interpolymer, carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, hydrogenated coconut oil, copovidone, corn syrup, corn syrup solids, dextrans, dextrin, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylene glycol and vinyl alcohol graft copolymer, gelatin, liquid glucose, glyceryl behenate, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hypromellose, hypromellose acetate succinate, inulin, alpha-lactalbumin, monohydrate lactose, maltodextrin, maltose, methacrylic acid copolymer, methacrylic acid copolymer dispersion, methacrylic acid and ethyl acrylate copolymer dispersion, methylcellulose, hydrogenated palm oil, polycarbophil, hydrogenated polydextrose, polyethylene oxide, polyvinyl acetate, povidone, pullulan, sodium alginate, pregelatinized starch, pregelatinized modified starch, corn starch, hydroxypropyl corn starch, pregelatinized hydroxypropyl corn starch, pea starch, hydroxypropyl pea starch, pregelatinized hydroxypropyl pea starch, potato starch, hydroxypropyl potato starch, pregelatinized hydroxypropyl potato starch, tapioca starch, wheat starch, hydrogenated starch hydrolysate, sucrose, sunflower oil, syrup, trehalose, hydrogenated vegetable oil, vitamin E polyethylene glycol succinate, zein, hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), methyl cellulose, ethyl cellulose, sodium carboxy methyl cellulose, polyethylene glycol (PEG), polyvinyl alcohols, polymethacrylate, starch paste, sodium starch, tragacanth, gelatin, alginate, sodium alginate, alginic acid, cellulose, candelilla wax, carnauba wax, copolyvidone, and lactose hydrous.

In embodiment (135), for the pharmaceutical composition of embodiment (133), the binder in the core of the second pharmaceutical bead composition is microcrystalline cellulose or starch.

In embodiment (136), for the pharmaceutical composition of any one of embodiments (133)-(135), the weight percentage of the binder in the core of the second pharmaceutical

bead composition is 1-50% of the weight of the core in the second pharmaceutical bead composition.

In embodiment (137), for the pharmaceutical composition of embodiment (136), the weight percentage of the binder in the core of the second pharmaceutical bead composition is 15-35% of the weight of the core in the second pharmaceutical bead composition.

In embodiment (138), for the pharmaceutical composition of any one of embodiments (127)-(137), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 1-20% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (139), for the pharmaceutical composition of embodiment (138), the weight percentage of the enteric coating in the second pharmaceutical bead composition coating is 5-15% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (140), for the pharmaceutical composition of embodiment (138), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 10-15% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (141), for the pharmaceutical composition of embodiment (138), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 11-13% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (142), for the pharmaceutical composition of embodiment (138), the weight percentage of the enteric coating in the second pharmaceutical bead composition is 12% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (143), for the pharmaceutical composition of any one of embodiments (127)-(142), the weight percentage of the functional coating in the second pharmaceutical bead composition is 1-30% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (144), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 1-20% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (145), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 4-12% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (146), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 1-10% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (147), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 10-15% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (148), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 4.5-5.5% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (149), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 5.0% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (150), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 5.0-6.0% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (151), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 5.5% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (152), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 11.5-12.5% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (153), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 12% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (154), for the pharmaceutical composition of embodiment (143), the weight percentage of the functional coating in the second pharmaceutical bead composition is 4.0-5.0% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (155), for the pharmaceutical composition of embodiment (154), the weight percentage of the functional coating in the second pharmaceutical bead composition is 4.5% of the total weight of the core in the second pharmaceutical bead composition.

In embodiment (156), for the pharmaceutical composition of any one of embodiments (82)-(155), the enteric coating in the second pharmaceutical bead composition comprises an excipient selected from the group consisting of a copolymer of methacrylic acid and methyl

methacrylate, a copolymer of methacrylic acid and ethyl acrylate, hypromellose phthalate (HPMCP), cellulose acetate phthalate.

In embodiment (157), for the pharmaceutical composition of embodiment (156), the enteric coating in the second pharmaceutical bead composition comprises a copolymer of methacrylic acid and methyl methacrylate.

In embodiment (158), for the pharmaceutical composition of embodiment (157), wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 0.8:1 to 1.2:1.

In embodiment (159), for the pharmaceutical composition of embodiment (158), wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 1:1 (Eudragit L100).

In embodiment (160), for the pharmaceutical composition of any one of embodiments (82)-(159), wherein the enteric coating in the second pharmaceutical bead composition comprises a plasticizer.

In embodiment (161), for the pharmaceutical composition of embodiment (160), the plasticizer in the enteric coating of the second pharmaceutical bead composition is selected from the group consisting of acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, castor oil, chlorobutanol, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, mannitol, polyethylene glycol, polyethylene glycol monomethyl ether, propylene glycol, pullulan, sorbitol, sorbitol sorbitan solution, triacetin, tributyl citrate, triethyl citrate and vitamin E.

In embodiment (162), for the pharmaceutical composition of embodiment (161), the plasticizer in the enteric coating of the second pharmaceutical bead composition is triethyl citrate.

In embodiment (163), for the pharmaceutical composition of embodiment (162), weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is from 1: 1 to 1:20.

In embodiment (164), for the pharmaceutical composition of embodiment (163), wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is 1:5.

In embodiment (165), for the pharmaceutical composition of any one of embodiments (82)-(164), the functional coating in the second pharmaceutical bead composition comprises a mixture of one or more water-insoluble polymer and one or more water-soluble polymer.

In embodiment (166), for the pharmaceutical composition of any one of embodiments (82)-(164), the functional coating in the second pharmaceutical bead composition comprises one or more excipients selected from the group consisting of polyvinylpyrrolidone (PVP), polyethylene oxide (PEO), glyceryl monostearate, hydroxyl propyl methyl cellulose (HPMC), SoluPlus, polyvinyl alcohol (PVA), polyvinyl alcohol (PVA), hydroxypropylmethylcellulose, acetate succinate (HPMCAS), ethylene vinyl acetate (EVA), methacrylates (Eudragit™), cellulose acetate butyrate (CAB), cellulose acetate phthalate (CAP), poly(ethylene glycol), poly(vinyl acetate) (PVAc), polylactide (PLA), polyglycolide (PGA), copolymers of PLA/PGA and polycaprolactone (PCL), polyvinylpyrrolidone-co-vinyl acetate (Kollidon VA-64), polyurethanes, poly(lactic acid), poly(glycolic acid), poly(anhydride-imides), poly(anhydride-esters), poly(iminocarbonates), poly(phosphazenes), poly(phosphoesters), ethylcellulose (EC), hydroxypropyl cellulose (HPC), alginic acid, carbomer copolymer, carbomer homopolymer, carbomer interpolymers, carboxymethylcellulose sodium, carrageenan, cellaburate, ethylcellulose aqueous dispersion, ethylcellulose dispersion Type B, glyceryl monooleate, guar gum, hydroxypropyl betadex, polyvinyl acetate dispersion, shellac, sodium alginate, pregelatinized starch, pregelatinized modified starch and xanthan gum.

In embodiment (167), for the pharmaceutical composition of any one of embodiments (82)-(164), the functional coating in the second pharmaceutical bead composition comprises a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC).

In embodiment (168), for the pharmaceutical composition of embodiment (167), the functional coating in the second pharmaceutical bead composition comprises a mixture of ETHOCEL™ 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel® (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water).

In embodiment (169), for the pharmaceutical composition of embodiment (167) or (168), the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 90:10 and 10:90.

In embodiment (170), for the pharmaceutical composition of embodiment (169), the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 20:80.

In embodiment (171), for the pharmaceutical composition of embodiment (169), the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 50:50.

In embodiment (172), for the pharmaceutical composition of embodiment (169), the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 75:25 and 60:40.

In embodiment (173), for the pharmaceutical composition of embodiment (169), the weight ratio of ethylcellulose to hydroxypropyl cellulose is 70:30.

In embodiment (174), for the pharmaceutical composition of embodiment (169), the weight ratio of ethylcellulose to hydroxypropyl cellulose is 65:35.

In embodiment (175), for the pharmaceutical composition of embodiment (166), wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 60:40.

In embodiment (176), for the pharmaceutical composition of any one of embodiments (82)-(164), the functional coating in the second pharmaceutical bead composition comprises a mixture of Eudragit<sup>®</sup> RS (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1) and Eudragit<sup>®</sup> RL (poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2).

In embodiment (177), for the pharmaceutical composition of embodiment (176), the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is between 95:5 to 5:95.

In embodiment (178), for the pharmaceutical composition of embodiment (176), the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is between 90:10 to 50:50.

In embodiment (179), for the pharmaceutical composition of embodiment (176), the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is between 90:10 to 60:40.

In embodiment (180), for the pharmaceutical composition of embodiment (176), the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is between 85:15 to 70:30.

In embodiment (181), for the pharmaceutical composition of embodiment (176), wherein the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is 75:25.

In embodiment (182), for the pharmaceutical composition of embodiment (176), wherein the weight ratio of Eudragit<sup>®</sup> RS to Eudragit<sup>®</sup> RL is 80:20.

In embodiment (183), for the pharmaceutical composition of any one of the embodiments (82), (84)-(127) and (129)-(182), the second pharmaceutical bead composition further comprises a second enteric coating surround the functional coating.

In embodiment (184), for the the pharmaceutical composition of embodiment (183), the second enteric coating comprises an excipient selected from the group consisting of a copolymer of methacrylic acid and methyl methacrylate, a copolymer of methacrylic acid and ethyl acrylate, hypromellose phthalate (HPMCP), cellulose acetate phthalate.

In embodiment (185), for the pharmaceutical composition of embodiment (183), the second enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate.

In embodiment (186), for the pharmaceutical composition of embodiment (185), the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 0.8:1 to 1.2:1.

In embodiment (187), for the pharmaceutical composition of embodiment (186), wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 1:1 (Eudragit L100).

In embodiment (188), for the pharmaceutical composition of any one of embodiments (183)-(187), the second enteric coating comprises a plasticizer.

In embodiment (189), for the pharmaceutical composition of embodiment (188), the plasticizer in the second enteric coating is selected from the group consisting of acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, castor oil, chlorobutanol, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, mannitol, polyethylene glycol, polyethylene glycol monomethyl ether, propylene glycol, pullulan, sorbitol, sorbitol sorbitan solution, triacetin, tributyl citrate, triethyl citrate and vitamin E.

In embodiment (190), for the pharmaceutical composition of embodiment (189), the plasticizer in the second enteric coating is triethyl citrate.

In embodiment (191), for the pharmaceutical composition of embodiment (190), the weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is from 1: 1 to 1:20.

In embodiment (192), for the pharmaceutical composition of embodiment (191), the weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is 1:5.

In embodiment (193), for the pharmaceutical composition of any one of embodiments (183)-(192), the weight percentage of the second enteric coating is 1-20% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (194), for the pharmaceutical composition of embodiment (193), the weight percentage of the second enteric coating is 5-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (195), for the pharmaceutical composition of embodiment (193), the weight percentage of the second enteric coating is 10-15% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (196), for the pharmaceutical composition of embodiment (193), the weight percentage of the second enteric coating is 11-13% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

In embodiment (197), for the pharmaceutical composition of embodiment (193), the weight percentage of the second enteric coating is 12% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.



In embodiment (198), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.5%-5.5% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer.

In embodiment (199), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 5.0%-6.0% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer.

In embodiment (200), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 11.5%-12.5% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer.

In embodiment (201), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.0%-5.0% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer.

In embodiment (202), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.0%-5.0% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 16-20% of the total weight of the inert core and the first layer.

In embodiment (203), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

a functional coating surrounding the first layer, wherein the weight percentage of the functional coating is 4.5%-5.5% of the total weight of the inert core and the first layer; and

an enteric coating surrounding the functional coating, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer;

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer.

In embodiment (204), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

a functional coating surrounding the first layer, wherein the weight percentage of the functional coating is 5.0%-6.0% of the total weight of the inert core and the first layer; and

an enteric coating surrounding the functional coating, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer.

In embodiment (205), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

a functional coating surrounding the first layer, wherein the weight percentage of the functional coating is 11.5%-12.5% of the total weight of the inert core and the first layer; and

an enteric coating surrounding the functional coating, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer;

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer.

In embodiment (206), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

a functional coating surrounding the first layer, wherein the weight percentage of the functional coating is 4.0%-5.0% of the total weight of the inert core and the first layer; and

an enteric coating surrounding the functional coating, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer;

wherein the weight percentage of the inert core is 16-20% of the total weight of the inert core and the first layer.

In embodiment (207), for the pharmaceutical composition of any one of embodiments (198)-(206), wherein the inert core in the second pharmaceutical bead composition comprises sucrose or starch; the binder in the second pharmaceutical bead composition is HPMC; the enteric coating in the second pharmaceutical bead composition comprises a copolymer of methacrylic acid and methyl methacrylate and the ratio of methacrylic acid to methyl methacrylate in the copolymer is 1:1; and the functional coating in the second pharmaceutical bead composition comprises of a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC) and the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) is 65:35.

In embodiment (208), for the pharmaceutical composition of embodiment (207), the enteric coating in the second pharmaceutical bead composition further comprises triethyl citrate and the weight ratio of the copolymer of methacrylic acid and methyl methacrylate to triethyl citrate is 5:1; and the functional coating in the second pharmaceutical bead composition comprises a mixture of ETHOCEL™ 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel® (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water), wherein the weight ratio of ETHOCEL™ 10 to JF Klucel® is 65:35.

In embodiment (209), for the pharmaceutical composition of any one of embodiments (198)-(206), wherein the inert core in the second pharmaceutical bead composition comprises sucrose or starch; the binder in the second pharmaceutical bead composition is HPMC; the enteric coating in the second pharmaceutical bead composition comprises a copolymer of methacrylic acid and methyl methacrylate and the ratio of methacrylic acid to methyl methacrylate in the copolymer is 1:1; and the functional coating in the second pharmaceutical bead composition comprises of a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC) and the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) is 60:40.

In embodiment (210), for the pharmaceutical composition of embodiment (209), the enteric coating in the second pharmaceutical bead composition further comprises triethyl citrate and the weight ratio of the copolymer of methacrylic acid and methyl methacrylate to triethyl citrate is 5:1; and the functional coating in the second pharmaceutical bead composition comprises a mixture of ETHOCEL<sup>TM</sup> 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel<sup>®</sup> (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water), wherein the weight ratio of ETHOCEL<sup>TM</sup> 10 to JF Klucel<sup>®</sup> is 60:40.

In embodiment (211), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

a core comprising an active substance, wherein the active substance is dimethyl fumarate;

an enteric coating surrounding the core, wherein the weight percentage of the enteric coating is 11%-13% of the total weight of the core; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.5%-5.5% of the total weight of the core,

wherein the weight percentage of dimethyl fumarate is 60%-80% of the total weight of the core.

In embodiment (212), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

a core comprising an active substance, wherein the active substance is dimethyl fumarate;

an enteric coating surrounding the core, wherein the weight percentage of the enteric coating is 11%-13% of the total weight of the core; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 5.0%-6.0% of the total weight of the core,

wherein the weight percentage of dimethyl fumarate is 60%-80% of the total weight of the core.

In embodiment (213), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

a core comprising an active substance, wherein the active substance is dimethyl fumarate;

an enteric coating surrounding the core, wherein the weight percentage of the enteric coating is 11%-13% of the total weight of the core; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 11.5%-12.5% of the total weight of the core,

wherein the weight percentage of dimethyl fumarate is 60%-80% of the total weight of the core.

In embodiment (214), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

a core comprising an active substance, wherein the active substance is dimethyl fumarate;

an enteric coating surrounding the core, wherein the weight percentage of the enteric coating is 11%-13% of the total weight of the core; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.0%-5.0% of the total weight of the core,

wherein the weight percentage of dimethyl fumarate is 60%-80% of the total weight of the core.

In embodiment (215), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

a core comprising an active substance, wherein the active substance is dimethyl fumarate;

a functional coating surrounding the core, wherein the weight percentage of the functional coating is 4.5%-5.5% of the total weight of the core,

an enteric coating surrounding the functional coating, wherein the weight percentage of the enteric coating is 11%-13% of the total weight of the core; and

wherein the weight percentage of dimethyl fumarate is 60%-80% of the total weight of the core.

In embodiment (216), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

a core comprising an active substance, wherein the active substance is dimethyl fumarate;

a functional coating surrounding the core, wherein the weight percentage of the functional coating is 5.0%-6.0% of the total weight of the core,

an enteric coating surrounding the functional coating, wherein the weight percentage of the enteric coating is 11%-13% of the total weight of the core; and

wherein the weight percentage of dimethyl fumarate is 60%-80% of the total weight of the core.

In embodiment (217), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

a core comprising an active substance, wherein the active substance is dimethyl fumarate;

a functional coating surrounding the core, wherein the weight percentage of the functional coating is 11.5%-12.5% of the total weight of the core,

an enteric coating surrounding the functional coating, wherein the weight percentage of the enteric coating is 11%-13% of the total weight of the core; and

wherein the weight percentage of dimethyl fumarate is 60%-80% of the total weight of the core.

In embodiment (218), for the pharmaceutical composition of any one of embodiments (1)-(81), wherein the second pharmaceutical bead composition comprises:

a core comprising an active substance, wherein the active substance is dimethyl fumarate;

a functional coating surrounding the core, wherein the weight percentage of the functional coating is 4.0%-5.0% of the total weight of the core,

an enteric coating surrounding the functional coating, wherein the weight percentage of the enteric coating is 11%-13% of the total weight of the core; and

wherein the weight percentage of dimethyl fumarate is 60%-80% of the total weight of the core.

In embodiment (219), for the pharmaceutical composition of any one of embodiments (211)-(218), the enteric coating in the second pharmaceutical bead composition comprises a copolymer of methacrylic acid and methyl methacrylate and the ratio of methacrylic acid to methyl methacrylate in the copolymer is 1:1; and the functional coating comprises of a

mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC) and the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) is 65:35.

In embodiment (220), for the pharmaceutical composition of embodiment (219), the enteric coating in the second pharmaceutical bead composition further comprises triethyl citrate and the weight ratio of the copolymer of methacrylic acid and methyl methacrylate to triethyl citrate is 5:1; and the functional coating comprises a mixture of ETHOCEL<sup>TM</sup> 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel<sup>®</sup> (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water), wherein the weight ratio of ETHOCEL<sup>TM</sup> 10 to JF Klucel<sup>®</sup> is 65:35.

In embodiment (221), for the pharmaceutical composition of any one of embodiments (211)-(218), the enteric coating in the second pharmaceutical bead composition comprises a copolymer of methacrylic acid and methyl methacrylate and the ratio of methacrylic acid to methyl methacrylate in the copolymer is 1:1; and the functional coating comprises of a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC) and the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) is 60:40.

In embodiment (222), for the pharmaceutical composition of embodiment (221), the enteric coating in the second pharmaceutical bead composition further comprises triethyl citrate and the weight ratio of the copolymer of methacrylic acid and methyl methacrylate to triethyl citrate is 5:1; and the functional coating comprises a mixture of ETHOCEL<sup>TM</sup> 10 (ethylcellulose polymer with viscosity in the range of 9-11 cP for 5% weight solution in 80% toluene and 20% ethanol) and JF Klucel<sup>®</sup> (hydroxypropyl cellulose polymer with viscosity in the range of 150-400 cP for 5% by weight solution in water), wherein the weight ratio of ETHOCEL<sup>TM</sup> 10 to JF Klucel<sup>®</sup> is 60:40.

In embodiment (223), for the pharmaceutical composition of any one of embodiments (32)-(55) and (60)-(81), the diameter of the core in the first pharmaceutical bead composition is in the range of 0.5 mm to 2.0 mm.

In embodiment (224), for the pharmaceutical composition of embodiment (223), the diameter of the core in the first pharmaceutical bead composition is in the range of 0.6 mm to 2.0 mm.

In embodiment (225), for the pharmaceutical composition of embodiment (223), the diameter of the core in the first pharmaceutical bead composition is in the range of 0.5 mm to 1.5 mm.



In embodiment (226), for the pharmaceutical composition of any one of embodiments (127)-(197) and (211)-(225), the diameter of the core in the second pharmaceutical bead composition is in the range of 0.5 mm to 2.0 mm.

In embodiment (227), for the pharmaceutical composition of embodiment (226), the diameter of the core in the second pharmaceutical bead composition is in the range of 0.6 mm to 2.0 mm.

In embodiment (228), for the pharmaceutical composition of embodiment (226), the diameter of the core in the second pharmaceutical bead composition is in the range of 0.5 mm to 1.5 mm.

The controlled-release pharmaceutical bead compositions (*i.e.*, the second pharmaceutical bead composition) of the present invention provide extended release of the active substance dimethyl fumarate when subjected to a dissolution test. The dissolution test can be carried out according to standard procedures published by USP-NF.

In one embodiment, the dissolution profile of the pharmaceutical composition of the present invention is determined by subjecting the pharmaceutical composition to an in vitro dissolution test employing 0.1 N hydrochloric acid as dissolution medium during the first 2 hours of the test and then USP Simulated Intestinal Fluid (SIF) without pancreatin as dissolution medium in a USP Apparatus II (paddle apparatus) (Test 1). Alternatively, the dissolution profile is determined by subjecting the pharmaceutical composition of the present invention to an in vitro dissolution test employing USP Simulated Gastric Fluid (SGF) without pepsin as dissolution medium during the first 2 hours of the test and then USP Simulated Intestinal Fluid (SIF) without pancreatin as dissolution medium in a USP Apparatus IV (flow-through cell) (Test 2). In yet another alternative, the dissolution profile is determined by subjecting the pharmaceutical composition of the present invention to an in vitro dissolution test employing USP Simulated Intestinal Fluid (SIF) without pancreatin in a USP Apparatus IV (flow-through cell) (Test 3). USP SIF and SGF solutions can be prepared according to procedures described in USP35-NF30.

In certain embodiments, when subjected to dissolution Test 1, the pharmaceutical bead composition of the present invention has the following dissolution profile:

within the first 2 hours of the test, less than 10% by weight of the active substance in the tablet is released;

within the first 4 hours of the test, 10-70% by weight of the active substance in the tablet is released; and

within the first 7 hours of the test, 50-100% by weight of the active substance in the tablet is released.

In certain embodiments, when subjected to dissolution Test 1, the tablet composition of the present invention has the following dissolution profile:

within the first 2 hours of the test, less than 10% by weight of the active substance in the tablet is released; and

within the first 4 hours of the test, 90-100% by weight of the active substance in the tablet is released.

In certain embodiments, when subjected to dissolution Test 2, the bead composition of the present invention has the following dissolution profile:

within the first 2 hours of the test, less than 10% by weight of the active substance in the tablet is released;

within the first 4 hours of the test, 10-70% by weight of the active substance in the tablet is released; and

within the first 9 hours of the test, 50-100% by weight of the active substance in the table is released.

In certain embodiments, when subjected to dissolution Test 2, the bead composition of the present invention has the following dissolution profile:

within the first 2 hours of the test, less than 10% by weight of the active substance in the tablet is released;

within the first 4 hours of the test, 70-90% by weight of the active substance in the tablet is released; and

within the first 9 hours of the test, 90-100% by weight of the active substance in the table is released.

In certain embodiments, The controlled-release pharmaceutical bead compositions (*i.e.*, the second pharmaceutical bead composition) of the present invention releases 80% of dimethyl fumarate from the composition within 3-10 hours, preferably within 4-8 hours, more preferably within 4-6 hours in an *in vivo* pharmacokinetic study described herein. In particular, dogs were administered with the pharmaceutical composition of the present invention containing 240 mg of DMF.

In certain embodiments, the pharmaceutical composition of the present invention is in the form of a capsule, wherein the first pharmaceutical bead composition and the second pharmaceutical composition are encapsulated in the capsule. Any type of capsules known in the art can be used in the present invention. In one embodiment, the capsule is a hard

capsule. In another embodiment, the capsule is a soft capsule. In yet another embodiment, the capsule is a gelatin capsule. In another embodiment, the capsule is a hard gelatin capsule. More specifically, the capsule is a size 0 hard gelatin capsule.

The present invention also provides a method of treating a subject having multiple sclerosis (e.g., relapsing-remitting MS, secondary progressive MS, primary progressive MS, progressive relapsing MS) comprising administering to the subject an effective amount of a pharmaceutical composition described herein. In one embodiment, the method of the present invention is for treating relapsing-remitting MS.

As used herein, the term **“treating”** or **“treatment”** refers to obtaining desired pharmacological and/or physiological effect. The effect can be therapeutic, which includes achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome; ameliorating or improving a clinical symptom or indicator associated with the disorder; or delaying, inhibiting or decreasing the likelihood of the progression of the disease, disorder or syndrome.

As used herein, the term **“subject”** and the term **“patient”** can be used interchangeable and they refer to a mammal in need of treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, pigs, horses, sheep, goats and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

The effective amount or therapeutic dosage of the pharmaceutical compositions described herein that is administered to treat a patient depends on a number of factors, which include, but are not limited to, weight and age of the patient, route of administration, the underlying causes of the disease to be treated, and the severity of the disease to be treated. In one embodiment, the effective dosage can range from 1 mg/kg to 50 mg/kg (*e.g.*, from 2.5 mg/kg to 20 mg/kg or from 2.5 mg/kg to 15 mg/kg). In one embodiment, an effective amount of DMF to be administered to a subject, for example orally, can be from 0.1 g to 1 g per day, for example, from 200 mg to 800 mg per day (*e.g.*, from 240 mg to 720 mg per day; or from 480 mg to 720 mg per day; or 480 mg per day; or 720 mg per day).

The daily dose can range, but is not limited to, a total amount of 60 mg to 800 mg, 60 mg to 720 mg, 60 mg to 500 mg, 60 mg to 480 mg, 60 mg to 420 mg, 60 mg to 360 mg, 60 mg to 240 mg, 60 mg to 220 mg, 60 mg to 200 mg, 60mg to 180 mg, 60 mg to 160 mg, 60 mg to 140 mg, 60 mg to 120 mg, 60 mg to 100 mg, 60 mg to 80 mg, 80 mg to 480 mg, 100 mg to 480 mg, 120 mg to 480 mg, 140 mg to 480 mg, 160 mg to 480 mg, 180 mg to 480 mg, 200 mg to 480 mg, 220 mg to 480 mg, 240 mg to 480 mg, 300 mg to 480 mg,

360 mg to 480 mg, 400 mg to 480 mg, 450 mg to 500 mg, 480 mg to 500 mg, 80 to 400 mg, 100 to 300 mg, 120 to 180 mg, or 140 mg to 160 mg.

In one embodiment, the daily dosage is 240 mg. Alternatively, the daily dosage is 480 mg.

The daily dose(s) of DMF may be administered in a single administration or in separate administrations of 2, 3, 4, or 6 equal doses. In one embodiment, the effective daily dose is 480 mg per day and is administered in one dose to a subject in need thereof. In another embodiment, the effective daily dose is 240 mg per day and is administered in one dose to a subject in need thereof.

In one embodiment, the pharmaceutical composition of the present invention is administered at least one hour before or after food is consumed by the subject in need thereof. In case the subject experiences side effects (e.g., flushing or GI discomfort), the subject can consume food shortly (e.g., 30 mins to an hour) before administered the pharmaceutical composition.

In one embodiment, the subject administered the pharmaceutical compositions of the present invention may take one or more non-steroidal anti-inflammatory drugs (e.g., aspirin) before (for example, 10 minutes to an hour, e.g., 30 minutes before) taking the pharmaceutical composition. In one embodiment, the subject administered the pharmaceutical composition takes the one or more non-steroidal anti-inflammatory drugs (e.g., aspirin) to control side effects (e.g., flushing). In another embodiment, the one or more non-steroidal anti-inflammatory drugs is selected from a group consisting of aspirin, ibuprofen, naproxen, ketoprofen, celecoxib, MK-0524, and combinations thereof. The one or more non-steroidal anti-inflammatory drugs can be administered in an amount of 50 mg to 500 mg before taking the dosage form described above. In one embodiment, a subject takes 325 mg aspirin before taking each dosage form described above.

In one embodiment, the subject in need of the treatment is administered a first dose of the pharmaceutical compositions described herein for a first dosing period; and administered a second dose of the pharmaceutical compositions described herein for a second dosing period. In one embodiment, the first dose is lower than the second dose (e.g., the first dose is half of the second dose). In one embodiment, the first dosing period is at least one week (e.g., 1-4 weeks). In one embodiment, the first dose of the pharmaceutical compositions comprises 240 mg of DMF and the pharmaceutical composition is administered to the subject once daily for the first dosing period. In one embodiment, the second dose of the pharmaceutical composition comprises 480 mg of DMF and the pharmaceutical composition is administered

to the subject once daily for the second dosing period. In one embodiment, if the subject, after being administered the dose at the second dosing period, experiences more than expected level of side effects (e.g., flushing or a gastrointestinal disturbance), the subject can use a lower dose (e.g., the dose at the first dosing period) for a period (e.g., 1-4 weeks or more) sufficient to allow the side effects to decrease before returning to the dose at the second dosing period.

In one embodiment, the first dose of the pharmaceutical composition comprises 240 mg of DMF and the pharmaceutical composition is administered to the subject once daily for at least one week, and the second dose of the pharmaceutical composition comprises 480 mg of DMF and the pharmaceutical composition is administered to the subject once daily for at least two weeks.

In one embodiment, the subject is administered a first dose for one week and a second dose for a second dosing period of at least 48 weeks. In another embodiment, the subject is administered a first dose for one week and a second dose for a second dosing period of at least two years. In another embodiment, the subject is administered a first dose for one week and a second dose until the subject does not require treatment.

In certain embodiments, the methods of treating a subject having multiple sclerosis described herein further comprises administering to the subject a second therapeutic agent.

In one embodiment, the second therapeutic agent is a disease modifying agent. In one embodiment, the second therapeutic agent alleviates the side effects of dimethyl fumarate. For example, the second therapeutic agent can be a therapeutic agent that can reduce the flushing (e.g., aspirin) or GI disturbance (e.g., loperamide).

In another embodiment, the second therapeutic agent is a Nrf-2 modulator.

In yet another embodiment, the second therapeutic agent can be, e.g., interferon beta-1a (Avonex<sup>®</sup>, Rebif<sup>®</sup>), glatiramer (Copaxone<sup>®</sup>), modafinil, azathioprine, prednisolone, mycophenolate, mofetil, mitoxantrone, natalizumab (Tysabri<sup>®</sup>), sphingosine-1 phosphate modulator e.g., fingolimod (Gilenya<sup>®</sup>), and other drugs useful for MS treatment such as teriflunomide (Aubagio<sup>®</sup>), piroxicam, and phenidone.

The pharmaceutical DMF compositions of the present invention and the second therapeutic agent may be administered concurrently (as separate compositions or together in a single dosage form) or consecutively over overlapping or non-overlapping intervals. In the sequential administration, the DMF composition and the second therapeutic agent can be administered in any order. In some embodiments, the length of an overlapping interval is more than 2, 4, 6, 12, 24, 48 weeks or longer.

In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

## EXAMPLES

### Example 1. Methods for Preparing Pharmaceutical Bead Compositions of The Present Invention

The following coating processes were conducted using a fluid bed granulator with a Wurster insert. API dimethyl fumarate was first layered onto the surface of sugar spheres by spraying a DMF containing solution (Table 1) onto the sugar spheres in a fluid bed.

**Table 1: DMF solution formulation**

Ingredients	Weight %
DMF	21%
HPMC (HPMC E5)	2%
Ethanol (96% v/v)	62%
DI Water	15%
TOTAL	100%

The API layered spheres were then enteric coated for acid protection.

**Table 2: Enteric coat formulation**

Ingredients	Weight %
Eudragit L100 (Methacrylic acid-methyl methacrylate copolymer)	6.5%
IPA	90.7%
Water	1.5%
Triethyl citrate	1.3%
TOTAL	100%

A sustained release functional coating (Tables 3, 4, 5 and 6) was then applied to the enteric coated spheres.

**Table 3: Coating solution formulation for EC/ HPC 65/ 35**

Ingredients	Weight %
EC (Ethocel 10)	3.9
HPC (Klucel JF)	2.1
Water	11.3

IPA	82.7
TOTAL	100%

**Table 4: Coating solution formulation for EC/ HPC 70/ 30**

<b>Ingredients</b>	<b>Weight %</b>
EC (Ethocel 10)	4.2
HPC (Klucel JF)	1.8
Water	11.3
IPA	82.7
TOTAL	100%

**Table 5: Coating solution formulation for RS/ RL 75/ 25**

<b>Ingredients</b>	<b>Weight %</b>
Eudragit RS	4.5
Eudragit RL	1.5
Water	11.3
IPA	82.7
TOTAL	100%

**Table 6: Coating solution formulation for RS/ RL 80/ 20**

<b>Ingredients</b>	<b>Weight %</b>
Eudragit RS	4.8
Eudragit RL	1.2
Water	11.3
IPA	82.7
TOTAL	100%

Specifically, Formulation D is prepared according to the general procedure described above using DMF solution described in Table 1 and enteric coating solution described in Table 2. Formulation D has no functional coating. Formulations E and F are prepared according to the procedures for Formulation D and is further coated with functional coating solution described in Table 3. The weight percentages of the functional coating in Formulation E is 2.5% of the total weight of the sugar sphere and DMF layer. The weight percentages of the functional coating in Formulation F is 5.0% of the total weight of the sugar sphere and DMF layer. Formulations D, E and F are beads having a diameter of 1-1.2 mm.

Formulation A is prepared according to the general procedure described above using DMF solution described in Table 1, enteric coating solution described in Table 2 and functional coating solution described in Table 3a below.

**Table 3a. Coating solution formulation for EC/ HPC 60/ 40**

<b>Ingredients</b>	<b>Weight %</b>
EC (Ethocel 10)	3.6
HPC (Klucel JF)	2.4
Water	11.3
IPA	82.7
TOTAL	100%

The weight percentage of each ingredients in Formulation A is as follows:

Sugar core – 19% of the total weight of the sugar sphere and the DMF layer;

DMF - 74% of the total weight of the sugar sphere and the DMF layer;

Binder – 7% of the total weight of the sugar sphere and the DMF layer;

Enteric coating - 12% of the total weight of the sugar sphere and the DMF layer; and

Functional coating - 4.5% of the total weight of the sugar sphere and DMF layer.

Formulation B is prepared according to the general procedure described above using DMF solution described in Table 1 and enteric coating solution described in Table 2.

Formulation B has no functional coating. The weight percentage of each ingredients in Formulation B is as follows:

Sugar core – 19% of the total weight of the sugar sphere and the DMF layer;

DMF - 74% of the total weight of the sugar sphere and the DMF layer;

Binder – 7% of the total weight of the sugar sphere and the DMF layer; and

Enteric coating - 12% of the total weight of the sugar sphere and the DMF layer.

**Example 2.** Preparation of Pharmaceutical Composition of the Present Invention (Mixed Beads Formulation)

A mixed beads formulation was prepared by combining and encapsulating the first pharmaceutical bead composition (Formulation B described above) and the second pharmaceutical bead composition (Formulation A described above) in size 0 hard gelatin capsules with a white opaque body and a white opaque cap using an encapsulator with two inputs, with each input for each type of beads. The weight ratio of the first pharmaceutical bead composition (Formulation B) and the second pharmaceutical bead composition (Formulation A) is 3:1.



**Example 3. Dissolution Profiles for Mixed Beads Formulations**

The dissolution profiles for various bead formulations with different weight ratios between the first pharmaceutical bead composition and the second pharmaceutical bead composition were determined according to methods described below, which are standard procedures published by USP-NF using USP apparatus II and IV.

Test 1. The pharmaceutical compositions of the present invention were subjected to an in vitro dissolution test employing 0.1 N hydrochloric acid as dissolution medium during the first 2 hours of the test and then USP Simulated Intestinal Fluid (SIF) without pancreatin as dissolution medium in a USP Apparatus II (paddle apparatus).

Test 2. The pharmaceutical compositions of the present invention were subjected to an in vitro dissolution test employing USP Simulated Gastric Fluid (SGF) without pepsin as dissolution medium during the first 2 hours of the test and then USP Simulated Intestinal Fluid (SIF) without pancreatin as dissolution medium in a USP Apparatus IV (flow-through cell).

Test 3. The pharmaceutical compositions of the present invention were subjected to an in vitro dissolution test employing USP Simulated Intestinal Fluid (SIF) without pancreatin as dissolution medium in a USP Apparatus IV (flow-through cell).

USP SIF solution can be prepared according to procedures described in USP35-NF30. For 1 L scale, the SIF solution can be prepared by dissolving 6.8 g of monobasic potassium phosphate in 250 mL of water followed by mixing. 77 mL of 0.2 N sodium hydroxide and 500 mL of water are added sequentially. The pH of the resulting solution is adjusted with either 0.2 N sodium hydroxide or 0.2 N hydrochloric acid to a pH of  $6.8 \pm 0.1$  followed by dilution with water to 1000 mL. USP SGF solution can be prepared according to procedures described in USP35-NF30. For 1 L scale, the SGF solution can be prepared by dissolving 2.0 g of sodium chloride (NaCl) in 7.0 mL of hydrochloric acid (HCl) and sufficient water to make 1000 mL.

Formulation 1 contains a mixture of bead Formulation B and bead Formulation A, wherein the weight ratio of Formulation B and Formulation A is 3:1. Formulation 2 contains a mixture of bead Formulation B and bead Formulation A, wherein the weight ratio of Formulation B and Formulation A is 1:3. Formulation 3 contains only bead Formulation A. The dissolution profiles for Formulations 1, 2 and 3 are shown in FIG. 1 (using Test 1) and FIG. 2 (using Test 2).

**Example 4. Methods of Preparing Bead Formulations By Extrusion Spheronization**

Alternatively, the beads formulation can be prepared using extrusion spheronization. DMF is first mixed with excipients and solvent into a wet mass. The wet mass is then forced through an extruder to form cylindrical pellets. The diameter of the pellets ranges from 0.6 mm to 2 mm depending on the equipment setting. The extruded pellets will then be spheronized in a spheronizer with a rotating disk. The diameter of the spheres can range from 0.6 to 2mm depending on the initial cylindrical pellet size. Tables 7 and 8 below list exemplary formulations.

**Table 7: Exemplary Formulations for Extrusion Spheronization**

DMF	65%	65%
Microcrystalline cellulose (Avicel PH101)	11%	/
Microcrystalline cellulose (Avicel PH102)	/	15%
Lactose Monohydrate Fast Flo	/	10%
Starch 1500	4%	/
Ac-Di-Sol	10%	10%
PEO	10%	/
PEO 4000	/	/

**Table 8: Exemplary Formulations for Extrusion Spheronization**

DMF	75%	75%
Microcrystalline Cellulose (Avicel PH101)	14%	14%
Starch 1500	4%	4%
Ac-Di-Sol	5%	
Explotab		5%
TEC	2%	2%

The DMF spheres are then coated with the enteric coating and the functional coating described above.

**Example 5. Methods of Preparing Bead Formulations by Fluid Bed Spheronization**

The bead formulations of the present invention can also be prepared utilizing the Glatt's CPS unit to spheronize dimethyl fumarate and excipients (MCC and disintegrant) with solvents (water, ethenol or API) into spheres with size ranging from 500 um to 1.5 mm.

## CLAIMS

We claim:

1. A pharmaceutical composition comprising a first pharmaceutical bead composition and a second pharmaceutical bead composition, wherein the first pharmaceutical bead composition is an enterically coated immediate-release composition and the second pharmaceutical bead composition is an enterically coated controlled-release composition, wherein the first pharmaceutical bead composition and the second pharmaceutical bead composition both comprise dimethyl fumarate, wherein

(1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder; and

an enteric coating surrounding the first layer; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder;

an enteric coating surrounding the first layer; and

an extended release functional coating surrounding the enteric coating.

2. The pharmaceutical composition of claim 1, wherein the inert core in the first pharmaceutical bead composition comprises one or more inert substance selected from the group consisting of starch, dextrose, sucrose, lactose, maltose, and microcrystalline cellulose; and wherein the inert core in the second pharmaceutical bead composition comprises one or more inert substance selected from the group consisting of starch, dextrose, sucrose, lactose, maltose, and microcrystalline cellulose.

3. The pharmaceutical composition of claim 1 or 2, wherein the weight percentage of the inert core in the first pharmaceutical bead composition is 15%-30%, 16%-26%, 16%-22% or 20%-24% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and wherein the weight percentage of the inert core in the second pharmaceutical bead composition is 15%-30%, 16%-26%, 16%-22% or 20%-24% of

the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

4. The pharmaceutical composition of any one of claims 1-3, wherein the inert core in the first pharmaceutical bead composition is a sphere having a diameter of 200-850  $\mu\text{m}$ , 250-350  $\mu\text{m}$ , 500-600  $\mu\text{m}$  or 700-850  $\mu\text{m}$ ; and wherein the inert core in the second pharmaceutical bead composition is a sphere having a diameter of 200-850  $\mu\text{m}$ , 250-350  $\mu\text{m}$ , 500-600  $\mu\text{m}$  or 700-850  $\mu\text{m}$ .

5. The pharmaceutical composition of any one of claims 1-4, wherein the weight percentage of dimethyl fumarate in the first pharmaceutical bead composition is 60%-80%, 72%-76%, 74%, 68%-72% or 70% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and wherein the weight percentage of dimethyl fumarate in the second pharmaceutical bead composition is 60%-80%, 72%-76%, 74%, 68%-72% or 70% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

6. The pharmaceutical composition of any one of claims 1-5, wherein the binder in the first pharmaceutical bead composition and the binder in the second pharmaceutical bead composition are independently selected from the group consisting of acacia, agar, alginic acid, amino methacrylate copolymer, ammonio methacrylate copolymer, ammonio methacrylate copolymer dispersion, calcium carbonate, calcium lactate, carbomer copolymer, carbomer homopolymer, carbomer interpolymer, carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, hydrogenated coconut oil, copovidone, corn syrup, corn syrup solids, dextrans, dextrin, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, ethylene glycol and vinyl alcohol graft copolymer, gelatin, liquid glucose, glyceryl behenate, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, hypromellose, hypromellose acetate succinate, inulin, alpha-lactalbumin, monohydrate lactose, maltodextrin, maltose, methacrylic acid copolymer, methacrylic acid copolymer dispersion, methacrylic acid and ethyl acrylate copolymer dispersion, methylcellulose, hydrogenated palm oil, polycarbophil, hydrogenated polydextrose, polyethylene oxide, polyvinyl acetate, povidone, pullulan, sodium alginate, pregelatinized starch, pregelatinized modified starch, corn starch, hydroxypropyl corn starch, pregelatinized hydroxypropyl corn starch, pea starch, hydroxypropyl pea starch, pregelatinized hydroxypropyl pea starch, potato starch,

hydroxypropyl potato starch, pregelatinized hydroxypropyl potato starch, tapioca starch, wheat starch, hydrogenated starch hydrolysate, sucrose, sunflower oil, syrup, trehalose, hydrogenated vegetable oil, vitamin E polyethylene glycol succinate, zein, hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), methyl cellulose, ethyl cellulose, sodium carboxy methyl cellulose, polyethylene glycol (PEG), polyvinyl alcohols, polymethacrylate, starch paste, sodium starch, tragacanth, gelatin, alginate, sodium alginate, alginic acid, cellulose, candelilla wax, caruba wax, copolyvidone, and lactose hydrous.

7. The pharmaceutical composition of any one of claims 1-6, wherein the weight percentage of the binder in the first pharmaceutical bead composition is 1%-20%, 5%-10% or 7% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and wherein the weight percentage of the binder in the second pharmaceutical bead composition is 1%-20%, 5%-10% or 7% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

8. The pharmaceutical composition of any one of claims 1-7, wherein the enteric coating in the first pharmaceutical bead composition comprises an excipient selected from the group consisting of a copolymer of methacrylic acid and methyl methacrylate, a copolymer of methacrylic acid and ethyl acrylate, hypromellose phthalate (HPMCP), cellulose acetate phthalate; and wherein the enteric coating in the second pharmaceutical bead composition comprises an excipient selected from the group consisting of a copolymer of methacrylic acid and methyl methacrylate, a copolymer of methacrylic acid and ethyl acrylate, hypromellose phthalate (HPMCP), cellulose acetate phthalate.

9. The pharmaceutical composition of claim 8, wherein the enteric coating in the first pharmaceutical bead composition and the enteric coating in the second pharmaceutical bead composition comprise a plasticizer, wherein the plasticizer is selected from the group consisting of acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, castor oil, chlorobutanol, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, mannitol, polyethylene glycol, polyethylene glycol monomethyl ether, propylene glycol, pullulan, sorbitol, sorbitol sorbitan solution, triacetin, tributyl citrate, triethyl citrate and vitamin E.

10. The pharmaceutical composition of any one of claims 1-9, wherein the weight percentage of the enteric coating in the first pharmaceutical bead composition is 5-15%, 10-

15% or 12% of the total weight of the inert core and the first layer in the first pharmaceutical bead composition; and wherein the weight percentage of the enteric coating in the second pharmaceutical bead composition is 5-15%, 10-15% or 12% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

11. The pharmaceutical composition of any one of claims 1-10, wherein the functional coating in the second pharmaceutical bead composition comprises one or more excipients selected from the group consisting of polyvinylpyrrolidone (PVP), polyethylene oxide (PEO), glyceryl monostearate, hydroxyl propyl methyl cellulose (HPMC), SoluPlus, polyvinyl alcohol (PVA), polyvinyl alcohol (PVA), hydroxypropylmethylcellulose, acetate succinate (HPMCAS), ethylene vinyl acetate (EVA), methacrylates (Eudragit™), cellulose acetate butyrate (CAB), cellulose acetate phthalate (CAP), poly(ethylene glycol), poly(vinyl acetate) (PVAc), polylactide (PLA), polyglycolide (PGA), copolymers of PLA/PGA and polycaprolactone (PCL), polyvinylpyrrolidone-co-vinyl acetate (Kollidon VA-64), polyurethanes, poly(lactic acid), poly(glycolic acid), poly(anhydride-imides), poly(anhydride-esters), poly(iminocarbonates), poly(phosphazenes), poly(phosphoesters), ethylcellulose (EC), hydroxypropyl cellulose (HPC), alginic acid, carbomer copolymer, carbomer homopolymer, carbomer interpolymers, carboxymethylcellulose sodium, carrageenan, cellaburate, ethylcellulose aqueous dispersion, ethylcellulose dispersion Type B, glyceryl monooleate, guar gum, hydroxypropyl betadex, polyvinyl acetate dispersion, shellac, sodium alginate, pregelatinized starch, pregelatinized modified starch and xanthan gum

12. The pharmaceutical composition of claim 11, wherein the functional coating comprises a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC); and wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 70:30 and 50:50, between 65:35 and 55:45, or the weight ratio of ethylcellulose to hydroxypropyl cellulose is 60:40 or 65:35.

13. The pharmaceutical composition of any one of claims 1-12, wherein the weight percentage of the functional coating in the second pharmaceutical bead composition is 4-12%, 4.0-5.0%, 4.5%, 4.5-5.5%, 5.0-6.0% or 11.5-12.5% of the total weight of the inert core and the first layer in the second pharmaceutical bead composition.

14. The pharmaceutical composition of claim 1, wherein:
- A. (1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer;

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4%-12% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 16-22% of the total weight of the inert core and the first layer;

B. (1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer;

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 68%-72% of the total weight of the inert core and the first layer and the weight percentage of the binder is 5-10% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4%-12% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 20-24% of the total weight of the inert core and the first layer; or

C. (1) the first pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer and the weight percentage of the binder is 6-8% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

(2) the second pharmaceutical bead composition comprises:

an inert core;

a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate and a binder and wherein the weight percentage of dimethyl fumarate is 72%-76% of the total weight of the inert core and the first layer and the weight percentage of the binder is 6-8% of the total weight of the inert core and the first layer;

an enteric coating surrounding the first layer, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer; and

a functional coating surrounding the enteric coating, wherein the weight percentage of the functional coating is 4.0%-5.0% of the total weight of the inert core and the first layer.

15. The pharmaceutical composition of claim 14, wherein the inert core in the first and the second pharmaceutical bead compositions comprises sucrose or starch; the binder in the first and the second pharmaceutical bead compositions is HPMC; the enteric coating the first and the second pharmaceutical bead compositions comprises a copolymer of methacrylic acid and methyl methacrylate and the ratio of methacrylic acid to methyl



methacrylate in the copolymer is 1:1; and the functional coating in the second pharmaceutical bead composition comprises of a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC) and the weight ratio of ethylcellulose (EC) to hydroxypropyl cellulose (HPC) is between 70:30 and 50:50, between 65:35 and 55:45, or the weight ratio is 65:35, or 60:40.

16. The pharmaceutical composition of claim 15, wherein the weight ratio of the first pharmaceutical bead composition to the second pharmaceutical bead composition is between 10:1 and 1:1, between 5:1 and 1.5:1, or between 4:1 and 2:1, or the weight ratio of the first pharmaceutical bead composition to the second pharmaceutical bead composition is 3:1.

17. The pharmaceutical composition of any one of claims 1-16, wherein the first pharmaceutical bead composition and the second pharmaceutical bead composition are in a capsule.

18. A method of treating a subject having multiple sclerosis comprising administering to the subject an effective amount of a pharmaceutical composition of any one of claims 1-17, optionally, wherein the multiple sclerosis is a relapsing form of multiple sclerosis, or relapsing-remitting multiple sclerosis.

19. The method of claim 18, wherein 240 mg or 480 mg of the active substance is administered to the subject per day.

20. The method of claim 18 or 19, wherein the subject is administered a second therapeutic agent, optionally the second therapeutic agent is a Nrf-2 modulator.

21. Use of a pharmaceutical composition of any one of claims 1-17 for the manufacture of a medicament for treating a subject having multiple sclerosis, optionally, wherein the multiple sclerosis is a relapsing form of multiple sclerosis, or relapsing-remitting multiple sclerosis.

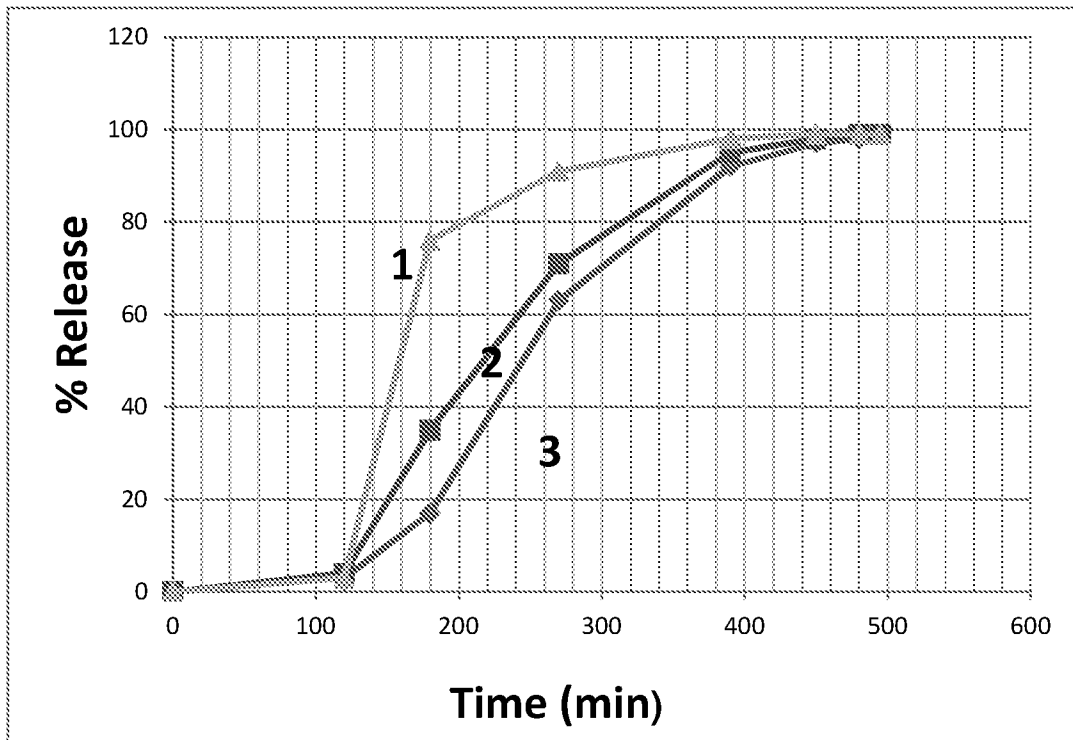


FIG.1 Dissolution of Formulations 1, 2, 3 using USP dissolution Apparatus II

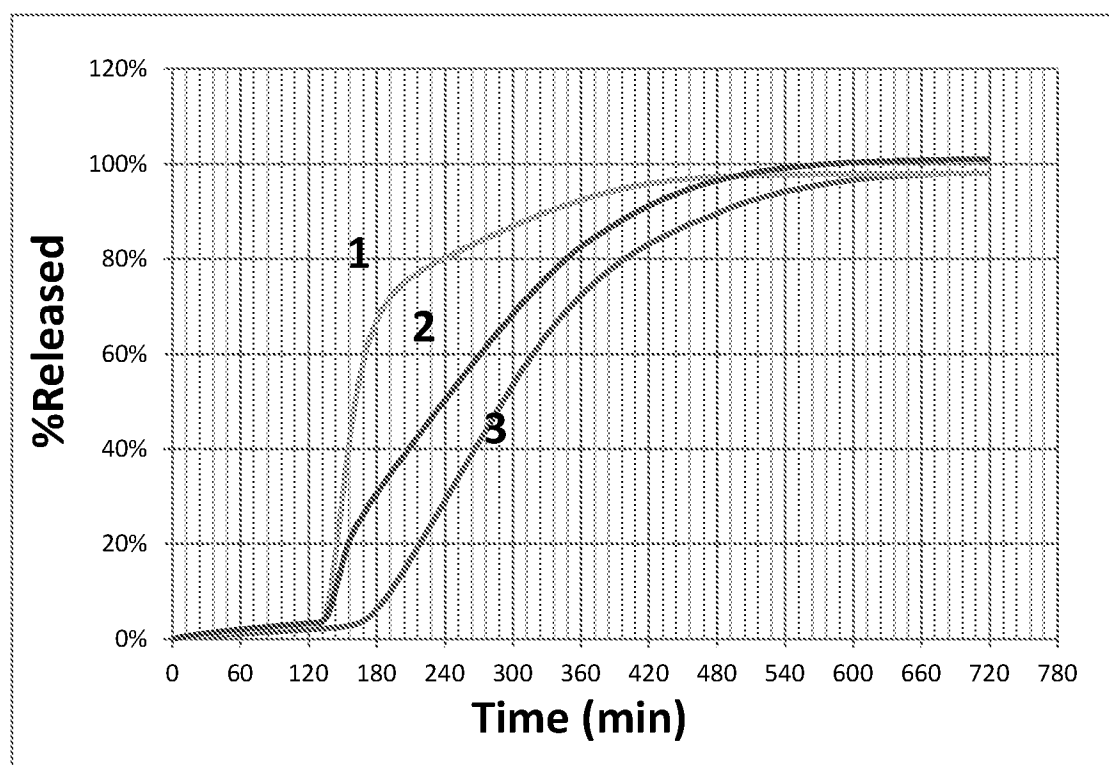


FIG.2 Dissolution of Formulations 1, 2, 3 using USP dissolution Apparatus IV