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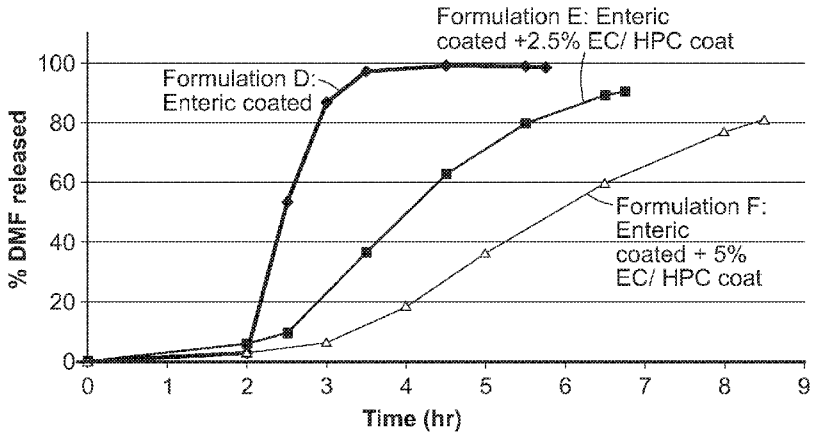

FIG. 1

(57) Abstract: The present invention provides novel pharmaceutical compositions of dimethyl fumarate. The pharmaceutical compositions of the present invention are in the form of a bead and comprise (i) an inert core; (ii) a first layer surrounding the inert core, wherein the first layer comprises dimethyl fumarate; and (iii) an enteric coating surrounding the first layer. Also provided are pharmaceutical compositions in the form of a bead comprising a core and an enteric coating surrounding the core, wherein the core comprises 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

REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing date, under 35 U.S.C. § 119(e), of U.S. Provisional Application No. 62/081,889, filed on November 19, 2014, the entire content of which, including all drawings, formulae, specification, and claims, is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Tecfidera® (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® 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. The pharmaceutical compositions of the present invention have AUC and/or C_{max} that are comparable with the currently approved twice-a-day formulation. 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 pharmacokinetic profiles show that the pharmaceutical compositions of the present invention have maximized absorption of dimethyl fumarate *in vivo*.

One aspect of the present invention is directed to a pharmaceutical composition in the form of a bead comprising:

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 one embodiment, the pharmaceutical composition can further comprises a functional coating surrounding the enteric coating.

In another aspect, the present invention is directed to a pharmaceutical composition in the form of a bead comprising:

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 another aspect, the present invention is directed to a pharmaceutical composition in the form of a bead comprising:

a core comprising dimethyl fumarate; and

an enteric coating surrounding the core.

In one embodiment, the pharmaceutical composition can further comprises a functional coating surrounding the enteric coating.

In yet another aspect, the present invention is directed to a pharmaceutical composition in the form of a bead comprising:

a core comprising dimethyl fumarate;

a functional coating surrounding the core; and

an enteric coating surrounding the functional coating.

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 formulations D, E and F of the present invention using dissolution test 1.

FIG 2. shows *in vitro* dissolution profiles for formulations D, E and F of the present invention using dissolution test 2.

FIG 3. shows *in vitro* dissolution profiles for formulations D, E and F of the present invention using dissolution test 3.

FIG. 4 shows *in vitro* dissolution profiles for bead formulations with various amounts of functional coatings (EC/HPC 65:35) using dissolution test 3.

FIG. 5 shows *in vitro* dissolution profiles for bead formulations with various amounts of functional coatings (EC/HPC 70:30) using dissolution test 3.

FIG. 6 shows *in vitro* dissolution profiles for bead formulations with various amounts of functional coatings (Eudragit RS/RL 75:25) using dissolution test 3.

FIG. 7 shows *in vitro* dissolution profiles for bead formulations with various amounts of functional coatings (Eudragit RS/RL 80:20) using dissolution test 3.

FIG. 8 shows *in vivo* pharmacokinetic profile of formulations D, E and F in a dog PK study.

FIG. 9 shows exemplary scheme for preparing bead formulations of the present invention using fluid bed coating method.

FIG. 10 shows exemplary scheme for preparing bead formulations of the present invention using extrusion spheronization method.

FIG. 11 shows SEM images of extended release DMF layered bead formulation of the present invention.

FIG. 12 shows *in vitro* dissolution profiles for bead formulations with various amounts of functional coatings (EC/HPC 60:40) using dissolution test 2.

FIG. 13 shows *in vitro* dissolution profiles for bead formulations with various amounts of functional coatings (EC/HPC 60:40) using dissolution test 1.

DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment, the present invention is directed to a pharmaceutical composition in the form of a bead comprising:

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 a second embodiment, the pharmaceutical composition described in the first embodiment can further comprises a functional coating surrounding the enteric coating.

In a third embodiment, the present invention is directed to a pharmaceutical composition in the form of a bead comprising:

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 first functional coating.

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 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 pharmaceutical compositions described in the first, second or third embodiment, 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.

In certain embodiments, for the pharmaceutical compositions described in the first, second or third embodiment, the inert core is a sphere having a diameter of 200-850 μm.

More specifically, the sphere has a diameter of 250-350 μm, 300-400 μm, 500-600 μm or 700-850 μm. Even more specifically, the sphere has a diameter of 350 μm, 550 μm or 750 μm.

In certain embodiment, for the pharmaceutical compositions described in the first, second or third embodiment, 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 pharmaceutical compositions described in the first, second or third embodiment, 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 pharmaceutical compositions described in the first, second or third embodiment, the weight percentage of dimethyl fumarate is 40%-80% , 50%-75%, 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 pharmaceutical compositions described in the first, second or third embodiment, 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 interpolymer, carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, hydrogenated coconut oil, copovidone, corn syrup, corn syrup solids, dextrates, 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 pharmaceutical compositions described in the first, second or third embodiment, 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 beads 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 in the first or second embodiment, 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 pharmaceutical compositions described in the third embodiment, 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 pharmaceutical compositions described in the first, second or third embodiment, 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® L 100 (poly(methacylic acid-co-methyl methacrylate) 1:1).

In certain embodiments, for the pharmaceutical compositions described in the first, second or third embodiment, 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 pharmaceutical compositions described in the first, second or third embodiment, the enteric coating of the present invention comprises EUDRAGIT® L 100 and triethyl citrate. More specifically, the weight ratio of the triethyl citrate to EUDRAGIT® L 100 is from 1:1 to 1:20. Even more specifically, the weight ratio of the triethyl citrate to EUDRAGIT® L 100 is 1:5.

In certain embodiments, for the pharmaceutical compositions described in the first, second or third embodiment, 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 one embodiment, for the pharmaceutical compositions described in the first, second or third embodiment, the weight percentage for the inert core is 10-60% to the total weight of

the inert core and the first layer; the weight percentage for dimethyl fumarate is 40-80% of the total weight of the inert core and the first layer; the weight percentage for the binder is 1-25% of the total weight of the inert core and the first layer; and the weight percentage for the enteric coating is 1-20% of the total weight of the inert core and the first layer. More specifically, the inert core comprises sucrose or starch and the binder is HPMC. Even more specifically, the inert core comprises sucrose or starch; the binder is HPMC and the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate. In a further more specific embodiment, the inert core comprises sucrose or starch; the binder is HPMC and the enteric coating comprises EUDRAGIT® L 100 (poly(methacylic acid-co-methyl methacrylate) 1:1) and triethyl citrate. Even more specifically, the weight ratio of triethyl citrate to Eudragit L100 is 1:5.

In another embodiment, for the pharmaceutical compositions described in the first, second or third embodiment, the weight percentage for the inert core is 20-40% to the total weight of the inert core and the first layer; the weight percentage for dimethyl fumarate is 50-75% of the total weight of the inert core and the first layer; the weight percentage for the binder is 1-20% of the total weight of the inert core and the first layer; and the weight percentage for the enteric coating is 5-15% of the total weight of the inert core and the first layer. More specifically, the inert core comprises sucrose or starch and the binder is HPMC. Even more specifically, the inert core comprises sucrose or starch; the binder is HPMC and the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate. In a further more specific embodiment, the inert core comprises sucrose or starch; the binder is HPMC and the enteric coating comprises EUDRAGIT® L 100 (poly(methacylic acid-co-methyl methacrylate) 1:1) and triethyl citrate. Even more specifically, the weight ratio of triethyl citrate to Eudragit L100 is 1:5.

In another embodiment, for the pharmaceutical compositions described in the first, second or third embodiment, the weight percentage for the inert core is 20-30% to the total weight of the inert core and the first layer; the weight percentage for dimethyl fumarate is 65-75% of the total weight of the inert core and the first layer; the weight percentage for the binder is 5-15% of the total weight of the inert core and the first layer; and the weight percentage for the enteric coating is 10-15% of the total weight of the inert core and the first layer. More specifically, the inert core comprises sucrose or starch and the binder is HPMC. Even more specifically, the inert core comprises sucrose or starch; the binder is HPMC and the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate. In a further more specific embodiment, the inert core comprises sucrose or starch; the binder is

HPMC and the enteric coating comprises EUDRAGIT® L 100 (poly(methacylic acid-co-methyl methacrylate) 1:1) and triethyl citrate. Even more specifically, the weight ratio of triethyl citrate to Eudragit L100 is 1:5.

In another embodiment, for the pharmaceutical compositions described in the first, second or third embodiment, the weight percentage for the inert core is 20-24% to the total weight of the inert core and the first layer; the weight percentage for dimethyl fumarate is 68-72% of the total weight of the inert core and the first layer; the weight percentage for the binder is 5-10% of the total weight of the inert core and the first layer; and the weight percentage for the enteric coating is 11-13% of the total weight of the inert core and the first layer. More specifically, the inert core comprises sucrose or starch and the binder is HPMC. Even more specifically, the inert core comprises sucrose or starch; the binder is HPMC and the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate. In a further more specific embodiment, the inert core comprises sucrose or starch; the binder is HPMC and the enteric coating comprises EUDRAGIT® L 100 (poly(methacylic acid-co-methyl methacrylate) 1:1) and triethyl citrate. Even more specifically, the weight ratio of triethyl citrate to Eudragit L100 is 1:5.

In certain embodiments, for the pharmaceutical compositions described in the second embodiment, 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 compositions described in the third embodiment, 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). As used herein, "extended release" means that the active substance dimethyl fumarate is released from the pharmaceutical 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® (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®.

In certain embodiments, for the pharmaceutical compositions described in the second or third embodiment, 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), polyrethanes, 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 pharmaceutical compositions described in the second or third embodiment, the functional coating of the present invention 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 or between 70:30 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 pharmaceutical compositions described in the second or third embodiment, 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-trimetylammonioethyl 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 pharmaceutical compositions described in the second or third embodiment, 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 or 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 or 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 or 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 or 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 or the functional coating is 12% of the total weight of the inert core and the first layer.

In a 1st specific embodiment, the pharmaceutical bead composition of the present invention 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 and the weight percentage of the binder is 1-25% 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 1-20% 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 1-30% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 10-60% of the total weight of the inert core and the first layer.

In a 2nd specific embodiment, the pharmaceutical bead composition of the present invention 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 and the weight percentage of the binder is 1-20% 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 5-15% 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 1-20% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 20-40% of the total weight of the inert core and the first layer.

In a 3rd specific embodiment, the pharmaceutical bead composition of the present invention 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 and the weight percentage of the binder is 5-15% 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 10-15% 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 1-10% or 10-15% of the total weight of the inert core and the first layer,

wherein the weight percentage of the inert core is 20-30% of the total weight of the inert core and the first layer.

In a 4th specific embodiment, the pharmaceutical bead composition of the present invention 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 2.0%-3.0% 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 a 5th specific embodiment, the pharmaceutical bead composition of the present invention 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 a 6th specific embodiment, the pharmaceutical bead composition of the present invention 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 a 7th specific embodiment, the pharmaceutical bead composition of the present invention 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 a 8th specific embodiment, the pharmaceutical bead composition of the present invention 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 2.0%-3.0% 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 a 9th specific embodiment, the pharmaceutical bead composition of the present invention 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 4.5%-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 a 10th specific embodiment, the pharmaceutical bead composition of the present invention 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 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 a 11th specific embodiment, the pharmaceutical bead composition of the present invention 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 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 a 12th specific embodiment, the pharmaceutical bead composition of the present invention 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 a 13th specific embodiment, the pharmaceutical bead composition of the present invention 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 and the weight percentage of the binder is 1-25% 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 1-30% 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 1-20% of the total weight of the inert core and the first layer;

wherein the weight percentage of the inert core is 10-60% of the total weight of the inert core and the first layer.

In a 14th specific embodiment, the pharmaceutical bead composition of the present invention 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 and the weight percentage of the binder is 1-20% 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 1-20% 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 5-15% of the total weight of the inert core and the first layer;

wherein the weight percentage of the inert core is 20-40% of the total weight of the inert core and the first layer.

In a 15th specific embodiment, the pharmaceutical bead composition of the present invention 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 and the weight percentage of the binder is 5-15% 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 1-10%, 4-12%, or 10-15% 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 10-15% of the total weight of the inert core and the first layer; and

wherein the weight percentage of the inert core is 20-30% of the total weight of the inert core and the first layer.

In a 16th specific embodiment, the pharmaceutical bead composition of the present invention 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 2.0%-3.0% 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 20-24% of the total weight of the inert core and the first layer.

In a 17th specific embodiment, the pharmaceutical bead composition of the present invention 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 a 18th specific embodiment, the pharmaceutical bead composition of the present invention 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; and

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,

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 a 19th specific embodiment, the pharmaceutical bead composition of the present invention 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 a 20th specific embodiment, the pharmaceutical bead composition of the present invention 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 2.0%-3.0% 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 20-24% of the total weight of the inert core and the first layer.

In a 21st specific embodiment, the pharmaceutical bead composition of the present invention 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 4.5%-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 a 22nd specific embodiment, the pharmaceutical bead composition of the present invention 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; and

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,

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 a 23rd specific embodiment, the pharmaceutical bead composition of the present invention 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 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 a 24th specific embodiment, the pharmaceutical bead composition of the present invention 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 4.5%-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.

More specifically, for the pharmaceutical bead composition in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, 21st, 22nd, 23rd or 24th 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™ 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 another more specific embodiment, for the pharmaceutical bead composition in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th, 17th, 18th, 19th, 20th, 21st, 22nd, 23rd or 24th 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 a fourth embodiment, the present invention is directed to a pharmaceutical composition in the form of a bead comprising:

a core comprising dimethyl fumarate; and

an enteric coating surrounding the core.

In a fifth embodiment, the pharmaceutical composition described in the fourth embodiment can further comprise a functional coating surrounding the enteric coating.

In a sixth embodiment, the present invention is directed to a pharmaceutical composition in the form of a bead comprising:

a core comprising dimethyl fumarate;

a functional coating surrounding the core; and

an enteric coating surrounding the functional core.

In certain embodiments, for the pharmaceutical compositions of the fourth, fifth or sixth embodiment, the DMF core is a sphere having a diameter of 0.5 – 2.0 mm. More specifically, the sphere has a diameter of 0.5-1.5 mm. In another specific embodiment, the sphere has a diameter of 0.6 – 2.0 mm.

In certain embodiments, for the pharmaceutical compositions of the fourth, fifth or sixth embodiment, the weight percentage of dimethyl fumarate is 40%-80% of the total weight of the core. The weight of the core is the total weight of each ingredient in the core, excluding exterior coating, such as an enteric coating. More specifically, the weight percentage of dimethyl fumarate is 60%-80%, 60-70% or 70-80% of the total weight of the core. Even more specifically, the weight percentage of dimethyl fumarate is 65% of the total weight of the core. Alternatively, the weight percentage of dimethyl fumarate is 75% of the total weight of the core.

In certain embodiments, for the pharmaceutical compositions of the fourth, fifth or sixth embodiment, the core 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 interpolymer, carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, hydrogenated coconut oil, copovidone, corn syrup, corn syrup solids, dextrates, 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 one embodiment, the binder is microcrystalline cellulose or starch.

The binder can be present in an amount of 1-50% by weight of the core. More specifically, the binder can be present in an amount of 15-35%.

In certain embodiments, for the pharmaceutical compositions of the fourth or fifth embodiment, the enteric coating is layered on the dimethyl fumarate core. More specifically, the enteric coating is layered on the core by spraying a solution containing enteric coating materials onto the dimethyl fumarate core in a fluid bed.

In certain embodiments, for the pharmaceutical composition of the sixth embodiment, 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 pharmaceutical compositions of the fourth, fifth or sixth embodiment, 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® L 100 (poly(methacylic acid-co-methyl methacrylate) 1:1).

In certain embodiments, for the pharmaceutical compositions of the fourth, fifth or sixth embodiment, 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 pharmaceutical compositions of the fourth, fifth or sixth embodiment, the enteric coating of the present invention comprises EUDRAGIT® L 100 and triethyl citrate. More specifically, the weight ratio of the triethyl citrate to EUDRAGIT® L 100 is from 1:1 to 1:20. Even more specifically, the weight ratio of the triethyl citrate to EUDRAGIT® L 100 is 1:5.

In certain embodiments, for the pharmaceutical compositions of the fourth, fifth or sixth embodiment, the weight percentage for the enteric coating is 1-20% or 5-15% of the total weight of the core. 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 core. In another more specific embodiment, the weight percentage for the enteric coating is 11-13% of the total weight of the core. Even more specifically, the weight percentage of the enteric coating is 12% of the total weight of the core.

In certain embodiments, for the pharmaceutical compositions of the fifth or sixth embodiment, 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), polyrethanes, 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 pharmaceutical compositions of the fifth or sixth embodiment, 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, or between 70:30 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 alternative, 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 pharmaceutical compositions of the fifth or sixth embodiment, the functional coating 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-trimetylammonioethyl 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 pharmaceutical compositions of the fifth or sixth embodiment, 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 4.5-5.5% 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 4.0-5.0% of the total weight of the inert core and the first layer. In another more specific embodiment, the weight percentage or 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 or 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 or 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 or 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 or the functional coating is 12% of the total weight of the inert core and the first layer.

In a 25th specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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 2.0%-3.0% of the total weight of the core,

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

In a 26th specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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 the core.

In a 27th specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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 the core.

In a 28th specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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%-12.50% of the total weight of the core,

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

In a 29th specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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 the core.

In a 30th specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising dimethyl fumarate;

a functional coating surrounding the core, wherein the weight percentage of the functional coating is 2.0%-3.0% 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;

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

In a 31st specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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; 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 core;

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

In a 32nd specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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; 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 core;

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

In a 33rd specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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; 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 core;

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

In a 34th specific embodiment, the pharmaceutical bead composition of the present invention comprises:

a core comprising 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; 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 core;

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

More specifically, for the pharmaceutical compositions in the 25th, 26th, 27th, 28th, 29th, 30th , 31st, 32nd, 33rd or 34th specific embodiment, 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™ 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 another more specific embodiment, for the pharmaceutical compositions in the 25th, 26th, 27th, 28th, 29th, 30th , 31st, 32nd, 33rd or 34th specific embodiment, 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 pharmaceutical compositions described in the second embodiment, the fifth embodiment or in the 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th, 12th, 25th, 26th, 27th, 28th or 29th specific embodiment can further comprise a second enteric coating surrounding the functional coating. Any enteric coating described above can be used as the second enteric coating.

In certain embodiment, the second enteric coating is layered on the functional coating. More specifically, the second 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 embodiment, 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. More specifically, the second 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® L 100 (poly(methacylic acid-co-methyl methacrylate) 1:1).

In certain embodiments, the second enteric coating 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, the second enteric coating of the present invention comprises EUDRAGIT® L 100 and triethyl citrate. More specifically, the weight ratio of the triethyl citrate to EUDRAGIT® L 100 is from 1:1 to 1:20. Even more specifically, the weight ratio of the triethyl citrate to EUDRAGIT® L 100 is 1:5.

In certain embodiments, the weight percentage for the second 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.

The pharmaceutical bead compositions 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 tablets of the present invention is determined by subjecting the tablets 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 tablets 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 Simularted 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 tablets of the present invention to an in vitro dissolution test employing USP Simularted Intestinal Fluid (SIF) without pancreatin in a USP Apparatus IV (flow-through cell) (Test 3). USP SIF ans SGF solutions can be prepared according to 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 pharmaceutical composition of the present invention releases 80% of dimethyl fumarate from the composition within 3-10 hours, perferably within 4-8 hours, more preferably within 4-6 hours in an *in vivo* pharmacokinetic study described herein. In particular, dogs were administerd with the pharmaceutical composition of the present invention containing 240 mg of DMF.

In certain embodiments, the amount of dimethyl fumarate in the pharmaceutical compositions described herein is from 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.

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 furthter comprises adminstering to the suject a second therapeutic agent.

In one embodiment, the second therapeutic agents is a disease modifying agent. In one embodiment, the second therapeutic agents alleviate 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 therapetic agent is a Nrf-2 modulator.

In yet another embodiment, the second therapeutic agents can be, e.g., interferon beta-1a (Avonex®, Rebif®), glatiramer (Copaxone®), modafinil, azathioprine, predisolone, mycophenolate, mofetil, mitoxantrone, natalizumab (Tysabri®), sphinogosie-1 phosphate modulator e.g., fingolimod (Gilenya®), and other drugs useful for MS treatment such as teriflunornide (Aubagio®), 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 Compositions of The Present Invention

The following coating processes are 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 (Methacylic 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

Ingredients	Weight %
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

Ingredients	Weight %
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

Ingredients	Weight %
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

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

The weight percentage of DMF in Formulation A is 74% of the total weight of the sugar sphere and the DMF layer. The weight percentage of the enteric coating in Formulation A is 12% of the total weight of the sugar sphere and the DMF layer. The weight percentage of the functional coating in Formulation A is 4.5% of the total weight of the sugar sphere and DMF layer.

Example 2. *In vitro* Dissolution Profiles

The *in vitro* dissolution profiles of the present pharmaceutical 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 Simularted 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 Simularted Intestinal Fluid (SIF) without pancreatin as dissolution medium in a USP Apparatus IV (flow-through cell).

USP SIF solution can be prepared according to 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 ± 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.

The dissolution profiles for various bead formulations with and without functional coatings were determined. The dissolution profiles for Formulations D, E and F are shown in FIG. 1 (using Test 1), FIG. 2 (using Test 2) and FIG. 3 (using Test 3). The dissolution profiles for Formulation A are shown in FIG. 12 (using Test 2) and FIG. 13 (using Test 1).

The dissolution profiles for additional bead formulations having EC/HPC functional coatings are shown in FIG. 4 (using Test 2) and FIG. 5 (using Test 3). All the formulations having functional coating show extended release *in vitro* dissolution profiles; while the formulation without any functional coating release DMF significantly faster than those with functional coatings.

Bead formulations with various amount of Eudragit RS/RL as functional coatings also exhibit extended release dissolution profiles, as shown in FIG. 6 (using Test 2) and FIG. 7 (using Test 2).

Example 3. *In vivo* Pharmacokinetic Profiles

Formulations D, E and F with different release profile were selected for a dog PK study.

Male dogs were divided into six test groups and 1 control group with 4 dogs in each group. Dogs in the control group were administered with currently approved Tecfidera® formulation. Dogs in the test groups were administered with Formulations D, E or F or other DMF formulations. Dogs were fasted overnight until 1 hour post dose. 240 mg DMF in size 0 capsules were administered to the dogs orally, followed by approximately 10 mL of water.

A second flush with approximately 10 mL of water may be administered if necessary to ensure capsule delivery.

Approximately 1 mL of blood was collected from each animal at 10 blood collection time points: predose and at 0.25, 0.5, 1, 2, 4, 8, 12, 16, and 24 hours postdose. Blood was collected via a jugular vein into tubes containing sodium heparin anticoagulant. Prior to blood collection, 40 µL of 250 mg/mL solution of aqueous sodium fluoride was added to each collection tube. The NaF solution may be prepared on the day prior to the study and stored refrigerated between uses and equilibrated to ambient temperature and vortexed prior to each use. The cephalic vein may be used as an alternative blood collection site.

At each protocol specified time point, 1 mL of blood was collected into a chilled sodium
heparin/ sodium fluoride tube and mixed immediately by gently inverting the tube 5 to 7 times to ensure uniform mixing. Avoid vigorous shaking to prevent hemolysis of the blood sample. Place the blood sample into wet ice or cryorack. Centrifuge samples within 30 minutes of collection at 4 ºC for 15 minutes at 1500 x g. Plasma was aliquoted equally into 1.8 or 2 mL cryovials and be maintained on dry ice prior to storage at approximately -70 ºC.

Plasma was then analyzed. MMF in the plasma was quantified by LC-MS/MS with calibration range of 10 ng/ml – 5000 ng/ml using ^{13}C-MMF as internal standard. Plasma can be diluted with 1:10 dilution if necessary.

As shown in FIG. 8 and Table 7 below, all three formulations have very similar AUC. The plasma profile of formulation F extends to later hours than formulation E and formulation D. This is consistent with the fact that the release time for formulation F> formulation E> formulation D.

Table 7: AUC, C_{max}, t_{max} and $t_{1/2}$ from the dog study

formulation	**AUC_∞/D** [ng*h*kg/ml/mg]		**C_{max}/D** [kg*ng/ml/mg]		**t_{max}** [hr]		**$t_{1/2}$** [hr]	
	mean	stdev	mean	stdev	mean	stdev	mean	stdev
Formulation **D**	644	78	186	63	1.5	0.7	1.2	0.1
Formulation **E**	722	211	121	33	2.5	1.0	2.2	1.2
Formulation **F**	784		85		4.0		3.0	

Example 4. Methods of Preparing Beads Formulation 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 8 and 9 below list exemplary formulations.

Table 8: 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 9: 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 excipents (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 in the form of a bead comprising:

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.

2. The pharmaceutical composition of claim 1, wherein the inert core 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 2, wherein the inert core comprises lactose.

4. The pharmaceutical composition of claim 2, wherein the inert core comprises sucrose.

5. The pharmaceutical composition of claim 2, wherein the inert core comprises starch.

6. The pharmaceutical composition of any one of claim 1-5, wherein the weight percentage of the inert core is 10%-60% of the total weight of the inert core and the first layer.

7. The pharmaceutical composition of claim 6, wherein the weight percentage of the inert core is 20%-40% of the total weight of the inert core and the first layer.

8. The pharmaceutical composition of claim 6, wherein the weight percentage of the inert core is 20%-30% of the total weight of the inert core and the first layer.

9. The pharmaceutical composition of claim 6, wherein the weight percentage of the inert core is 20%-24% of the total weight of the inert core and the first layer.

10. The pharmaceutical composition of any one of claims 1-9, wherein the inert core is a sphere having a diameter of 200-850 μm.

11. The pharmaceutical composition of claim 10, wherein the sphere has a diameter of 250-350 μm, 500-600 μm or 700-850 μm.

12. The pharmaceutical composition of claim 10, wherein the sphere has a diameter of 350 μm, 550 μm, or 750 μm.

13. The pharmaceutical composition of any one of claims 1-12, wherein the weight percentage of dimethyl fumarate is 40%-80% of the total weight of the inert core and the first layer.

14. The pharmaceutical composition of claim 13, wherein the weight percentage of dimethyl fumarate is 50%-75% of the total weight of the inert core and the first layer.

15. The pharmaceutical composition of claim 13, wherein the weight percentage of dimethyl fumarate is 65%-75% of the total weight of the inert core and the first layer.

16. The pharmaceutical composition of claim 13, wherein the weight percentage of dimethyl fumarate is 68%-72%.

17. The pharmaceutical composition of claim 13, wherein the weight percentage of dimethyl fumarate is 72-76%,

18. The pharmaceutical composition of any one of claims 1-17, wherein the first layer further comprises a binder.

19. The pharmaceutical composition of claim 18, wherein the binder 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, dextrates, 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.

20. The pharmaceutical composition of claim 19, wherein the binder is hydroxypropyl methylcellulose (HPMC).

21. The pharmaceutical composition of any one of claims 18-20, wherein the weight percentage of the binder is 1%-25% of the total weight of the inert core and the first layer.

22. The pharmaceutical composition of claim 21, wherein the weight percentage of the binder is 1%-20% of the total weight of the inert core and the first layer.

23. The pharmaceutical composition of claim 21, wherein the weight percentage of the binder is 5%-15% of the total weight of the inert core and the first layer.

24. The pharmaceutical composition of claim 21, wherein the weight percentage of the binder is 5%-10% of the total weight of the inert core and the first layer.

25. The pharmaceutical composition of claim 21, wherein the weight percentage of the binder is 7% of the total weight of the inert core and the first layer.

26. The pharmaceutical composition of any one of claims 1-25, wherein 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.

27. The pharmaceutical composition of claim 26, wherein the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate.

28. The pharmaceutical composition of claim 27, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 0.8:1 to 1.2:1.

29. The pharmaceutical composition of claim 28, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 1:1 (Eudragit L100).

30. The pharmaceutical composition of any one of claims 1-29, wherein the enteric coating comprises a plasticizer.

31. The pharmaceutical composition of claim 30, 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.

32. The pharmaceutical composition of claim 31, wherein the plasticizer is triethyl citrate.

33. The pharmaceutical composition of claim 32, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is from 1: 1 to 1:20.

34. The pharmaceutical composition of claim 33, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is 1:5.

35. The pharmaceutical composition of any one of claims 1-34, wherein the weight percentage of the enteric coating is 1-20% of the total weight of the inert core and the first layer.

36. The pharmaceutical composition of claim 35, wherein the weight percentage of the enteric coating is 5-15% of the total weight of the inert core and the first layer.

37. The pharmaceutical composition of claim 35, wherein the weight percentage of the enteric coating is 10-15% of the total weight of the inert core and the first layer.

38. The pharmaceutical composition of claim 35, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer.

39. The pharmaceutical composition of claim 35, wherein the weight percentage of the enteric coating is 12% of the total weight of the inert core and the first layer.

40. The pharmaceutical composition of any one of claims 1-39, further comprising a functional coating surrounding the enteric coating.

41. The pharmaceutical composition of claim 40, wherein the functional coating comprises a mixture of one or more water-insoluble polymer and one or more water-soluble polymer.

42. The pharmaceutical composition of claim 40, wherein 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), polyrethanes, 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.

43. The pharmaeutical composition of claim 40, wherein the functional coating comprises a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC).

44. The pharmaceutical composition of claim 43, wherein 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% tolune 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).

45. The pharmaceutical composition of claim 43 or 44, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 90:10 and 10:90.

46. The pharmaceutical composition of claim 45, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 20:80.

47. The pharmaceutical composition of claim 45, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 50:50.

48. The pharmaceutical composition of claim 45, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 75:25 and 60:40.

49. The pharmaceutical composition of claim 45, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 70:30.

50. The pharmaceutical composition of claim 45, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 65:35.

51. The pharmaceutical composition of claim 45, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 60:40.

52. The pharmaceutical composition of claim 40, wherein the functional coating 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-trimetylammonioethyl methacrylate chloride) 1:2:0.2).

53. The pharmaceutical composition of claim 52, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 95:5 to 5:95.

54. The pharmaceutical composition of claim 52, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 90:10 to 50:50.

55. The pharmaceutical composition of claim 52, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 90:10 to 60:40.

56. The pharmaceutical composition of claim 52, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 85:15 to 70:30.

57. The pharmaceutical composition of claim 52, wherein the weight ratio of Eudragit® RS to Eudragit® RL is 75:25.

58. The pharmaceutical composition of claim 52, wherein the weight ratio of Eudragit® RS to Eudragit® RL is 80:20.

59. The pharamceutical composition of any one of claims 40-58, wherein the weight percentage of the functional coating is 1-30% of the total weight of the inert core and the first layer.

60. The pharamceutical composition of claim 59, wherein the weight percentage of the functional coating is 1-20% of the total weight of the inert core and the first layer.

61. The pharmaceutical composition of claim 59, wherein the weight percentage of the functional coating is 4-12% of the total weight of the inert core and the first layer.

62. The pharamceutical composition of claim 59, wherein the weight percentage of the functional coating is 1-10% of the total weight of the inert core and the first layer.

63. The pharamceutical composition of claim 59, wherein the weight percentage of the functional coating is 10-15% of the total weight of the inert core and the first layer.

64. The pharamceutical composition of claim 59, 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.

65. The pharamceutical composition of claim 59, wherein the weight percentage of the functional coating is 2.5% of the total weight of the inert core and the first layer.

66. The pharamceutical composition of claim 59, 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.

67. The pharamceutical composition of claim 59, wherein the weight percentage of the functional coating is 5.0% of the total weight of the inert core and the first layer.

68. The pharamceutical composition of claim 59, 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.

69. The pharmaceutical composition of claim 59, wherein the weight percentage of the functional coating is 4.5% of the total weight of the inert core and the first layer.

70. The pharamceutical composition of claim 59, 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.

71. The pharamceutical composition of claim 59, wherein the weight percentage of the functional coating is 5.5% of the total weight of the inert core and the first layer.

72. The pharamceutical composition of claim 59, 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.

73. The pharamceutical composition of claim 59, wherein the weight percentage of the functional coating is 12% of the total weight of the inert core and the first layer.

74. A pharmaceutical composition in the form of a bead comprising:

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 2.0%-3.0% 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.

75. The pharmaceutical composition of claim 74, wherein 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.

76. The pharmaceutical composition of claim 75, wherein 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 65:35.

77. The pharmaceutical composition of claim 74, wherein 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.

78. The pharmaceutical composition of claim 77, wherein 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.

79. A pharmaceutical composition in the form of a bead comprising:

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.

80. The pharmaceutical composition of claim 79, wherein 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 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.

81. The pharmaceutical composition of claim 80, wherein 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 65:35.

82. The pharmaceutical composition of claim 79, wherein 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 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.

83. The pharmaceutical composition of claim 82, wherein 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.

84. A pharmaceutical composition in the form of a bead comprising:

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.

85. The pharmaceutical composition of claim 84, wherein 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 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.

86. The pharmaceutical composition of claim 85, wherein 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 65:35.

87. The pharmaceutical composition of claim 84, wherein 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 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.

88. The pharmaceutical composition of claim 87, wherein 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.

89. A pharmaceutical composition in the form of a bead comprising:

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.

90. The pharmaceutical composition of claim 89, wherein 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 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.

91. The pharmaceutical composition of claim 90, wherein 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 65:35.

92. The pharmaceutical composition of claim 89, wherein 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 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.

93. The pharmaceutical composition of claim 92, wherein 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 65:35.

94. A pharmaceutical composition in the form of a bead comprising:

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.

95. The pharmaceutical composition of claim 94, wherein 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 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.

96. The pharmaceutical composition of claim 95, wherein 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 65:35.

97. The pharmaceutical composition of claim 96, wherein 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 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.

98. The pharmaceutical composition of claim 97, wherein 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.

99. A pharmaceutical composition in the form of a bead comprising:

a core comprising dimethyl fumarate; and

an enteric coating surrounding the core.

100. The pharmaceutical composition of claim 99, wherein the weight percentage of dimethyl fumarate is 40%-80% of the total weight of the core.

101. The pharmaceutical composition of claim 100, wherein the weight percentage of dimethyl fumarate is 60%-80%, 60-70% or 70-80% of the total weight of the core.

102. The pharmaceutical composition of claim 101, wherein the weight percentage of dimethyl fumarate is 65% of the total weight of the core.

103. The pharmaceutical composition of claim 101, wherein the weight percentage of dimethyl fumarate is 75% of the total weight of the core.

104. The pharmaceutical composition of any one of claims 99-103, wherein the core further comprises a binder.

105. The pharmaceutical composition of claim 104, wherein the binder 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, dextrates, 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.

106. The pharmaceutical composition of claim 105, wherein the binder is microcrystalline cellulose or starch.

107. The pharmaceutical composition of claim 105 or 106, wherein the weight percentage of the binder is 1-50% of the weight of the core.

108. The pharmaceutical composition of claim 105 or 106, wherein the weight percentage of the binder is 15-35% of the weight of the core.

109. The pharmaceutical composition of any one of claims 99-108, wherein 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) and cellulose acetate phthalate.

110. The pharmaceutical composition of claim 109, wherein the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate.

111. The pharmaceutical composition of claim 110, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 0.8:1 to 1.2:1.

112. The pharmaceutical composition of claim 110, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 1:1 (Eudragit L100).

113. The pharmaceutical composition of any one of claims 99-112, wherein the enteric coating comprises a plasticizer.

114. The pharmaceutical composition of claim 113, wherein the plasticizer is triethyl citrate.

115. The pharmaceutical composition of claim 114, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is from 1:1 to 1:20.

116. The pharmaceutical composition of claim 114, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is 1:5.

117. The pharmaceutical composition of any one of claims 99-116, wherein the weight percentage of the enteric coating is 1-20% of the total weight of the core.

118. The pharmaceutical composition of claim 117, wherein the weight percentage of the enteric coating is 5-15% of the total weight of the core.

119. The pharmaceutical composition of claim 117, wherein the weight percentage of the enteric coating is 10-15% of the total weight of the core.

120. The pharmaceutical composition of claim 117, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the core.

121. The pharmaceutical composition of claim 117, wherein the weight percentage of the enteric coating is 12% of the total weight of the core.

122. The pharmaceutical composition of any one of claims 99-121, further comprising a functional coating surrounding the enteric coating.

123. The pharmaceutical composition of claim 122, wherein the functional coating comprises a mixture of one or more water-insoluble polymer and one or more water-soluble polymer.

124. The pharmaceutical composition of claim 122, wherein the functional coating comprises one or more excipient 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), polyrethanes, poly(lactic acid), poly(glycolic acid), poly(anhydride–imides), poly(anhydride–esters), poly(iminocarbonates), poly(phosphazenes), poly(phosphoesters), ethylcellulose (EC) and hydroxypropyl cellulose (HPC).

125. The pharmaeutical composition of claim 122, wherein the functional coating comprises a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC).

126. The pharmaceutical composition of claim 125, wherein 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).

127. The pharmaceutical composition of claim 125 or 126, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 90:10 and 10:90.

128. The pharmaceutical composition of claim 127, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 20:80.

129. The pharmaceutical composition of claim 127, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 50:50.

130. The pharmaceutical composition of claim 127, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 75:25 and 60:40.

131. The pharmaceutical composition of claim 127, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 70:30.

132. The pharmaceutical composition of claim 127, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 65:35.

133. The pharmaceutical composition of claim 127, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 60:40.

134. The pharmaceutical composition of claim 122, wherein the functional coating 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-trimetylammonioethyl methacrylate chloride) 1:2:0.2).

135. The pharmaceutical composition of claim 134, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 95:5 to 5:95.

136. The pharmaceutical composition of claim 134, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 90:10 to 50:50.

137. The pharmaceutical composition of claim 134, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 90:10 to 60:40.

138. The pharmaceutical composition of claim 134, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 85:15 to 70:30.

139. The pharmaceutical composition of claim 134, wherein the weight ratio of Eudragit® RS to Eudragit® RL is 75:25.

140. The pharmaceutical composition of claim 134, wherein the weight ratio of Eudragit® RS to Eudragit® RL is 80:20.

141. The pharamceutical composition of any one of claims 134-140, wherein the weight percentage of the functional coating is 1-30% of the total weight of the core.

142. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 1-20% of the total weight of the core.

143. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 4-12% of the total weight of the core

144. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 1-10% of the total weight of the core.

145. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 10-15% of the total weight of the core.

146. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 2.0-3.0% of the total weight of the core.

147. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 2.5% of the total weight of the core.

148. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 4.5-5.5% of the total weight of the core.

149. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 5.0% of the total weight of the core.

150. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 5.0-6.0% of the total weight of the core.

151. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 5.5% of the total weight of the core.

152. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 11.5-12.5% of the total weight of the core.

153. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 12% of the total weight of the core.

154. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 4.0-5.0% of the total weight of the core.

155. The pharamceutical composition of claim 141, wherein the weight percentage of the functional coating is 4.5% of the total weight of the core.

156. A pharmaceutical composition in the form of a bead comprising:

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 2.0%-3.0% of the total weight of the core,

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

157. The pharmaceutical composition of claim 156, wherein the enteric coating 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.

158. The pharmaceutical composition of claim 157, wherein 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 65:35.

159. The pharmaceutical composition of claim 156, wherein the enteric coating 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.

160. The pharmaceutical composition of claim 159, wherein 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.

161. A pharmaceutical composition in the form of a bead comprising:

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 the core.

162. The pharmaceutical composition of claim 161, wherein the enteric coating 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.

163. The pharmaceutical composition of claim 162, wherein 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 65:35.

164. The pharmaceutical composition of claim 161, wherein the enteric coating 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.

165. The pharmaceutical composition of claim 164, wherein 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.

166. A pharmaceutical composition in the form of a bead comprising:

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 the core.

167. The pharmaceutical composition of claim 166, wherein the enteric coating 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.

168. The pharmaceutical composition of claim 167, wherein 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 65:35.

169. The pharmaceutical composition of claim 166, wherein the enteric coating 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.

170. The pharmaceutical composition of claim 169, wherein 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.

171. A pharmaceutical composition in the form of a bead comprising:

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 the core.

172. The pharmaceutical composition of claim 171, wherein the enteric coating 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.

173. The pharmaceutical composition of claim 172, wherein 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 65:35.

174. The pharmaceutical composition of claim 171, wherein the enteric coating 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.

175. The pharmaceutical composition of claim 174, wherein 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.

176. The pharmaceutical composition of any one of claims 99-175, wherein the diameter of the core is in the range of 0.5 mm to 2.0 mm.

177. The pharmaceutical composition of claim 176, wherein the diameter is in the range of 0.6 mm to 2.0 mm.

178. The pharmaceutical composition of claim 176, wherein the diameter is in the range of 0.5 mm to 1.5 mm.

179. The pharmaceutical composition of any one of claims 40-98 and 122-178, further comprising a second enteric coating surrounding the functional coating.

180. The pharmaceutical composition of claim 179, wherein 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.

181. The pharmaceutical composition of claim 179, wherein the second enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate.

182. The pharmaceutical composition of claim 181, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 0.8:1 to 1.2:1.

183. The pharmaceutical composition of claim 182, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 1:1 (Eudragit L100).

184. The pharmaceutical composition of any one of claims 179-183, wherein the second enteric coating comprises a plasticizer.

185. The pharmaceutical composition of claim 184, 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.

186. The pharmaceutical composition of claim 185, wherein the plasticizer is triethyl citrate.

187. The pharmaceutical composition of claim 186, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is from 1: 1 to 1:20.

188. The pharmaceutical composition of claim 187, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is 1:5.

189. The pharmaceutical composition of any one of claims 179-188, wherein the weight percentage of the second enteric coating is 1-20% of the total weight of the inert core and the first layer.

190. The pharmaceutical composition of claim 189, wherein the weight percentage of the second enteric coating is 5-15% of the total weight of the inert core and the first layer.

191. The pharmaceutical composition of claim 189, wherein the weight percentage of the second enteric coating is 10-15% of the total weight of the inert core and the first layer.

192. The pharmaceutical composition of claim 189, wherein the weight percentage of the second enteric coating is 11-13% of the total weight of the inert core and the first layer.

193. The pharmaceutical composition of claim 189, wherein the weight percentage of the second enteric coating is 12% of the total weight of the inert core and the first layer.

194. A pharmaceutical composition in the form of a bead comprising:

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.

195. The pharmaceutical composition of claim 194, wherein the inert core comprises one or more inert substance selected from the group consisting of starch, dextrose, sucrose, lactose, maltose, and microcrystalline cellulose.

196. The pharmaceutical composition of claim 195, wherein the inert core comprises lactose.

197. The pharmaceutical composition of claim 195, wherein the inert core comprises sucrose.

198. The pharmaceutical composition of claim 195, wherein the inert core comprises starch.

199. The pharmaceutical composition of any one of claim 194-198, wherein the weight percentage of the inert core is 10%-60% of the total weight of the inert core and the first layer.

200. The pharmaceutical composition of claim 199, wherein the weight percentage of the inert core is 20%-40% of the total weight of the inert core and the first layer.

201. The pharmaceutical composition of claim 199, wherein the weight percentage of the inert core is 20%-30% of the total weight of the inert core and the first layer.

202. The pharmaceutical composition of claim 199, wherein the weight percentage of the inert core is 20%-24% of the total weight of the inert core and the first layer .

203. The pharmaceutical composition of any one of claims 194-202, wherein the inert core is a sphere having a diameter of 200-850 μm.

204. The pharmaceutical composition of claim 203, wherein the sphere has a diameter of 250-350 μm, 500-600 μm or 700-850 μm.

205. The pharmaceutical composition of claim 203, wherein the sphere has a diameter of 350 μm, 550 μm, or 750 μm.

206. The pharmaceutical composition of any one of claims 194-205, wherein the weight percentage of dimethyl fumarate is 40%-80% of the total weight of the inert core and the first layer.

207. The pharmaceutical composition of claim 206, wherein the weight percentage of dimethyl fumarate is 50%-75% of the total weight of the inert core and the first layer.

208. The pharmaceutical composition of claim 206, wherein the weight percentage of dimethyl fumarate is 65%-75% of the total weight of the inert core and the first layer.

209. The pharmaceutical composition of claim 206, wherein the weight percentage of dimethyl fumarate is 68%-72%.

210. The pharmaceutical composition of claim 206, wherein the weight percentage of dimethyl fumarate is 72%-76%.

211. The pharmaceutical composition of any one of claims 194-210, wherein the first layer further comprises a binder.

212. The pharmaceutical composition of claim 211, wherein the binder 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, dextrates, 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.

213. The pharmaceutical composition of claim 211, wherein the binder is hydroxypropyl methylcellulose (HPMC).

214. The pharmaceutical composition of any one of claims 211-213, wherein the weight percentage of the binder is 1%-25% of the total weight of the inert core and the first layer.

215. The pharmaceutical composition of claim 214, wherein the weight percentage of the binder is 1%-20% of the total weight of the inert core and the first layer.

216. The pharmaceutical composition of claim 214, wherein the weight percentage of the binder is 5%-15% of the total weight of the inert core and the first layer.

217. The pharmaceutical composition of claim 214, wherein the weight percentage of the binder is 5%-10% of the total weight of the inert core and the first layer.

218. The pharmaceutical composition of claim 214, wherein the weight percentage of the binder is 7% of the total weight of the inert core and the first layer.

219. The pharmaceutical composition of any one of claims 194-218, wherein 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.

220. The pharmaceutical composition of claim 219, wherein the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate.

221. The pharmaceutical composition of claim 220, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 0.8:1 to 1.2:1.

222. The pharmaceutical composition of claim 221, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 1:1 (Eudragit L100).

223. The pharmaceutical composition of any one of claims 194-222, wherein the enteric coating comprises a plasticizer.

224. The pharmaceutical composition of claim 223, 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.

225. The pharmaceutical composition of claim 224, wherein the plasticizer is triethyl citrate.

226. The pharmaceutical composition of claim 225, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is from 1: 1 to 1:20.

227. The pharmaceutical composition of claim 226, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is 1:5.

228. The pharmaceutical composition of any one of claims 194-227, wherein the weight percentage of the enteric coating is 1-20% of the total weight of the inert core and the first layer.

229. The pharmaceutical composition of claim 228, wherein the weight percentage of the enteric coating is 5-15% of the total weight of the inert core and the first layer.

230. The pharmaceutical composition of claim 229, wherein the weight percentage of the enteric coating is 10-15% of the total weight of the inert core and the first layer.

231. The pharmaceutical composition of claim 229, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the inert core and the first layer.

232. The pharmaceutical composition of claim 231, wherein the weight percentage of the enteric coating is 12% of the total weight of the inert core and the first layer.

233. The pharmaceutical composition of any one of claims 194-232, wherein the functional coating comprises a mixture of one or more water-insoluble polymer and one or more water-soluble polymer.

234. The pharmaceutical composition of any one of claims 194-232, wherein 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), polyrethanes, 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.

235. The pharmaeutical composition of any one of claims 194-232, wherein the functional coating comprises a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC).

236. The pharmaceutical composition of claim 235, wherein 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).

237. The pharmaceutical composition of claim 235 or 236, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 90:10 and 10:90.

238. The pharmaceutical composition of claim 237, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 20:80.

239. The pharmaceutical composition of claim 237, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 50:50

240. The pharmaceutical composition of claim 239, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 75:25 and 60:40.

241. The pharmaceutical composition of claim 239, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 70:30.

242. The pharmaceutical composition of claim 239, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 65:35.

243. The pharmaceutical composition of claim 239, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 60:40.

244. The pharmaceutical composition of any one of claims 194-232, wherein the functional coating 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-trimetylammonioethyl methacrylate chloride) 1:2:0.2).

245. The pharmaceutical composition of claim 244, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 95:5 to 5:95.

246. The pharmaceutical composition of claim 244, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 90:10 to 50:50.

247. The pharmaceutical composition of claim 244, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 90:10 to 60:40.

248. The pharmaceutical composition of claim 244, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 85:15 to 70:30.

249. The pharmaceutical composition of claim 244, wherein the weight ratio of Eudragit® RS to Eudragit® RL is 75:25.

250. The pharmaceutical composition of claim 244, wherein the weight ratio of Eudragit® RS to Eudragit® RL is 80:20.

251. The pharamceutical composition of any one of claims 194-250, wherein the weight percentage of the functional coating is 1-30% of the total weight of the inert core and the first layer.

252. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 1-20% of the total weight of the inert core and the first layer.

253. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 4-12% of the total weight of the inert core and the first layer

254. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 1-10% of the total weight of the inert core and the first layer.

255. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 10-15% of the total weight of the inert core and the first layer.

256. The pharamceutical composition of claim 251, 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.

257. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 2.5% of the total weight of the inert core and the first layer.

258. The pharamceutical composition of claim 251, 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.

259. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 5.0% of the total weight of the inert core and the first layer.

260. The pharamceutical composition of claim 251, 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

261. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 4.5% of the total weight of the inert core and the first layer.

262. The pharamceutical composition of claim 251, 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.

263. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 5.5% of the total weight of the inert core and the first layer.

264. The pharamceutical composition of claim 251, 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.

265. The pharamceutical composition of claim 251, wherein the weight percentage of the functional coating is 12% of the total weight of the inert core and the first layer.

266. A pharmaceutical composition in the form of a bead comprising:

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 2.0%-3.0% 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 20-24% of the total weight of the inert core and the first layer.

267. The pharmaceutical composition of claim 266, wherein 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.

268. The pharmaceutical composition of claim 267, wherein 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 65:35.

269. The pharmaceutical composition of claim 266, wherein 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.

270. The pharmaceutical composition of claim 269, wherein 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.

271. A pharmaceutical composition in the form of a bead comprising:

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.

272. The pharmaceutical composition of claim 271, wherein 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 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.

273. The pharmaceutical composition of claim 272, wherein 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 65:35.

274. A pharmaceutical composition in the form of a bead comprising:

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.

275. The pharmaceutical composition of claim 274, wherein 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 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.

276. The pharmaceutical composition of claim 275, wherein 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 65:35.

277. The pharmaceutical composition of claim 274, wherein 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 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.

278. The pharmaceutical composition of claim 277, wherein 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.

279. A pharmaceutical composition in the form of a bead comprising:

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.

280. The pharmaceutical composition of claim 279, wherein 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 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.

281. The pharmaceutical composition of claim 280, wherein 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 65:35.

282. The pharmaceutical composition of claim 279, wherein 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 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.

283. The pharmaceutical composition of claim 282, wherein 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.

284. A pharmaceutical composition in the form of a bead comprising:

a core comprising dimethyl fumarate;

a functional coating surrounding the core; and

an enteric coating surrounding the functional coating.

285. The pharmaceutical composition of claim 284, wherein the weight percentage of dimethyl fumarate is 40%-80% of the total weight of the core.

286. The pharmaceutical composition of claim 285, wherein the weight percentage of dimethyl fumarate is 60%-80%, 60-70% or 70-80% of the total weight of the core.

287. The pharmaceutical composition of claim 285, wherein the weight percentage of dimethyl fumarate is 65% of the total weight of the core.

288. The pharmaceutical composition of claim 285, wherein the weight percentage of dimethyl fumarate is 75% of the total weight of the core.

289. The pharmaceutical composition of any one of claims 284-288, wherein the core further comprises a binder.

290. The pharmaceutical composition of claim 289, wherein the binder 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, dextrates, 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.

291. The pharmaceutical composition of claim 290, wherein the binder is microcrystalline cellulose or starch.

292. The pharmaceutical composition of any one of claims 289-291, wherein the weight percentage of the binder is 1-50% of the weight of the core.

293. The pharmaceutical composition of claim 292, wherein the weight percentage of the binder is 15-35% of the weight of the core.

294. The pharmaceutical composition of any one of claims 284-293, wherein 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) and cellulose acetate phthalate.

295. The pharmaceutical composition of claim 294, wherein the enteric coating comprises a copolymer of methacrylic acid and methyl methacrylate.

296. The pharmaceutical composition of claim 295, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 0.8:1 to 1.2:1.

297. The pharmaceutical composition of claim 296, wherein the ratio of the methacrylic acid to the methyl methacrylate in the copolymer is 1:1 (Eudragit L100).

298. The pharmaceutical composition of any one of claims 284-297, wherein the enteric coating comprises a plasticizer.

299. The pharmaceutical composition of claim 298, wherein the plasticizer is triethyl citrate.

300. The pharmaceutical composition of claim 299, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is from 1:1 to 1:20.

301. The pharmaceutical composition of claim 299, wherein weight ratio of the triethyl citrate to the copolymer of methacrylic acid and methyl methacrylate is 1:5.

302. The pharmaceutical composition of any one of claims 284-301, wherein the weight percentage of the enteric coating is 1-20% of the total weight of the core.

303. The pharmaceutical composition of claim 302, wherein the weight percentage of the enteric coating is 5-15% of the total weight of the core.

304. The pharmaceutical composition of claim 302, wherein the weight percentage of the enteric coating is 10-15% of the total weight of the core.

305. The pharmaceutical composition of claim 302, wherein the weight percentage of the enteric coating is 11-13% of the total weight of the core.

306. The pharmaceutical composition of claim 302, wherein the weight percentage of the enteric coating is 12% of the total weight of the core.

307. The pharmaceutical composition of any one of claims 284-306, wherein the functional coating comprises a mixture of one or more water-insoluble polymer and one or more water-soluble polymer.

308. The pharmaceutical composition of any one of claims 284-306, wherein the functional coating comprises one or more excipient 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), polyrethanes, poly(lactic acid), poly(glycolic acid), poly(anhydride–imides), poly(anhydride–esters), poly(iminocarbonates), poly(phosphazenes), poly(phosphoesters), ethylcellulose (EC) and hydroxypropyl cellulose (HPC).

309. The pharmaeutical composition of any one of claims 284-306, wherein the functional coating comprises a mixture of ethylcellulose (EC) and hydroxypropyl cellulose (HPC).

310. The pharmaceutical composition of claim 309, wherein 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% tolunee 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).

311. The pharmaceutical composition of claim 309 or 310, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 90:10 and 10:90.

312. The pharmaceutical composition of claim 311, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 20:80.

313. The pharmaceutical composition of claim 311, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 80:20 and 50:50.

314. The pharmaceutical composition of claim 311, wherien the weight ratio of ethylcellulose to hydroxypropyl cellulose is between 75:25 and 60:40.

315. The pharmaceutical composition of claim 311, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 70:30.

316. The pharmaceutical composition of claim 311, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 65:35.

317. The pharmaceutical composition of claim 311, wherein the weight ratio of ethylcellulose to hydroxypropyl cellulose is 60:40.

318. The pharmaceutical composition of any one of claims 284-306, wherein the functional coating 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-trimetylammonioethyl methacrylate chloride) 1:2:0.2).

319. The pharmaceutical composition of claim 318, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 95:5 to 5:95.

320. The pharmaceutical composition of claim 318, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 90:10 to 50:50.

321. The pharmaceutical composition of claim 318, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 90:10 to 60:40.

322. The pharmaceutical composition of claim 318, wherein the weight ratio of Eudragit® RS to Eudragit® RL is between 85:15 to 70:30.

323. The pharmaceutical composition of claim 318, wherein the weight ratio of Eudragit® RS to Eudragit® RL is 75:25.

324. The pharmaceutical composition of claim 318, wherein the weight ratio of Eudragit® RS to Eudragit® RL is 80:20.

325. The pharamceutical composition of any one of claims 284-324, wherein the weight percentage of the functional coating is 1-30% of the total weight of the core.

326. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 1-20% of the total weight of the core.

327. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 4-12% of the total weight of the core.

328. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 1-10% of the total weight of the core.

329. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 10-15% of the total weight of the core.

330. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 2.0-3.0% of the total weight of the core.

331. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 2.5% of the total weight of the core.

332. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 4.5-5.5% of the total weight of the core.

333. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 5.0% of the total weight of the core.

334. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 5.0-6.0% of the total weight of the core.

335. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 5.5% of the total weight of the core.

336. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 11.5-12.5% of the total weight of the core.

337. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 12% of the total weight of the core.

338. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 4.0-5.0% of the total weight of the core.

339. The pharamceutical composition of claim 325, wherein the weight percentage of the functional coating is 4.5% of the total weight of the core

340. A pharmaceutical composition in the form of a bead comprising:

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 2.0%-3.0% of the total weight of the core; 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 core;

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

341. The pharmaceutical composition of claim 340, wherein the enteric coating 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.

342. The pharmaceutical composition of claim 341, wherein 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 65:35.

343. The pharmaceutical composition of claim 340, wherein the enteric coating 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.

344. The pharmaceutical composition of claim 343, wherein 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.

345. A pharmaceutical composition in the form of a bead comprising:

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; 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 core;

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

346. The pharmaceutical composition of claim 345, wherein the enteric coating 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.

347. The pharmaceutical composition of claim 346, wherein 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 65:35.

348. The pharmaceutical composition of claim 345, wherein the enteric coating 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.

349. The pharmaceutical composition of claim 348, wherein 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.

350. A pharmaceutical composition in the form of a bead comprising:

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; 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 core;

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

351. The pharmaceutical composition of claim 350, wherein the enteric coating 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.

352. The pharmaceutical composition of claim 351, wherein 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 65:35.

353. The pharmaceutical composition of claim 350, wherein the enteric coating 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.

354. The pharmaceutical composition of claim 353, wherein 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.

355. A pharmaceutical composition in the form of a bead comprising:

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; 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 core;

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

356. The pharmaceutical composition of claim 355, wherein the enteric coating 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.

357. The pharmaceutical composition of claim 356, wherein 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 65:35.

358. The pharmaceutical composition of claim 355, wherein the enteric coating 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.

359. The pharmaceutical composition of claim 358, wherein 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.

360. The pharmaceutical composition of any one of claims 284-359, wherein the diameter of the core is in the range of 0.5 mm to 2.0 mm.

361. The pharmaceutical composition of claim 360, wherein the diameter is in the range of 0.6 mm to 2.0 mm.

362. The pharmaceutical composition of claim 361, wherein the diameter is in the range of 0.5 mm to 1.5 mm.

363. The pharmaceutical composition of any one of claims 1-362, wherein when 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 without pancreatin as dissolution medium in a USP Apparatus 2, the composition has the following dissolution profile:

within the first 2 hours of the test, less than 10% by weight of dimethyl fumarate in the bead is released;

within the first 4 hours of the test, 10-70% by weight of dimethyl fumarate in the bead is released; and

with the first 7 hour of the test, 50-100% by weight of dimethyl fumarate in the bead is released.

364. The pharmaceutical composition of any one of claims 1-362, wherein when 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 without pancreatin as dissolution medium in a USP Apparatus 2, the composition has the following dissolution profile:

within the first 2 hours of the test, less than 10% by weight of dimethyl fumarate in the bead is released; and

within the first 4 hours of the test, 90-100% by weight of dimethyl fumarate in the bead is released.

365. The pharmaceutical composition of any one of claims 1-362, wherein when subjected to an in vitro dissolution test employing USP Simulated Gastric Fluid without pepsin as dissolution medium during the first 2 hours of the test and then USP Simulated Intestinal Fluid without pancreatin as dissolution medium in a USP Apparatus 4, the composition has the following dissolution profile:

within the first 2 hours of the test, less than 10% by weight of dimethyl fumarate in the bead is released;

within the first 4 hours of the test, 10-70% by weight of dimethyl fumarate in the bead is released; and

with the first 7 hour of the test, 50-100% by weight of dimethyl fumarate in the bead is released.

366. The pharmaceutical composition of any one of claims 1-362, wherein when 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 without pancreatin as dissolution medium in a USP Apparatus 2, the composition has the following dissolution profile:

within the first 2 hours of the test, less than 10% by weight of dimethyl fumarate in the bead is released; and

within the first 4 hours of the test, 70-90% by weight of dimethyl fumarate in the bead is released; and

within the first 7 hours of the test, 90-100% by weight of dimethyl fumarate in the bead is released.

367. 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 1-366.

368. The method of claim 367, wherein 240 mg of the active substance is administered to the subject per day.

369. The method of claim 367, wherein 480 mg of the active substance is administered to the subject per day.

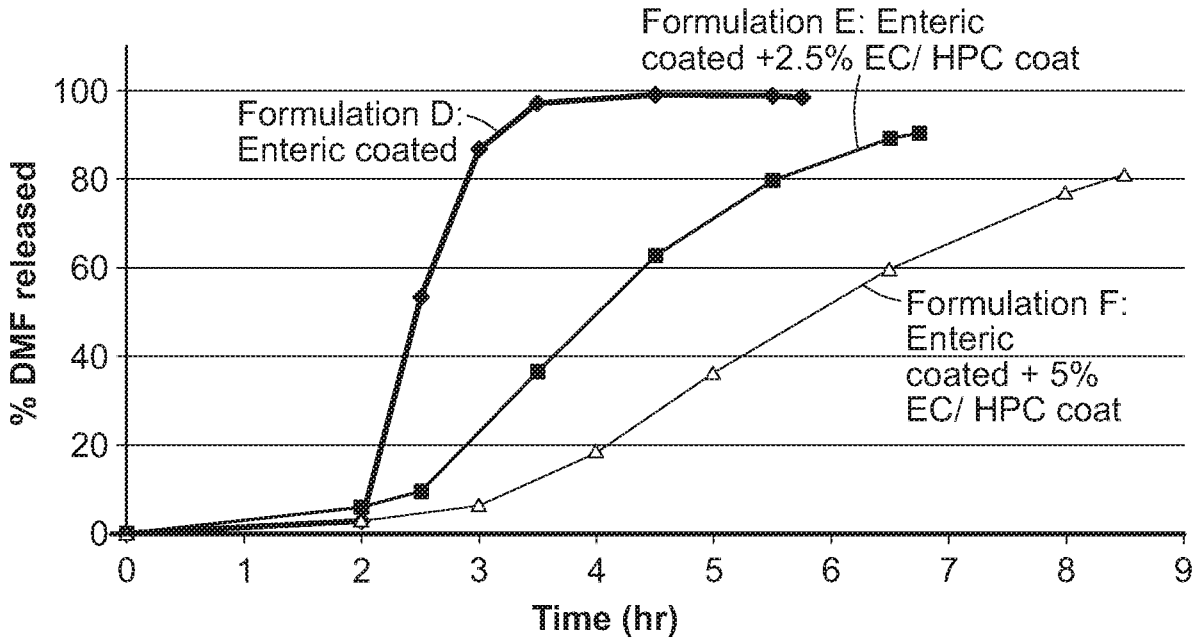
370. The method of any one of claims 367-369, werein the subject is administered orally once per day an effective amount of the pharmaceutical compositon.

371. The method of any one of claims 367-370, wherein the subject is admistered a second therapeutic agent.

372. The method of claim 371, wherein the second therapeutic agent is a Nrf-2 modulator.

373. The method of any one of claims 367-372, wherein the subject has a relapsing form of multiple sclerosis.

374. The method of claim 373, wherein the subject has relapsing-remitting multiple sclerosis.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Formulation D: Enteric coated
Formulation F: Enteric coated + 5% EC/ HPC coat
% DMF released
Time (hr)
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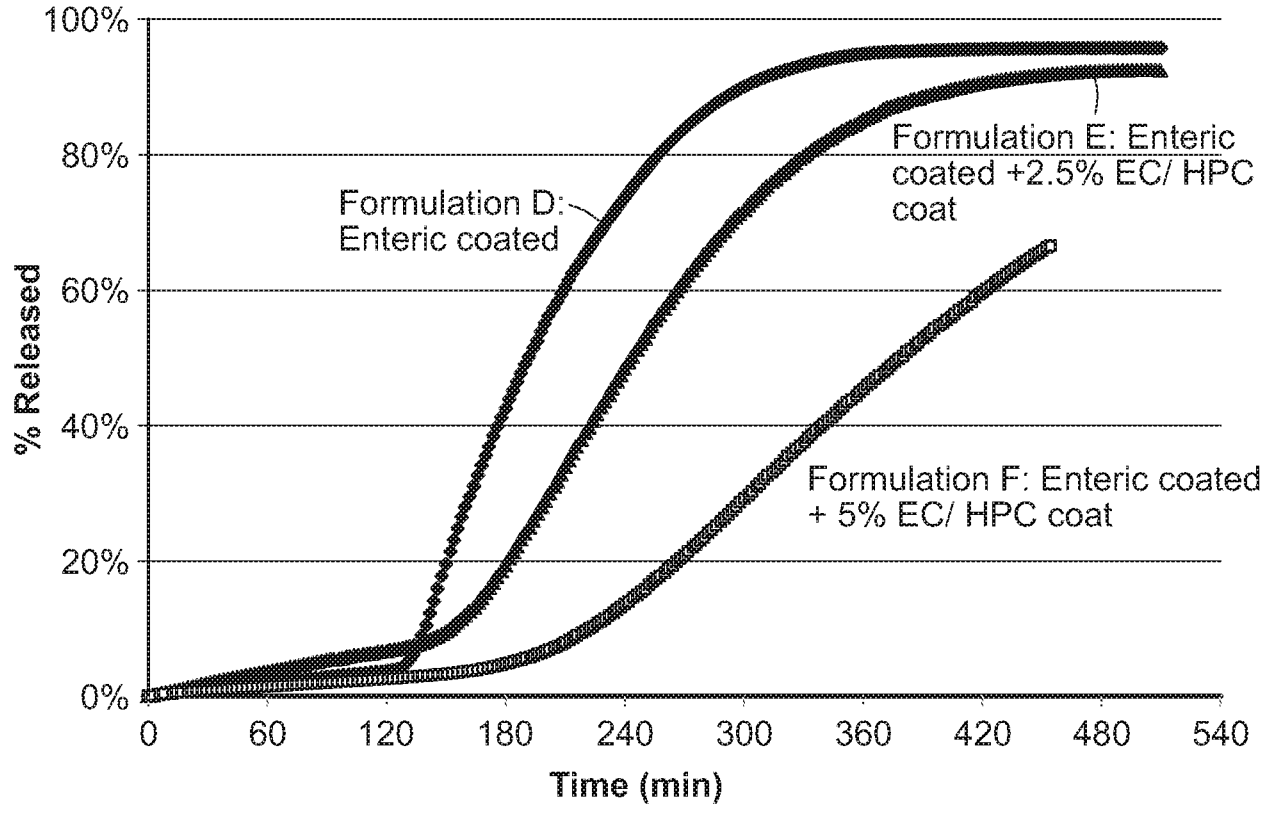
40
60
80
100
0
1
2
3
4
5
6
7
8
9

FIG. 1


Formulation E: Enteric coated +2.5% EC/ HPC coat
Formulation D: Enteric coated
Formulation F: Enteric coated + 5% EC/ HPC coat
% Released
Time (min)
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20%
40%
60%
80%
100%
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60
120
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240
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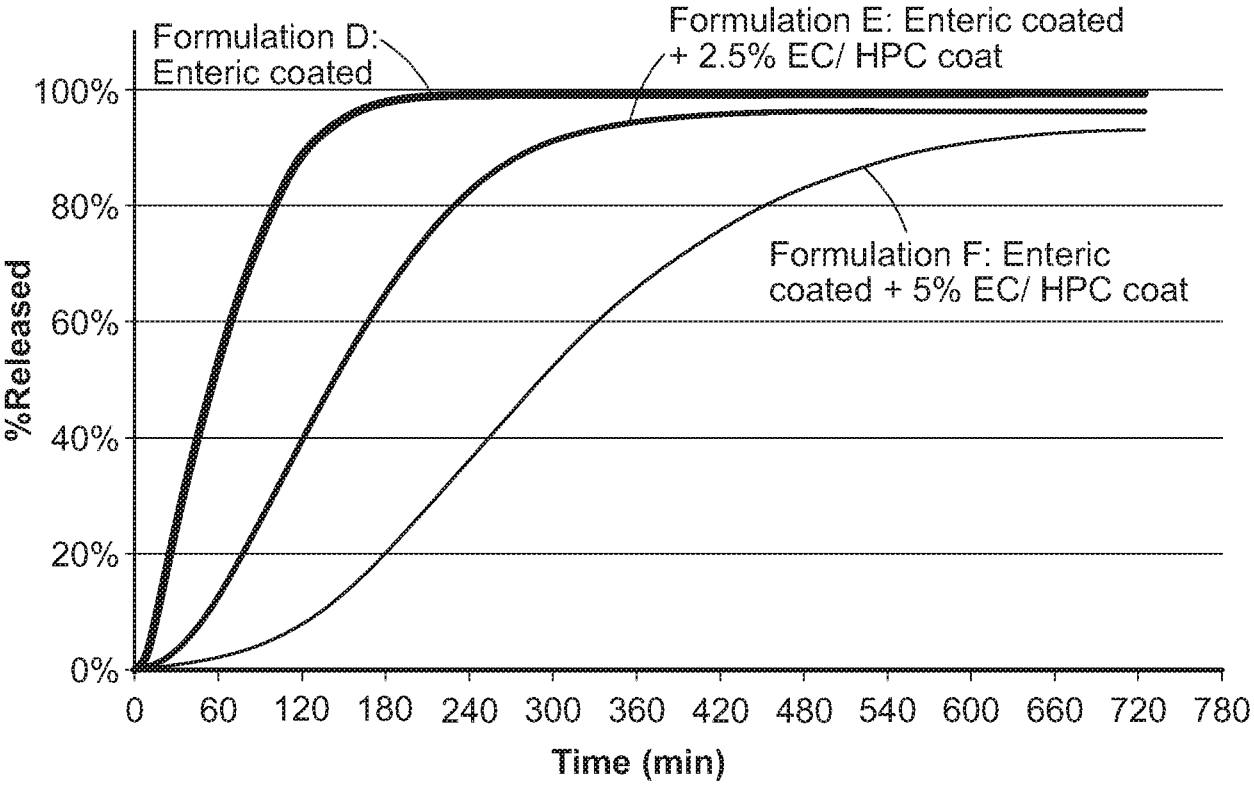
420
480
540

FIG. 2


Formulation D:
Enteric coated
Formulation E: Enteric coated
+ 2.5% EC/ HPC coat
Formulation F: Enteric
coated + 5% EC/ HPC coat
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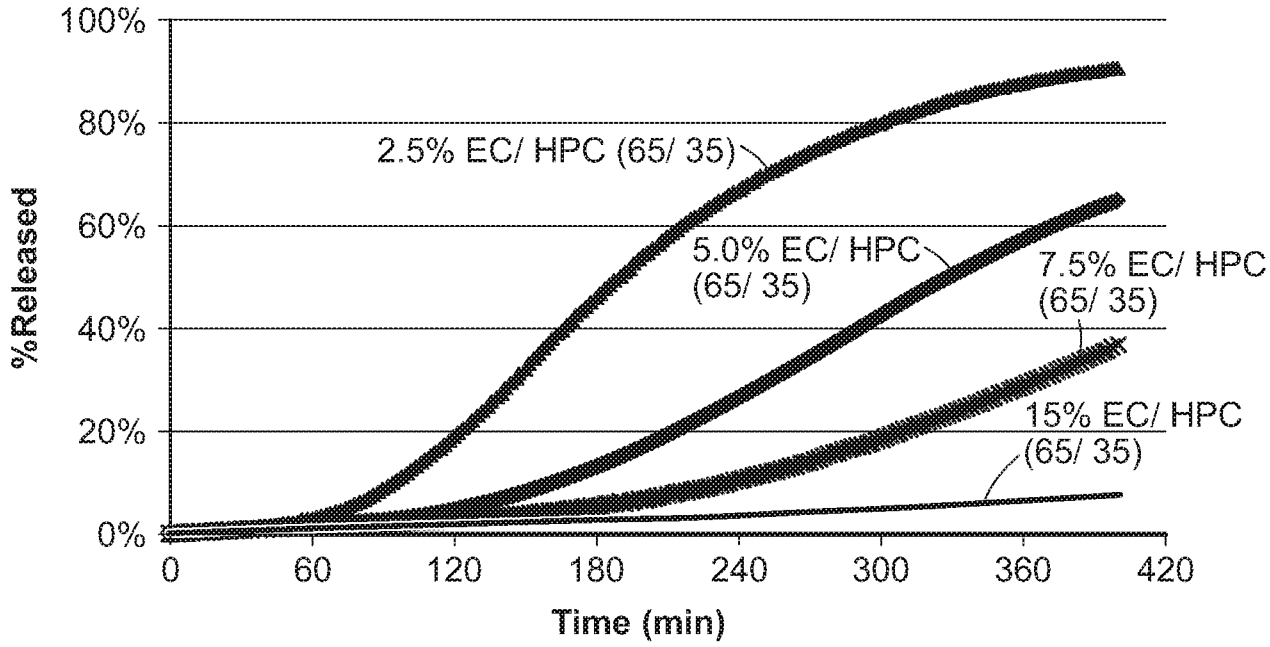
80%
60%
40%
20%
0%
%Released
0
60
120
180
240
300
360
420
480
540
600
660
720
780
Time (min)

FIG. 3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80%
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40%
20%
0%
%Released
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5.0% EC/ HPC
(65/ 35)
7.5% EC/ HPC
(65/ 35)
15% EC/ HPC
(65/ 35)
0
60
120
180
240
300
360
420
Time (min)

FIG. 4

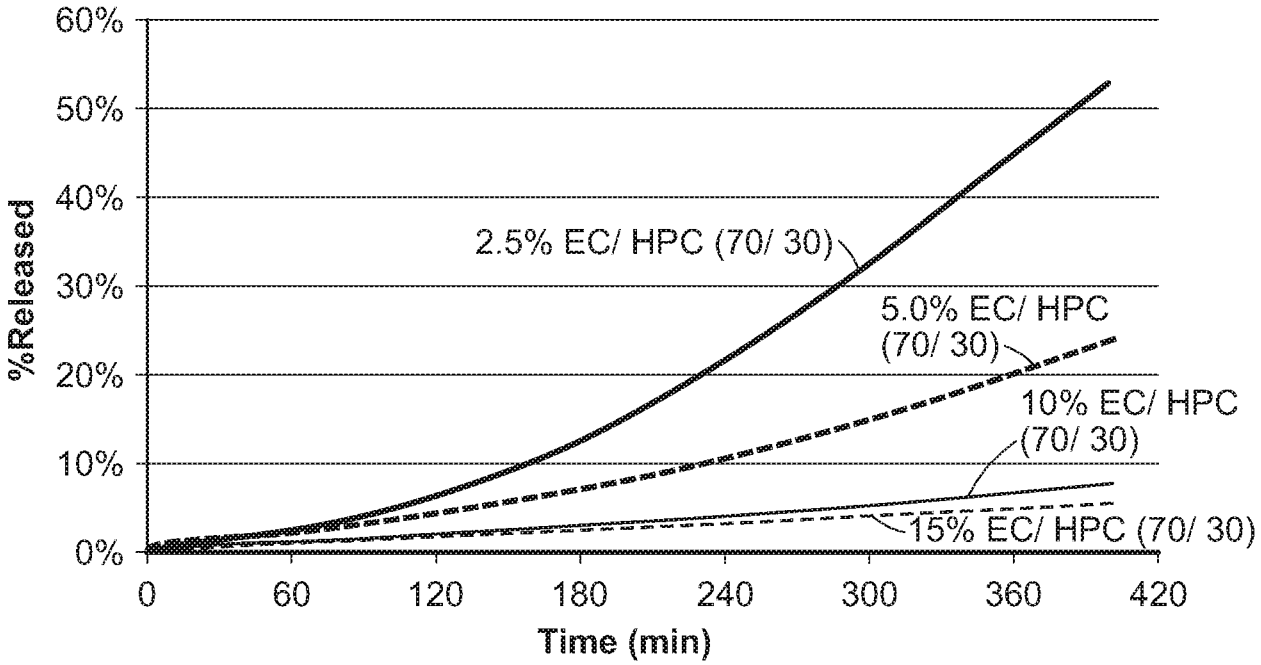

60%
50%
40%
30%
20%
10%
0%
%Released
2.5% EC/ HPC (70/ 30)
5.0% EC/ HPC (70/ 30)
10% EC/ HPC (70/ 30)
15% EC/ HPC (70/ 30)
0
60
120
180
240
300
360
420
Time (min)

FIG. 5

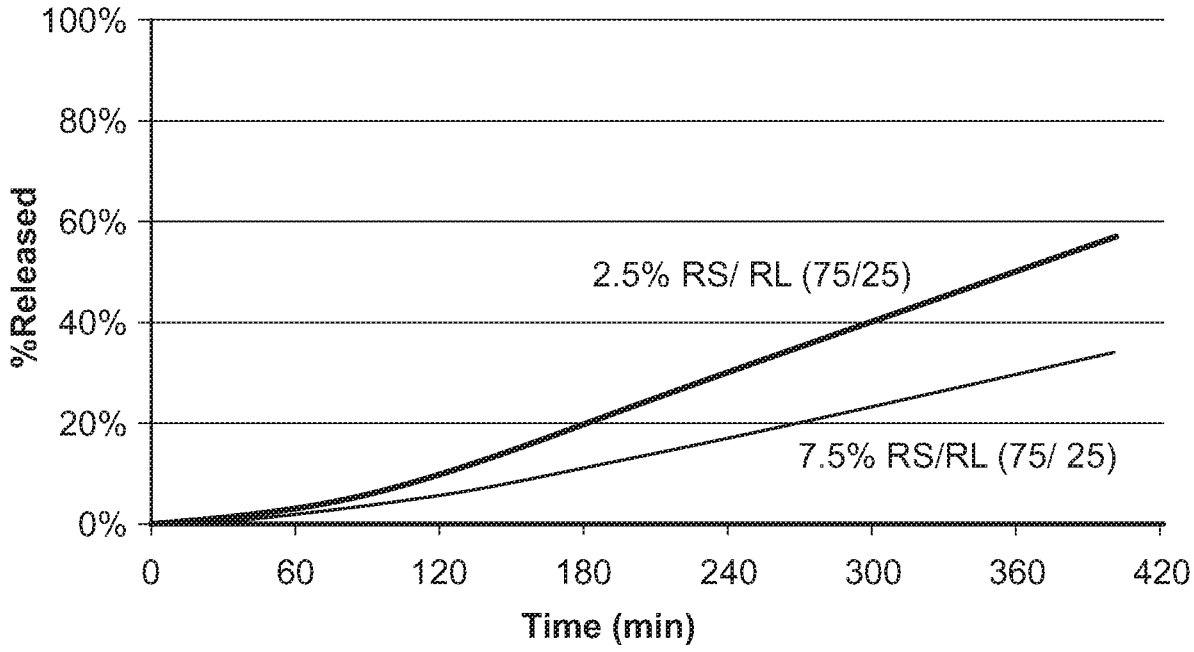

100%
80%
60%
40%
20%
0%
%Released
2.5% RS/ RL (75/25)
7.5% RS/RL (75/ 25)
0
60
120
180
240
300
360
420
Time (min)

FIG. 6

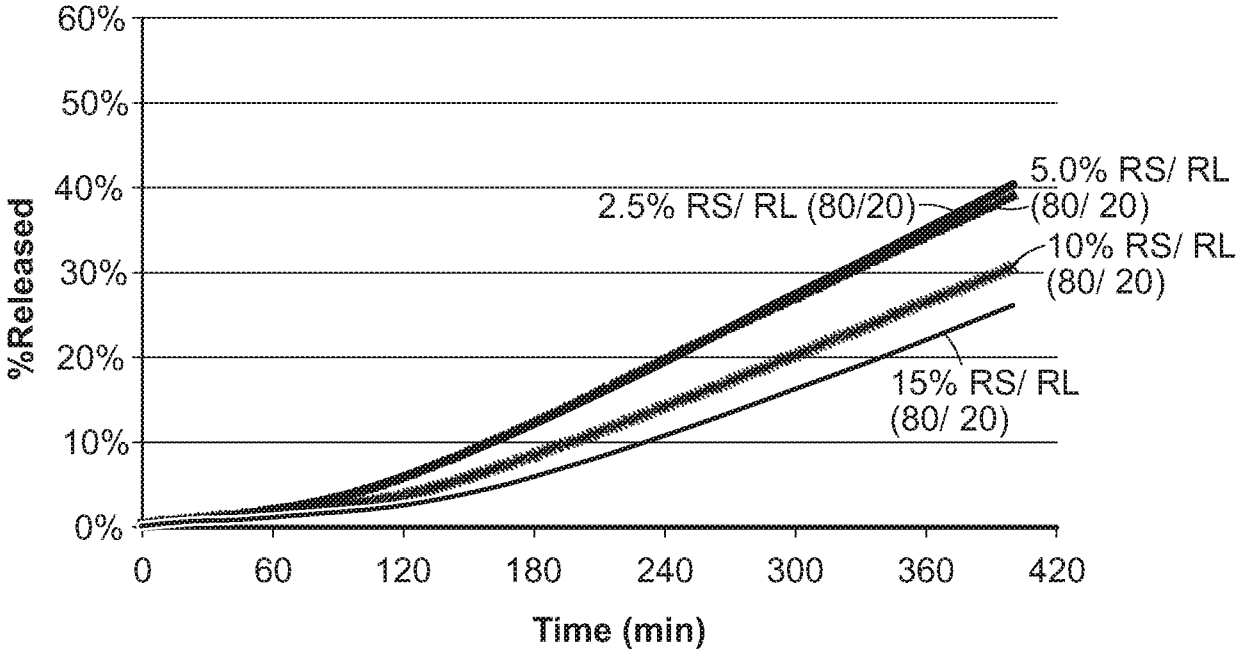

60%
50%
40%
30%
20%
10%
0%
%Released
0
60
120
180
240
300
360
420
Time (min)
2.5% RS/ RL (80/20)
5.0% RS/ RL (80/ 20)
10% RS/ RL (80/ 20)
15% RS/ RL (80/ 20)

FIG. 7

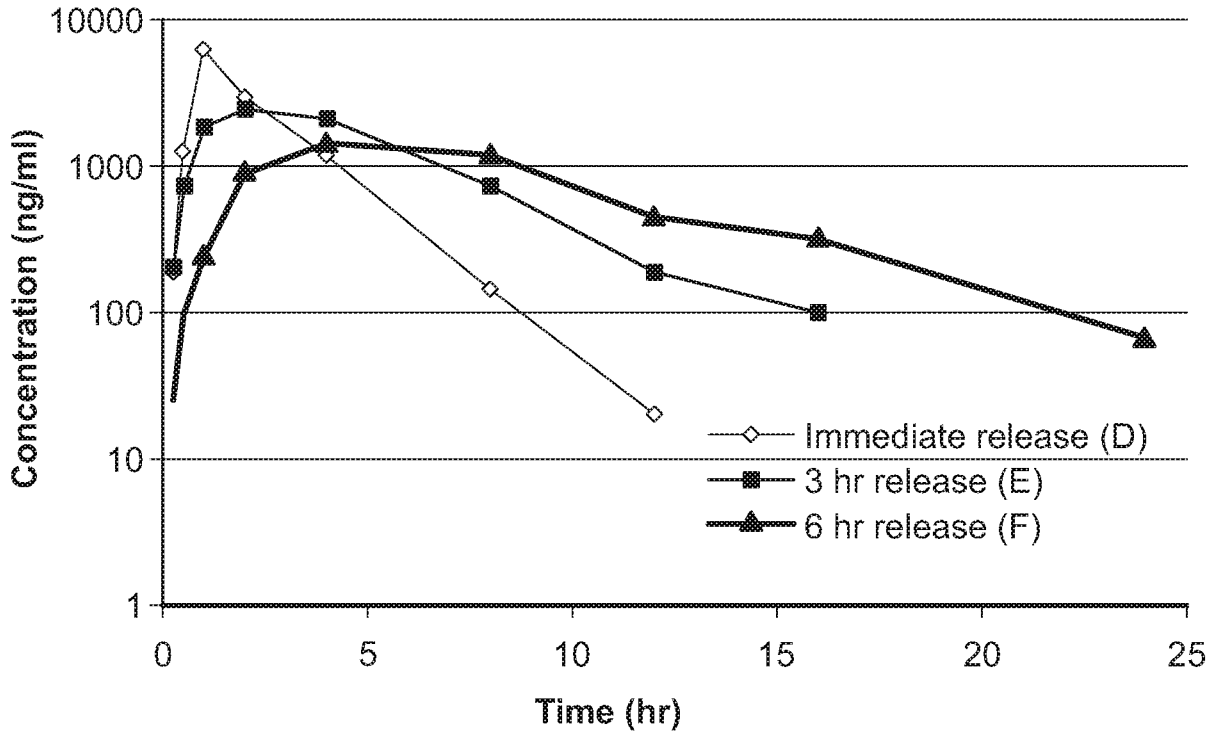

10000
1000
100
10
1
Concentration (ng/ml)
0
5
10
15
20
25
Time (hr)
Immediate release (D)
3 hr release (E)
6 hr release (F)

FIG. 8

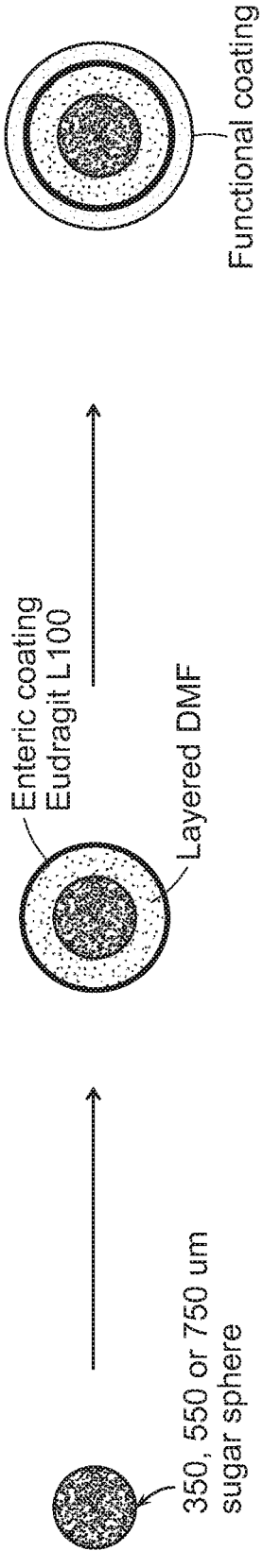

350, 550 or 750 um
sugar sphere
Layered DMF
Enteric coating
Eudragit L100
Functional coating

FIG. 9

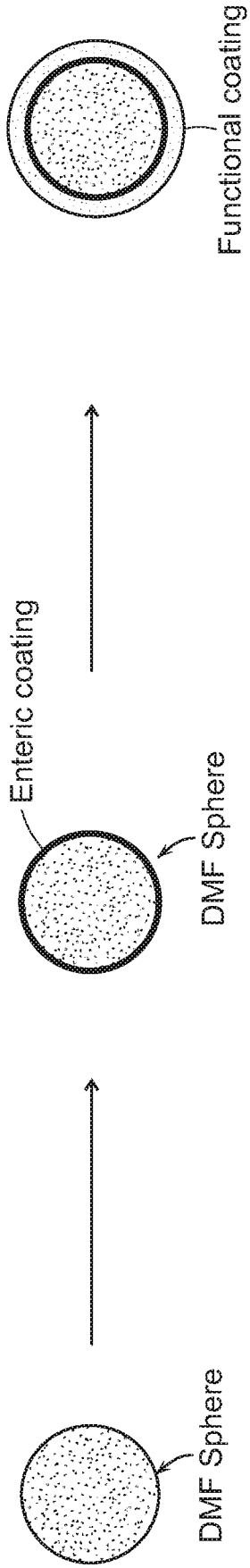
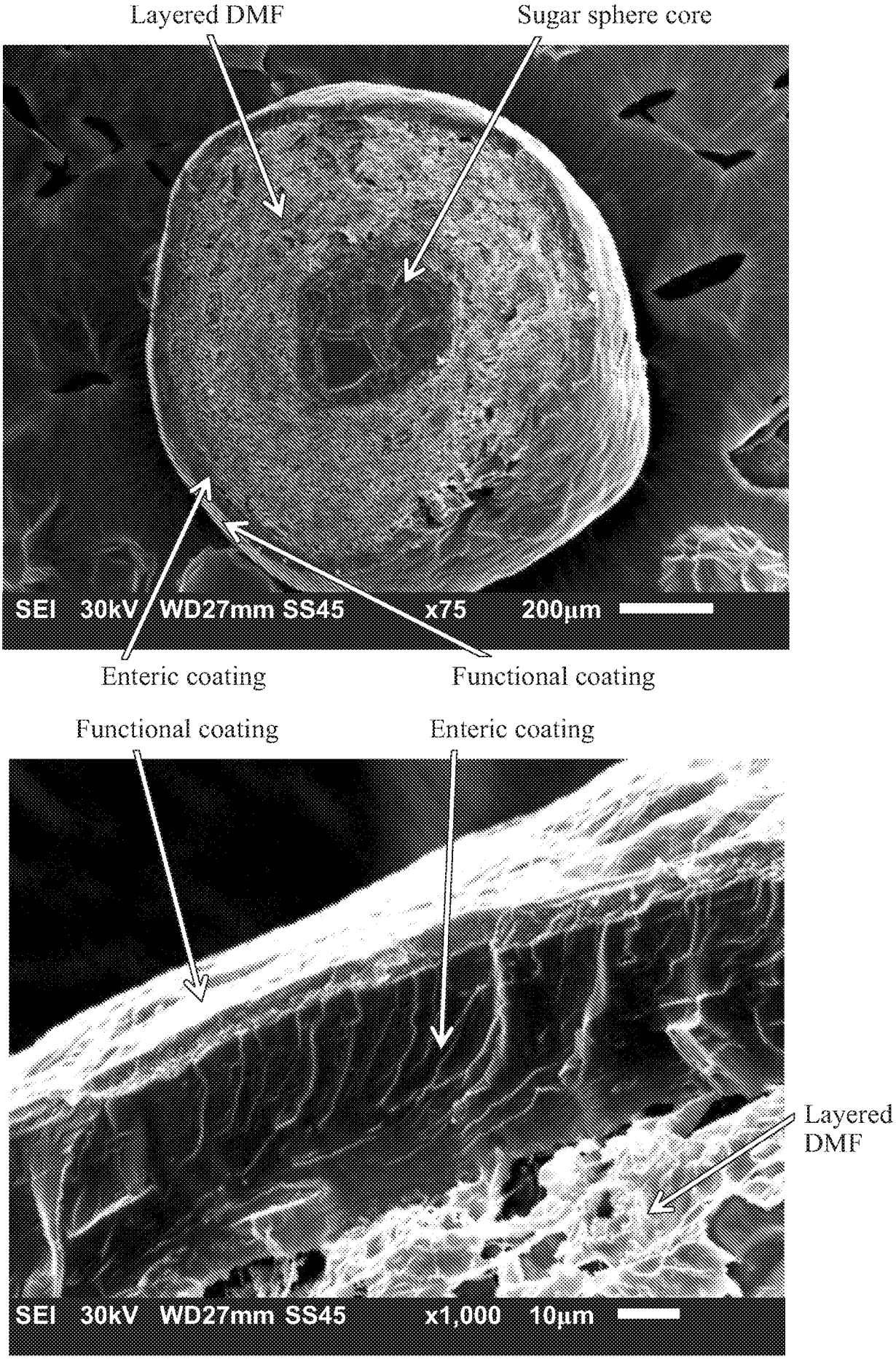

DMF Sphere
DMF Sphere
Enteric coating
Functional coating

FIG. 10

FIG. 11


Layered DMF
Sugar sphere core
SEI 30kV WD27mm SS45 x75 200µm
Enteric coating
Functional coating
Functional coating
Enteric coating
Layered DMF
SEI 30kV WD27mm SS45 x1,000 10µm

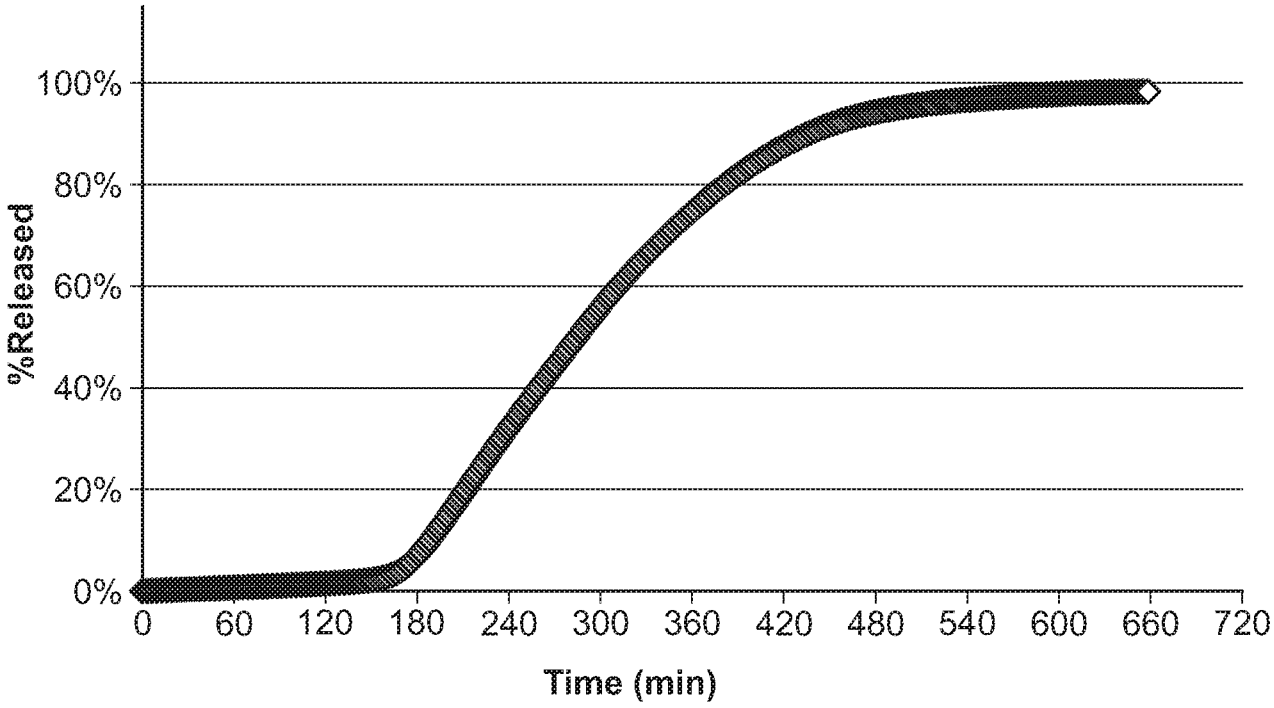

100%
80%
60%
40%
20%
0%
%Released
0
60
120
180
240
300
360
420
480
540
600
660
720
Time (min)

FIG. 12

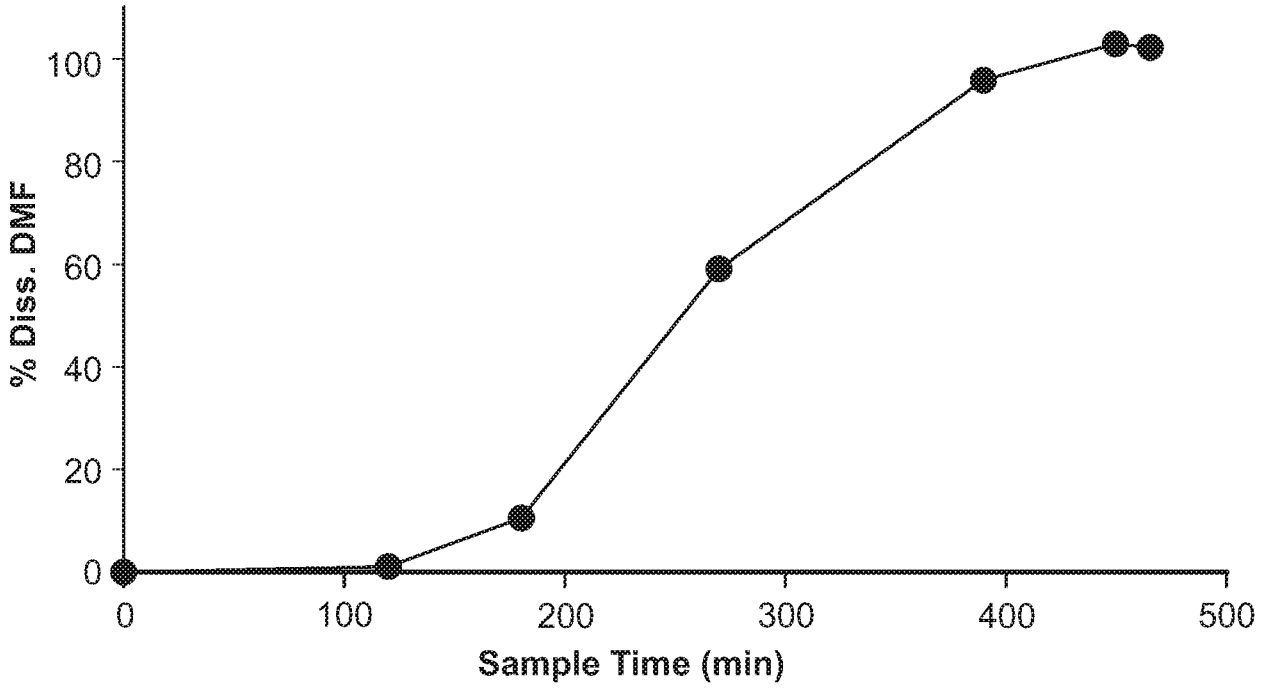

100
80
60
40
20
0
% Diss. DMF
0
100
200
300
400
500
Sample Time (min)

FIG. 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/061456

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/28 A61K9/24 A61K9/16 A61K9/50 A61K31/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/034916 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; BECKER DIETER [DE]; BUERG) 21 April 2005 (2005-04-21) the whole document -----	1-374
X	WO 2006/024479 A2 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; BECKER DIETER [DE]; BEYER) 9 March 2006 (2006-03-09) the whole document -----	1-374
X	WO 2013/119677 A1 (BIOGEN IDEC INC [US]) 15 August 2013 (2013-08-15) the whole document paragraphs [0001], [0133] -----	1-374

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2016	26/01/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Giese, Hans-Hermann

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/100589 A1 (BIOGEN IDEC INC [US]; GOELZ SUSAN [US]; DAWSON KATE [US]; LINKER RALF) 18 August 2011 (2011-08-18) the whole document paragraph [0084]; example 7	1-374
X	WO 2014/020156 A1 (FORWARD PHARMA AS [DK]) 6 February 2014 (2014-02-06) the whole document claims 1,22,23	1-374
X	WO 2014/143146 A1 (XENOPORT INC [US]) 18 September 2014 (2014-09-18) the whole document example 1	1-374
X	WO 2013/076216 A1 (SYNTHON BV [NL]) 30 May 2013 (2013-05-30) the whole document claim 1	1-374
X	US 2014/171504 A1 (GANAPATHY VADIVEL [US]) 19 June 2014 (2014-06-19) the whole document	1-374
A	US 5 213 811 A (FRISBEE STEVEN E [US] ET AL) 25 May 1993 (1993-05-25) claim 1	1-362
A	COHEN ET AL: "The future of multiple sclerosis treatment", JOURNAL OF NEUROLOGICAL SCIENCES, ELSEVIER SCIENTIFIC PUBLISHING CO, AMSTERDAM, NL, vol. 277, 1 February 2009 (2009-02-01), pages S55-S61, XP025912540, ISSN: 0022-510X, DOI: 10.1016/S0022-510X(09)70015-2 [retrieved on 2009-02-01] abstract	1-374

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/061456

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005034916 A1	21-04-2005	AR 045957 A1	16-11-2005
		AU 2004280078 A1	21-04-2005
		BR PI0414864 A	28-11-2006
		CA 2538099 A1	21-04-2005
		EP 1670437 A1	21-06-2006
		JP 2007507458 A	29-03-2007
		MX PA06003646 A	05-06-2006
		PE 07552005 A1	28-11-2005
		TW 200520759 A	01-07-2005
		US 2007036857 A1	15-02-2007
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WO 2006024479 A2	09-03-2006	AR 050717 A1	15-11-2006
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		CA 2577311 A1	09-03-2006
		CN 101010070 A	01-08-2007
		EP 1791526 A2	06-06-2007
		JP 2008511570 A	17-04-2008
		KR 20070046152 A	02-05-2007
		PE 05072006 A1	17-07-2006
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		EA 201491484 A1	27-02-2015
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		JP 2015506377 A	02-03-2015
		KR 20150001726 A	06-01-2015
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		US 2013216615 A1	22-08-2013
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		ES 2555279 T3	30-12-2015
		HR P20151350 T1	01-01-2016
		PT 2533634 E	28-12-2015
		US 2013287732 A1	31-10-2013
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		EP 2692344 A1	05-02-2014
		EP 2879672 A1	10-06-2015
		JP 2015523407 A	13-08-2015

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/061456

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		KR 20150040338 A	14-04-2015
		US 2015164849 A1	18-06-2015
		WO 2014020156 A1	06-02-2014
WO 2014143146 A1	18-09-2014	US 2014275250 A1	18-09-2014
		US 2015190360 A1	09-07-2015
		WO 2014143146 A1	18-09-2014
WO 2013076216 A1	30-05-2013	RU 2014125430 A	27-12-2015
		WO 2013076216 A1	30-05-2013
US 2014171504 A1	19-06-2014	NONE	
US 5213811 A	25-05-1993	NONE	

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

DAVIS, Steven, G.
McCarter & English, LLP
265 Franklin Street
Boston, MA 02110
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing *(day/month/year)*
20 March 2017 (20.03.2017)

Applicant's or agent's file reference
123429-02120

IMPORTANT NOTIFICATION

International application No.
PCT/US2015/061456

International filing date *(day/month/year)*
19 November 2015 (19.11.2015)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
BIOGEN MA INC.
250 Binney Street
Cambridge, MA 02142
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
BIOGEN MA INC.
225 Binney Street
Cambridge, MA 02142
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 10

Authorized officer
Tsukada Michiyo
e-mail pct.team8@wipo.int
Telephone No. +41 22 338 74 08

摘要

本發明提供了富馬酸二甲酯的新型藥物組合物。本發明的藥物組合物呈珠粒形式，並且包含(i)惰性核；(ii)圍繞惰性核的第一層，其中第一層包含富馬酸二甲酯；和(iii)圍繞第一層的腸溶包衣。還提供了包含核和圍繞核的腸溶包衣的呈珠粒形式的藥物組合物，其中核包括富馬酸二甲酯。還包括使用本發明的藥物組合物治療多發性硬化癥的方法。