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(54) **FORMULATIONS COMPRISING IBRUTINIB**

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(57) **ABSTRACT**

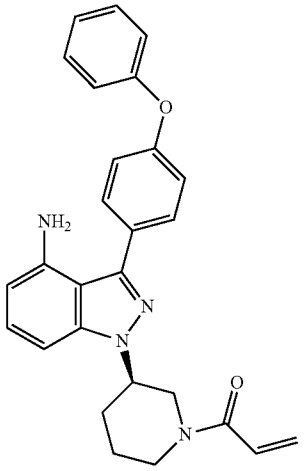
Oral pharmaceutical formulations of ibrutinib and/or a pharmaceutically acceptable salt thereof, methods for their administration, process of their production, and use of these formulations for the treatment of diseases treatable by ibrutinib such as cancer, inflammatory diseases, and autoimmune diseases.

FORMULATIONS COMPRISING IBRUTINIB

[0001] The present disclosure provides certain oral pharmaceutical formulations of ibrutinib, certain methods for their administration, certain processes of their production, and certain uses of these formulations for the treatment of diseases treatable by ibrutinib such as cancer, inflammatory diseases, and autoimmune diseases.

[0002] Bruton's tyrosine kinase (BTK) is a member of the Tec tyrosine kinase family. BTK is expressed in most hematopoietic cells such as B cells, mast cells, and macrophages, but not in T cells, natural killer cells, and plasma cells. BTK plays a role in the development and activation of B cells. Mutations in the human BTK gene cause the inherited disease X-linked agammaglobulinemia (XLA), with lack of peripheral B cells and low levels of serum Ig. In XLA, the primary immune deficit is B cell specific. The development of drugs which inhibit BTK can have therapeutic significance in the treatment of both B cell-related hematological cancers (e.g. non-Hodgkin lymphoma (NHL) and B cell chronic lymphocytic leukemia (B-CLL), and autoimmune diseases (e.g. rheumatoid arthritis, Sjogrens syndrome, IBD, lupus, and asthma).

[0003] PCI-32765 (ibrutinib) is disclosed in U.S. Pat. No. 7,514,444, issued on Apr. 7, 2009, and has the following structure:



[0004] Ibrutinib is an orally available drug that targets Bruton's tyrosine kinase (BTK). Ibrutinib is an irreversible small molecule BTK inhibitor that is in Ph Ib/II of clinical trials in a variety of B-cell malignancies including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (cancer of plasma cells, a type of white blood cell present in bone marrow). At present ibrutinib is administered orally in clinical trials, via the gastrointestinal tract, at high clinical doses (420 mg/day or 840 mg/day) to patients with CLL and SLL to obtain the desired thereapeutic effect. The need for such high doses of ibrutinib may be due to low bioavailability (the oral bioavailability of ibrutinib is reported to be 22.8% in rats) and may be responsible for the adverse side effects associated with the use of ibrutinib such as nausea or emesis, dizziness and diarrhea. Moreover, low bioavailability results in more variable

[0005] As stated above, at present ibrutinib is administered orally, via the gastrointestinal tract, at high clinical doses (420 mg/day or 840 mg/day) to patients to obtain the desired clinical benefit. It is presently disclosed that when ibrutinib is administered intraduodenally versus via the gastrointestinal tract in rats, the oral bioavailability of ibrutinib unexpectedly increased from 21% to 100% as determined by AUC. This unexpected increase in oral bioavailability of ibrutinib can translate into a number of desirable practical benefits. The increase in oral bioavailability should enable administration of ibrutinib at a significantly lower therapeutically effective dose than is currently being used. The lower variability associated with this greater bioavailability should lead to a more reliable therapeutic response as well as more predictable drug absorption. And avoidance of exposure of Ibtrutinib to the stomach and/or use of lower therapeutically effective dose of ibrutinib can reduce or altogether eliminate potential adverse side effects of this drug such as diahrrea, nausea or emesis, and dizziness. U.S. Pat. No. 7,514,444, mentioned above, discloses administration of 0.02-5000 mg/kg and 1-1500 mg of ibrutinib/per day and in clinical trials 420 or 840 mg/day of ibrutinib is being administered to the patients with CLL and SLL. There is no reasonable expectation in the art that ibrutinib can be adminstered orally at lower efficacious doses to the patients with CLL and SLL, particularly as evidenced by the 420 or 840 mg/day of ibrutinib being administered in clinical trials to those patients. Moreover, other than for active agents that are unstable in the stomach or at acidic pH delivery of any active agent with low bioavailability further along in the gastrointestinal tract reduces the path length for drug absorption and would be expected to reduce bioavailability. Therefore, it was unexpected to achieve delivery of ibruntinib directly to the small intestine with greater bioavailability.

[0006] Accordingly, in one aspect, the present disclosure provides a solid oral dosage form comprising:

[0007] (i) ibrutinib and/or a pharmaceutically acceptable salt thereof;

[0008] (ii) means for release of ibrutinib in the intestine; and

[0009] (iii) at least one pharmaceutically acceptable excipient.

[0010] In one embodiment of above aspect, ibrutinib and/or a pharmaceutically acceptable salt thereof is released in the small intestine. In another embodiment, ibrutinib and/or a pharmaceutically acceptable salt thereof is released to a region of the intestine in which the pH is about 5, or 5, or greater than 5. In another embodiment, said ibrutinib and/or a pharmaceutically acceptable salt thereof is released to a region of the intestine in which the pH is about 5.5, or greater than about pH 5.5. For example, the release is in one or more of the duodenum, jejunum, ileum, and colon. In one embodiment, the release is in one or more of the duodenum, jejunum, or ileum. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings and non-enteric time-delayed release coatings. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof

is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or the dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings wherein the enteric coatings are chosen from polymeric coatings. In another embodiment, the enteric coating is is an anionic polymer such as polymethacrylates (e.g., methacrylic acid ethacrylate poly, methacrylic acid methyl methacrylate poly); cellulose-based polymers (e.g., cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), cellulose acetate succinate (CAS), hydroxypropylmethyl-cellulose phthalate (HPMCP), and hydroxypropylmethylcellulose acetate succinate (HPMCAS)) or polyvinyl derivatives such as polyvinyl acetate phthalate (PVAP). When a non-enteric coating is employed, the time-delayed release dosage forms are administered in fasted state and the time-delayed release coating is designed to erode, burst, or become hightly permeable in about 0.3 to about 3 hours or in about 0.5 to about 2 hours after administration to release ibrutinib and/or a pharmaceutically acceptable salt thereof.

[0011] In a second aspect, the present disclosure provides a solid oral dosage form comprising:

[0012] (i) ibrutinib and/or a pharmaceutically acceptable salt thereof;

[0013] (ii) means for increasing the oral bioavailability of ibrutinib, as measured by the area under the curve (AUC), as compared to when said ibrutinib and/or said pharmaceutically acceptable salt thereof are administered in an immediate release dosage form; and

[0014] (iii) at least one pharmaceutically acceptable excipient.

[0015] In one embodiment of the second aspect, the increase in the oral bioavailability of ibrutinib and/or a pharmaceutically acceptable salt thereof is due to the release of the ibrutinib and/or a pharmaceutically acceptable salt thereof in the intestine. In another embodiment of the second aspect, the increase in the oral bioavailability of ibrutinib and/or a pharmaceutically acceptable salt thereof is due to the release of the ibrutinib and/or a pharmaceutically acceptable salt thereof in the small intestine. In another embodiment of the second aspect, ibrutinib and/or a pharmaceutically acceptable salt thereof is released in one or more of the duodenum, jejunum, or ileum. In one embodiment, the release to the above regions of the intestine is achieved by coating ibrutinib and/or a pharmaceutically acceptable salt thereof or a a dosage form containing ibrutinib and/or a pharmaceutically acceptable salt thereof with at least one coating chosen from enteric coatings and a non-enteric time-delayed release coatings. When the delayed release dosage forms are administered in fasted state, the time-delayed release coating is designed to erode, burst, or become very permeable in about 0.3 to about 3 hours or in about 0.5 to about 2 hours after administration to release ibrutinib and/or a pharmaceutically acceptable salt thereof. When the dosage form comprised of said compound is coated with a non-enteric coating, it is generally administered in the fasted state to avoid variability or delays in gastric emptying with meals and the resulting variability in the initiation of efficacious plasma levels.

[0016] In a third aspect, the present disclosure provides a solid oral dosage form comprising:

[0017] (i) ibrutinib and/or a pharmaceutically acceptable salt thereof;

[0018] (ii) at least one coating chosen from enteric coatings and non-enteric time-delayed release coatings; and

[0020] In one embodiment, the said at least one coating is chosen from enteric coatings. In one embodiment, the said at least one coating is chosen from polymeric coatings. In one embodiment, the said at least one coating is chosen from enteric coatings where the enteric coating is a polymer which erodes to release ibrutinib and/or a pharmaceutically acceptable salt thereof at about pH 5 and above. In another embodiment, ibrutinib and/or a pharmaceutically acceptable salt thereof is released at about pH 5.5 and above or from about 5.5 to about 6.5. In yet another embodiment of the third aspect, ibrutinib and/or a pharmaceutically acceptable salt thereof is released in one or more of the duodenum, jejunum, or ileum. In one embodiment of the third aspect and embodiments contained therein the dosage form is coated. In one embodiment of the third aspect and embodiments contained therein said ibrutinib and/or said pharmaceutically acceptable salt thereof are coated.

[0021] In a fourth aspect, the present disclosure provides a solid oral dosage from comprising:

[0022] (i) about 20 mg to about 450 mg of ibrutinib and/or a pharmaceutically acceptable salt thereof;

[0023] (ii) at least one coating chosen from an enteric coating and/or a non-enteric time-delayed release coating; and

[0024] (iii) at least one pharmaceutically acceptable excipient;

[0025] wherein said oral dosage form increases the oral bioavailability, as measured by the area under the curve (AUC), of said ibrutinib and/or said pharmaceutically acceptable salt thereof by at least 20% as compared to the bioavailability obtained from an immediate release solid oral dosage form comprising the same dose of said ibrutinib and/or said pharmaceutically acceptable salt thereof and said at least one pharmaceutically acceptable excipient under the same conditions. In one embodiment, the increase in bioavailability is at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In another embodiment the increase in bioavailability is independently at least 70%, or 75%, or 80%, or 85%, or 90%, 95% or 100%.

[0026] In one embodiment of the first to fourth aspect and embodiments contained therein, the dosage form contains from about 20 mg to about 450 mg of said ibrutinib and/or said pharmaceutically acceptable salt thereof. In another embodiment of the fourth aspect and embodiments contained therein, the dosage form contains from about 20 mg to about 420 mg of said ibrutinib and/or said pharmaceutically acceptable salt thereof. In another embodiment of the fourth aspect and embodiments contained therein, the dosage form contains from about 20 or 30 mg to about 300 or 350 mg of said ibrutinib and/or said pharmaceutically acceptable salt thereof. In another embodiment of the fourth aspect and embodiments contained therein, the dosage form contains from about 50 mg to about 200, or 220, or 250 mg of said ibrutinib and/or said pharmaceutically acceptable salt thereof.

[0027] In one embodiment, the solid oral dosage forms disclosed above are coated with at least one coating chosen from enteric coatings and non-enteric time-delayed release coatings. Within this embodiment, in one embodiment, the at least one coating is chosen from enteric coatings. Within the above embodiments, the enteric coatings are chosen from polymeric coatings.

[0028] In another embodiment, the solid oral dosage form

chosen from enteric coatings and non-enteric time-delayed release coatings. Within this embodiment, in one embodiment, the at least one coating is chosen from enteric coatings. Within the above embodiments, the enteric coatings are chosen from polymeric coatings. Within the above embodiments, the enteric coating is an anionic polymer such as polymethacrylates (e.g., methacrylic acid ethacrylate poly, methacrylic acid methyl methacrylate poly); cellulose-based polymers (e.g., cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), cellulose acetate succinate (CAS), hydroxypropylmethyl-cellulose phthalate (HPMCP), and hydroxypropylmethylcellulose acetate succinate (HPMCAS)) or polyvinyl derivatives such as polyvinyl acetate phthalate (PVAP).

[0029] In one embodiment, the solid oral dosage forms are a tablet or capsule. When the dosage form is capsule, ibrutinib and/or a pharmaceutically acceptable salt thereof can be present in a non-solid form. In another embodiment, the solid oral dosage form disclosed above comprises ibrutinib.

[0030] The therapeutically effective amount of ibrutinib and/or a pharmaceutically acceptable salt thereof when administered into the intestine by bypassing the stomach can be from about 20 mg per day to about 450 mg/day, or 20 mg/day to about 420 mg/day; or about 20 mg/day or 30 mg/day to about 300 or 350 mg/day; or about 30 or 50 mg/day to about 200, or 220 or 250 mg/day; or about 30 or 50 mg/day to about 100 or 150 mg/day and can be administered in single or multiple doses. Accordingly, any of the formulations disclosed herein can contain from about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 175, 170, 175, 180, 185, 190, 195, 200, 225, 250, 300, 325, 350, 375, 400, 425, or 450 milligrams of ibrutinib or a pharmaceutically acceptable salt thereof. In one embodiment, the tablets or capsules can contain about 20, 25, 30, 50, 75, 100, 150, 200, or 220 milligrams of ibrutinib and/or a pharmaceutically acceptable salt thereof.

[0031] In one embodiment, any of the formulations disclosed herein contain, unless stated otherwise, one or more pharmaceutically acceptable excipient(s) such as glidants, polymers, binders, surfactants, disintegrants, diluents, buffering agents, antiadherents, retardants, solubilizers, antioxidants, antifoaming agents, fillers, flavors, colors, lubricants, sorbents, plasticizers, or sweeteners, preservatives, or mixtures thereof, which facilitate processing of ibrutinib and/or a pharmaceutically acceptable salt thereof or into preparations which can be used pharmaceutically. Any of the well-known techniques and excipients may be used as suitable and as understood in the art, see for example, Remington: The Science and Practice of Pharmacy, Twenty-first Ed., (Pharmaceutical Press, 2005); Liberman, H. A., Lachman, L., and Schwartz, J. B. Eds., Pharmaceutical Dosage Forms, Vol. 1-2 Taylor & Francis 1990; and R. I. Mahato, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Second Ed. (Taylor & Francis, 2012).

[0032] In certain embodiments, the formulations may include one or more pH adjusting agents or buffering agents, for example, acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylamibases, and buffers are added in an amount required to maintain pH of the composition in an acceptable range.

[0033] In certain embodiments, the formulations may also include one or more salts in an amount that is required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium, or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, or bisulfite anions. Suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite, and ammonium sulfate.

[0034] In certain embodiments, the formulations may also include one or more antioxidants, such as non-thiol antioxidants, e,g., ascorbic acid, butylated hydroxytoluene (BHT), butylated hydroxyanisole, sodium ascorbate, and tocopherol or derivatives thereof. In certain embodiments, antioxidants enhance chemical stability where required.

[0035] In certain embodiments, the formulations may also include one or more antifoaming agents. The foaming agent (s) are added to reduce foaming during processing which can result in coagulation of aqueous dispersions, bubbles in the finished film, or generally impair processing. Examples of suitable anti-foaming agents include silicon emulsions or sorbitan sesquoleate.

[0036] In certain embodiments, the formulations may also include one or more preservatives. Preservatives are used to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal, stabilized chlorine dioxide, and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide, and cetylpyridinium chloride.

[0037] In certain embodiments, the formulations may also include one or more binders. Binders impart cohesive qualities. Exemplary binders include, e.g., alginic acid and salts thereof; cellulose derivatives, such as carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Kiucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinyl-pyrrolidone/vinyl acetate copolymer; crosspovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), and lactose; a natural or synthetic gum such as *acacia*, tragacanth, ghatti gum mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, polyethylene oxide, waxes, sodium alginate, and the like. In general, binder levels of about 10 to about 70% are used in powder-filled gelatin capsule formulations. Binder usage level in tablet formulations varies on whether direct compression, wet granulation, or roller compaction process is used to make the tablet, and/or on types of other excipients used to make the formulation e.g, fillers which itself can act as moderate binder.

[0038] In certain embodiments, the formulations may also include dispersing agents and/or viscosity modulating agents. Dispersing agents and/or viscosity modulating agents include materials that control the diffusion and homogeneity of a drug through liquid media or a granulation method or blend method. In some embodiments, these agents also facilitate the

polymers, electrolytes, Tween®60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdone®), and the carbohydrate-based dispersing agents, for example, hydroxypropyl celluloses (e.g., HPC, H-PC-SL, and HPC-L), hydroxypropyl methylcelluloses (e.g., HPMC K100, RPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethyl-cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropyl-methylcellulose acetate stearate (HPMCAS), noncrystalline cellulose, magnesium. aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), vinyl pyrrolidone/vinyl acetate copolymer (S630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), polyethylene oxide (e.g., PolyOx or PEO), poloxamers which are block copolymers of ethylene oxide and propylene oxide (e.g., Pluronics F68®, F88®, and F108®; and poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)), polyvinylpyrrolidone K12, K17, K25, or K30, polyvinylpyrrolidone/vinyl acetate copolymer (S-630), polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 5400 to about 7000, polysorbate-80, sodium alginate, gums, such as, e.g., gum tragacanth and gum *acacia*, guar gum, xanthans, including xanthan gum, sugars, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone, carbomers, polyvinyl alcohol (PVA), alginates, chitosans, and combinations thereof. Dispersing agents particularly useful in liposomal dispersions and self-emulsifying dispersions are dimyristoyl phosphatidyl choline, natural phosphatidyl choline from eggs, natural phosphatidyl glycerol from eggs, cholesterol, and isopropyl myristate.

[0039] In certain embodiments, the formulations may also include one or more "diluents" which refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution. In certain embodiments, diluents increase bulk of the composition to facilitate compression or create sufficient bulk for homogenous blend for capsule filling. Such compounds include e.g., lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose such as Avicel®; dibasic calcium phosphate, dicalcium phosphate dihydrate; tricalcium phosphate, calcium phosphate; anhydrous lactose, spray-dried lactose; pregelatinized starch, compressible sugar, such as Di-Pac® (Amstar); hydroxypropyl-methylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose-based diluents, confectioner's sugar; monobasic calcium sulfate monohydrate, calcium sulfate dihydrate; calcium lactate trihydrate, dextrates; hydrolyzed cereal solids, amylose; powdered cellulose, calcium carbonate; glycine, kaolin; mannitol, sodium chloride; inositol, bentonite, and the like.

[0040] In certain embodiments, the formulations may also include one or more "disintegrants" which facilitate the breakup or disintegration of the dosage form when it comes in contact with the gastrointestinal fluid. Examples of disintegrants include starch, sodium starch glycolate such as Explotab® National 1551 or sodium starch glycolate such as Promogel®. or Explotab®, a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH 102, Avicel® PH105, Elceme® P100, Emcocel®, Vivacel®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethyl-cellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crosspovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[0041] In certain embodiments, the formulations may also include erosion facilitators which include materials that control the erosion of a particular material in gastrointestinal fluid. Exemplary erosion facilitators include, e.g., hydrophilic polymers, electrolytes, proteins, peptides, and amino acids.

[0042] In certain embodiments, the formulations may also include one or more filling agents which include compounds such as lactose, xylitol, lactitol, mannitol, sorbitol, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, sucrose, sodium chloride, polyethylene glycol, and the like.

[0043] In certain embodiments, the formulations may also include one or more flavoring agents and/or "sweeteners" e.g., *acacia* syrup, acesulfame K, alitame, anise, apple, aspartame, banana, orange, pear, peach, peppermint, peppermint cream, Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, *stevia*, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sylitol, sucralose, sorbitol, tagatose, tangerine, thaumatin, vanilla, walnut, watermelon, wild cherry, xylitol, or any combination of thereof. these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-*eucalyptus*, orange-cream, vanilla-mint, and mixtures thereof. The flavoring agent may be incorporated with or without a polymeric coating or may be mixed directly in a formulation or first incorporated into one or more polymers.

[0044] In certain embodiments, the formulations may also include one or more plasticizers which are compounds used to soften the enteric or delayed release coatings to make them less brittle. Suitable plasticizers include, e.g., polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl citrate, dibutyl sebacate, triethyl cellulose, and triacetin. In some embodiments, plasticizers can also function as dispersing agents or wetting agents.

[0045] In certain embodiments, the formulations may also include one or more lubricants and glidants which are compounds that prevent, reduce or inhibit adhesion or friction of materials. Exemplary lubricants include, e.g., stearic acid, calcium hydroxide, talc, sodium stearyl lumerate, a hydrocar-

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