PHARMACEUTICAL COMPOSITIONS HAVING A SWELLABLE COATING

INTRODUCTION TO THE INVENTION

Throughout this application, several patent and other documents are mentioned. The contents of these documents are hereby incorporated by reference.

The invention relates to solid pharmaceutical dosage forms having coatings that protect contained pharmaceutical active ingredients against degradation by acidic gastric fluid. In particular, the dosage forms have coatings comprising substances that swell upon contact with aqueous fluids.

A number of pharmaceutical active ingredients are not chemically stable in acidic environments. For this reason, oral administration cannot be effective without some means for protecting the substances against contact with gastric fluid. This, however, also has the generally undesired effect of delaying availability of the substance to the body, since systemic absorption will not commence until the substance has been released from its dosage form.

Approaches have been devised to protect pharmaceutical dosage forms from being affected by the acidic stomach contents, and permitting active ingredients to be made available only after the dosage form enters a more alkaline environment, such as in the duodenum, jejunum, or ileum. This typically involves coating the dosage form or particles containing an active pharmaceutical agent with a material that resists acid attack, but dissolves or becomes permeable in a more alkaline environment.

Lovgren et al., in U.S. Patent 4,786,505, describe a stable pharmaceutical preparation of omeprazole that resists acid attack, but dissolves rapidly in neutral or alkaline media. Particles of omeprazole are mixed with a water-soluble alkaline-reacting substance and the particles are coated with a "separating layer" that acts as a pH buffering zone to prevent contact of the drug and acidic groups that are present in the final coating material. Finally, the bi-layered composition is coated with an enteric polymer coating that does not react with acids.

U.S. Patent 5,035,899 to Saeki et al. relates to compositions of acid-unstable drugs, which are protected against contact with gastric acid. A core that contains the drug is coated first with fine particles of a material having a low water

solubility, then are coated with an enteric film-forming material such as ethylcellulose.

Mazer et al., in U.S. Patent 5,160,742, discloses a sustained release system for an acid-sensitive drug such as a β-lactam antibiotic. Coated drug particles, suitable for inclusion in syrups or other formulations are prepared by forming a core that contains the drug, coating the core with a prolamine, and applying a final exterior coating of an enteric substance such as a methacrylic acid copolymer. Optionally, an additional coating of prolamine can be applied onto the enteric coating layer. The drug is released over a prolonged time, beginning after the coated particles enter a high-pH environment.

U.S. Patent 5,472,712 to Oshlack et al. teaches controlled release formulations having drug-containing core and a controlled release hydrophobic coating of ethylcellulose, optionally containing a hydrophilic pore forming substance such as hydroxypropyl methylcellulose. Optionally, the cores can have an intermediate "barrier" coating of a substance such as hydroxypropyl methylcellulose, which preferably does not affect the dissolution rate of the final product.

In U.S. Patent 5,609,909 to Meyer et al., oral formulations in which the unpleasant taste of a drug substance is masked, but in which the drug is immediately bioavailable upon exposure to acidic fluid in the stomach, are prepared by coating a drug-containing core particle with a mixture of a prolamine and a nonpolymeric plasticizer.

U.S. Patent 5,811,388 to Friend et al. teaches the preparation of a dosage form in which drug is not released to the upper gastrointestinal tract, but is released in the lower gastrointestinal tract for directly treating diseases of the colon. The dosage form includes a core tablet containing the drug and a large amount of a plant-derived hydrocolloid, optionally coated with a film of an enteric substance.

Lerner et al. describe, in U.S. Patent 5,840,332, a composition that delivers a drug to a particular portion of the gastrointestinal tract, wherein a drug-containing core is coated with a water-insoluble material having embedded particles of water-insoluble hydrophilic matter. The coated core can optionally be further coated with an enteric polymer.

U.S. Patent 6,346,269 to Hsiao et al. teaches oral formulations for acid-sensitive drugs, where the drug substance is mixed with an alkaline material such as trisodium phosphate and coated onto a core, such as a tablet, then an enteric coating is applied over the drug substance layer.

Methods for the production of films, sheets, and articles from zein are taught in U.S. Patent 6,635,206 to Padua et al.

A need exists for a drug-containing dosage form in which drug substances will not be exposed to acid in the stomach, but will be rapidly released when the dosage form enters a more alkaline environment.

SUMMARY OF THE INVENTION

In one embodiment, the invention includes a pharmaceutical dosage form comprising: a solid core comprising a pharmaceutical active and a disintegrant; a swellable coating surrounding the core; and an enteric coating surrounding the swellable coating. The dosage form can have different embodiments, including coated tablets or capsules containing coated pellets or coated minitablets.

A preferred aspect of the invention is a dosage form in which the pharmaceutical active is substantially retained while the dosage form is present in the stomach, but where the pharmaceutical active is rapidly released after the dosage form enters an environment having a pH value at least about 5.

Also included in the invention is a pharmaceutical dosage form comprising: a solid core comprising an acid-sensitive pharmaceutical active and a disintegrant; a swellable coating comprising a hydrocolloid-forming component, surrounding the core; and an enteric coating surrounding the swellable coating.

The invention further includes a pharmaceutical dosage form comprising: a solid core comprising a benzimidazole and a disintegrant; a swellable coating comprising one or more hydrocolloid-formers selected from zein, crospovidone, and a hydroxypropyl cellulose, surrounding the core: and an enteric coating comprising a copolymer of methacrylic acid and ethyl acrylate, surrounding the swellable coating.

Another aspect of the invention is a method of treating a medical condition comprising orally administering a pharmaceutical dosage form according to any of the preceding aspects and embodiments, in which method: the dosage form

remains substantially intact during stomach transit; the enteric coating is removed in digestive system environments having pH values above about 5; aqueous fluids penetrate areas of the dosage form where the enteric coating has been removed, causing hydrocolloid formation in the swellable coating; aqueous fluids pass through the hydrocolloid to hydrate the core; and the hydrated core becomes fragmented, releasing the pharmaceutical active from the dosage form.

Further, the invention includes a method of preparing a pharmaceutical dosage form, comprising the steps of: combining components comprising a pharmaceutical active and a disintegrant, and forming a solid core; coating the core with a swellable coating comprising a hydrocolloid-forming component; and applying an outer coating comprising an acid-resistant enteric substance.

Preferred swelling agents in the swellable coating include prolamines; vinylpyrrolidone polymers; cellulose derivatives; starches; carboxyvinyl polymers; alginates; pectins; agar; and gums. Zein, crospovidone, or a hydroxypropyl cellulose are more preferred for use as the swelling agent.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention provides a pharmaceutical dosage form comprising a core that comprises a pharmaceutical active ingredient, and a swellable coating surrounding the core. The core comprises at least 50%, at least 60%, at least 70%, preferably at least 80%, preferably at least 82.5%, preferably at least 85%, preferably at least 87%, preferably at least 88%, preferably at least 89% of the total pharmaceutical composition. The core may also comprise at least 90%, at least 91%, at least 92% or at least 93% of the total pharmaceutical composition.

In this application, the terms "pharmaceutical active ingredient" "pharmaceutical active" and "active" are used interchangeably to refer to a component of a pharmaceutical dosage form that provides a therapeutic effect upon administration to a subject. This invention is particularly applicable to acid-sensitive pharmaceutical actives, which exhibit instability in a low-pH environment, such as the benzimidazole derivatives, including their optically active isomers. Specific examples of useful benzimidazole compounds include rabeprazole, omeprazole, esomeprazole, lansoprazole, and pantoprazole. Other drugs for which the invention will be useful include, without limitation thereto:

pharmaceutical actives that react with enteric coating components, examples being drugs that form insoluble complexes with the enteric coatings, such as fluoxetine and duloxetine; and highly alkaline drugs that can react with acidic groups to reduce the acid-insolubility of the coating, such as diclofenac sodium and piroxicam.

As contemplated herein, a "swellable coating" is a coating that increases in volume upon contact with aqueous fluids. This swelling usually occurs through imbibition of water. The swellable coating adds 0.1-10%, 0.5-8%, 0.7-7%, 1-5%, 1.3-3%, 1.5-2%, about 2%, or about 1.5% to the weight of the core. In another embodiment, the swellable coating adds 0.1- 5%, 0.1- 4%, 0.1- 3%, 0.1-2%, or 0.1-1% to the weight of the core.

Generally, the swellable coating, upon wetting, becomes a hydrocolloid, which is a gelatinous suspension of microscopic particles in water. Preferably, the hydrocolloid is formed from a prolamine, such as gliadan, hordein, or, more preferably, zein. Zein is extracted from corn as a granular, straw to pale yellow colored amorphous powder or fine flakes and various commercial extracts have molecular weights in the range of 25,000-35,000. Zein is insoluble in water and insoluble in alcohols, but soluble in aqueous alcohol solutions. Chemically, zein is fairly abundant in glutamine and devoid of lysine and tryptophan. Zein comprises about 20-22% glutamic acid and glutamine, 17-20% leucine, 5-9% proline, 8-10% alanine, 4-7% phenylalanine, 3-7% isoleucine, 4-6% serine, 4-5% asparginine and 3-5% tyrosine. All of the other amino acids in zein each comprise less than 3%. Zein has been generally recognized as safe (GRAS) by the United States Food and Drug Administration since March, 1985 for use in food and pharmaceutical products. Zein is available commercially from several sources, including Freeman Industries LLC, Tuckahoe, New York USA; among the commercial zein products sold by this company are those designated Zein F4000, Zein 4400, Zein F6000, Zein G-10, Aqua Zein, and Aqua Zein Neutral.

A presently preferred zein for the present invention is the Zein F6000, which has been re-extracted to reduce its color (from xanthophyll) level. Zein F6000 is a very light yellow granular powder with an approximate molecular weight of 35,000 and a bulk density of 0.125-0.21 g/ml. It contains 90-96% zein protein, calculated on a dry basis.

The hydrocolloid can also be formed from a hydroxypropyl methylcellulose. The viscosity of a 2 weight percent aqueous solution of various hydroxypropyl methylcellulose products ranges from about 4,000 mPa·s to about 100,000 mPa·s. In one embodiment, the hydroxypropyl methylcellulose is United States Pharmacopeia Substitution Type 2208, also called hypromellose 2208, with a viscosity of about 15,000 mPa·s, which is commercially available as Methocel K15M. In another embodiment, the hydroxypropyl methylcellulose is United States Pharmacopeia Substitution Type 2910, also known as hypermellose 2910, with a viscosity of about 4,000 mPa·s, which is marketed as Methocel E4M. METHOCEL is a trademark of Dow Chemical Company, Midland, Michigan U.S.A.

Other useful substances for forming a hydrocolloid include, without limitation, crospovidone; croscarmellose sodium; cellulose derivatives such as hydroxyethylcellulose, hydroxypropyl cellulose, or methylcellulose; gums such as seaweed extracts, plant extracts, plant exudates, plant seed extracts, and microbial fermentation products; starches including pregelatinized and modified starches; and synthetics such as carboxyvinyl polymers, including carbopols. Additional specific examples include alginates, pectins, low methoxy pectins, agar, carrageenan, plus arabic, tragacanth, karaya, ghatti, locust bean (carob), guar, dextran, xanthan, carrageenan, tara, Khaya grandfolia, gellan, Konjac mannan, galactomannan, funoran, acetan, welan, rhamsan, furcelleran, succinoglycan, scieroglycan, schizophylan, curdlan, pullulan, karaya and tamarind gums.

In addition to the pharmaceutical active, the core further comprises a disintegrant that, in an aqueous environment, assists in the physical fragmentation of any material with which is it combined. A disintegrant does not promote dissolution or a chemical change in the material being fragmented. The following are examples of useful disintegrants: starches such as potato or tapioca starch, modified starches (such as sodium starch glycolate) and partially pregelatinized starches (such as Starch 1500); polyvinylpyrrolidones, including modified polyvinylpyrrolidones (such as crospovidone, polymerized under conditions that promote crosslinking); celluloses such as microcrystalline cellulose, modified celluloses (such as low substituted hydroxypropyl cellulose, croscarmellose sodium and calcium carboxymethyl cellulose); formaldehyde-casein compounds (such as Esma-Spreng.RTM); resins, such as the polacrilin potassium sold by Rohm and Haas Company, Philadelphia, Pennsylvania U.S.A., using the

trademark AMBERLITE IRP88; defatted soybean extracts; alginic acid; agar-agar; calcium carbonate; calcium phosphate; and sodium carbonate. U.S. Patent 6,696,085 to Rault et al. teaches that acrylic polymers are useful as tablet disintegrants.

In addition to the foregoing, the core can contain any desired components such as binders, lubricants, antioxidants, etc., as are well known in the art and further discussed below.

The pharmaceutical dosage form further comprises an enteric coating surrounding the swellable coating. An "enteric coating" is a coating that is substantially insoluble at the acidic pH conditions of the stomach but is substantially soluble or water-permeable at the higher pH conditions of the intestines. In this invention, the enteric coating protects the swellable coating against contact with the acidic stomach environment but permits contact of the swellable coating with the more alkaline intestinal fluid. The enteric coating can be chosen to provide targeted release to a particular section of the intestine. For instance, an enteric coating can provide delivery to the duodenum (pH > 5.5), to the jejunum (pH 6-7), or to the ileum (pH up to 7.5). Intermediate delivery points can be achieved by combining different coating materials or varying the thickness of the coating. Enteric coating materials include cellulose-based coatings, such as cellulose acetate phthalate and hydroxypropylmethyl cellulose phthalate, methacrylate-based coatings, polyvinyl acetate phthalate-based coatings, and shellac-based coatings.

In the present invention, methacrylate-based coatings are preferred and several useful products are commercially available from Röhm GmbH & Co., Darmstadt, Germany under the trademark EUDRAGIT. Eudragit L100-55 is especially preferred. Eudragit L 100-55 is a powder, spray-dried Eudragit L 30 D-55 which can be reconstituted. Eudragit L 30 D-55 is an aqueous dispersion of a pH dependent polymer soluble at or above pH 5.5 for targeted delivery in the duodenum. Eudragit L 100-55 retains the pH dependency of Eudragit L 30 D-55 and thus, is soluble at or above pH 5.5 and provides delivery to the duodenum. Eudragit L 100-55 and Eudragit L 30 D-55 are copolymers of methacrylic acid and ethyl acrylate in a 1:1 ratio. They have the molecular formula: $(C_5H_2O_2 \cdot C_4H_6O_2)_x$ and have been assigned the Chemical Abstracts Registry No.

25212-88-8. Eudragit L100-55 also meets the United States Pharmacopeia specificiation for Methacrylic Acid Copolymer Type C.

In one embodiment, the enteric coating comprises 1-40%, 3-35%, 5-30%, 6-20%, or 7-10% or 8% of the total composition. In another embodiment, the enteric coating comprises at most 20%, at most 17.5%, at most 15%, at most 12.5%, at most 10%, at most 9%, at most 8%, at most 7%, at most 6%, at most 5%, or at most 4% of the total composition.

Optionally, an excipient that modulates the release of the pharmaceutical active is added to the swellable coating. Modulation may be achieved by facilitating or impeding the access of water to the core. Useful excipients include plasticizers such as lactic acid, lactic acid acetamide, glycerin, glyceryl monostearate, triacetin, sorbitol, triethyl citrate, polyvinylpyrrolidone, triethylene glycol, tricresyl phosphate, dibutyl tartrate, ethylene glycol monooleate, palmitic acid, stearic acid, oleic acid, dibutyl sebacate, aceylated monoglycerides, and other oils and waxes, as well as polyethylene glycol 300, 400, 600, 1450, 3350 and 8000. Additional excipients that modulate the rate of release of the active include water soluble surfactants, such as sodium lauryl sulfate and docusate sodium, and enteric coating materials, such as Eudragit L 100-55, which are mixed into the swellable coating.

Without being limited to any single theory of operation, it is believed that enteric coating material incorporated in the swellable coating dissolves upon contact with the intestinal fluid and forms channels in the swellable coating, which facilitate the entry of the intestinal fluids into the core. In one embodiment, the enteric coating material constitutes about 0.1-30%, 0.5-20%, 1-17.5%, preferably 5-15%, or more preferably 5-10% of the swellable coating. In another embodiment, the enteric coating material comprises 10-50%, 15-40%, preferably 20-30% of the swellable coating.

Again, without being limited to any theory, it is postulated that the water soluble surfactant causes rapid wetting of the swellable coating upon exposure to the intestinal fluids, thereby assisting entry of fluid into the core. When the water soluble surfactant is present, it constitutes about 0.001-30%, 0.005-20%, 0.01-10%, 0.03-8%, 0.05-6%, 0.07-4%, 0.09-2%, or 0.1-1% by weight of the swellable coating. A preferred range is 0.01-10%.

For instance, where zein is present in the swellable coating, the extent of the swelling controls its permeability and the greatest permeation is achieved at the largest swelling volume. See Y. K. Oh et al., "Swelling and Permeability Characteristics of Zein Membranes," *PDA Journal of Pharmaceutical Science and Technology*, Vol. 57, pages 208-217 (2003) for additional information concerning diffusion through hydrated zein films.

The addition of plasticizers to zein affects its permeability to water. The combination of zein with hygroscopic plasticizers such as glycerol, triethyelene glycol, and levulinic acid produces more water absorption than in unplasticized zein. However, incorporating into zein hydrophobic plasticizers such as dibutyl tartrate and oleic acid results in less water absorption than unplasticized zein. The greater the degree of water permeation, the weaker the tensile strength and the coating can simply give way to provide full release of the pharmaceutical active. See J. W. Lawton, "Plasticizers for Zein: Their Effect on Tensile Properties and Water Absorption of Zein Films," *Cereal Chemistry*, Vol. 81, pages 1-5 (2004) for a discussion of the water absorption characteristics of cast plasticized zein films.

The modulation of the release profile of the pharmaceutical active by an excipient, such as a plasticizer, is not limited to zein. In general, varying the amount and type of plasticizer affects the tensile strength of coatings. The use of hygroscopic versus hydrophobic excipients also affects the release profile in the same manner as discussed regarding zein.

To form the cores of the invention, the pharmaceutical active is blended with one or more pharmaceutically acceptable carriers, such as water, saline, sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starch, lactose, sucrose, glucose, mannitol, or silicic acid; binders, such as carboxymethylcellulose, alginates, gelatin, copolyvidonum (such as the PLASDONE™ S-630 copolymer of N-vinyl-2-pyrrolidone and vinyl acetate, sold by International Specialty Products, Wayne, New Jersey U.S.A,), copolymers of ethylene oxide and propylene oxide such as Poloxamer 407, sucrose, or acacia; humectants, such as glycerol; disintegrants, such as starch, polyvinyl pyrrolidones, celluloses, formaldehyde-casein compounds, defatted soybean extracts, alginic acid, agar-agar, calcium carbonate, calcium phosphate, potato or tapioca starch or sodium carbonate; lubricants such as talc, calcium stearate,

magnesium stearate or solid polyethylene glycol; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as cetyl alcohol and glycerol monostearate; surfactants, such as sodium lauryl sulfate or docusate sodium; absorbents, such as kaolin or bentonite clay; and stabilizing agents. The pharmaceutical active may also be blended with buffering agents such as alkali metal carbonates and alkaline earth metal oxides. This listing is not exhaustive, many other functional components that are known in the art will also be useful in the present invention.

The cores of the invention may be in the form of tablets, minitablets, granules, particulates or pellets. The tablets and minitablets can be manufactured by direct compression or any other process known to those of skill in the art. Dry granulation, wet granulation, melt granulation, or any other process known to those of skill in the art may be used to form granules. The particulates and pellets may be manufactured by any method known to those of skill in the art, such as extrusion or spheronization. Pellets may also be made by melt pelletization or by coating non-pareil seeds. Wet cores are dried by conventional drying procedures such as air drying, or drying under heated and/or low pressure conditions.

The cores of invention are coated with a swellable coating, followed by the application of an outer enteric coating. In general, coatings may be applied by any techniques known in the art, such as pan coating (including perforated closed system pan coating), coacervation, or fluidized bed coating. The fluidized bed may contain a rotor insert and/or a Wurster column insert. The coatings can be generally classified according to their polymer base, such as: cellulose-based, including cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxypropylethyl cellulose, ethyl cellulose, methyl cellulose, microcrystalline cellulose; carrageenan; methacrylate- or methacrylic acid-based, such as methacrylic acid, methacrylate, acrylate, methacrylate, ethacrylate, methylmethacrylate, or copolymers thereof; or polyvinyl acetate phthalate-based. Typically, the polymer is combined with a solvent, such as water, and a plasticizer, such as polyethylene glycol, lactic acid, lactic acid, acetamide, glycerin, glyceryl monostearate, triacetin, sorbitol, triethyl citrate, polyvinylpyrrolidone, triethylene glycol, tricresyl phosphate, dibutyl tartrate, ethylene glycol monooleate, palmitic acid, stearic acid, oleic acid, or dibutyl sebacate. Optionally, one may also add any of the following elements:

an anti-tack agent, an anti-foam agent, a filler, a surfactant, a colorant, a flavoring agent, and combinations of any two or more thereof.

Following application of the enteric coating, the pharmaceutical composition may have identifying information printed thereon using inks and procedures known in the art, such as offset gravure printing. Pharmaceutically acceptable inks that may be used with offset gravure printing include Markem™ 2200, 2202, 2212 and 2222, from Markem Corporation, Keene, New Hampshire USA. These inks are typically shellac-based and contain pigments. Thinners may be added to any of these inks to increase or decrease the drying rate and/or modify the viscosity. Following application, these inks are normally air dried. Other pharmaceutically acceptable inks include those products sold as Opacode™ and Opacode™ WB, both of which contain pigments, titanium dioxide, and a solvent and are sold by Colorcon, West Point, Pennsylvania USA. Many other printing inks are known to those skilled in the art, and any of these will be useful for the dosage forms of the invention.

Optionally, the enteric-coated dosage forms can be further coated with a thin film. Frequently, the film will be colored to facilitate product identification and for esthetic purposes; in this instance, any desired printing of information will be done after the film coating has been applied. Many suitable film coating products are commercially available, including those sold by Colorcon, West Point, Pennsylvania USA using the OPADRY and OPAGLOS trademarks. These products from Colorcon are dry powders, containing a polymer, plasticizer, and pigment, that are mixed with water or a solvent such as alcohol, and sprayed onto tablets or other solid dosage forms. This film coating procedure, and alternative film coating products, are well known in the art.

The coated tablets, pellets, granules, or particulates may be encased in capsules for ease of administration. The encasement may be accomplished by any method known in the art, such as filling a pre-formed capsule. Such capsules may be comprised of gelatin or any other material known to those of skill in the art.

Without being limited to any theory, it is postulated that after an enteric coating dissolves in the intestine, the swellable coating imbibes intestinal fluids and expands outwardly. Thus, initially, the swellable coating expands like a balloon being inflated and does not burst. As the coating swells, its permeability

to water increases. It is hypothesized that the swellable coating contains microchannels, through which water enters by diffusion and reaches the core. The water causes the core to begin to fragment. Some of these fragments can puncture the swellable coating, leading to the ingress of more water. The additional water produces even more fragmentation of the core, which is thought to cause more fragments to puncture the swellable coating. This cycle is believed to continue until the pharmaceutical active is fully released or until the swellable coating is so weakened by the imbibition that the coating ruptures.

Further without being limited to any theory, it is believed that the release of the active may be modulated by several factors other than the presence of an enteric coating. One such factor is the selection of a hydrocolloid-forming substance in the swellable coating. Hydrocolloids vary in their swelling ability and hence their permeability to intestinal fluid. The permeability of the hydrocolloid is postulated to affect the hydration rate of the core and the resultant fragmentation of the core. Hydrocolloids also differ in tensile strength, which is thought to affect the percentage of core fragments that are able to puncture the swellable coating upon fragmentation. The number of fragments that are able to achieve egress directly affects the release of the pharmaceutical active. It is also believed that the number of openings created in the swellable coating further affects the release of the active by permitting more intestinal fluid into the core, producing more fragmentation. Tensile strength additionally affects whether and when a swellable coating ruptures due to the weakening caused by the imbibition of water, resulting in complete release of the active. Furthermore, some hydrocolloids erode upon swelling, which affects the ease with which core fragments are able to puncture the swellable coating.

Another factor can be the optional addition of an excipient to the swellable coating that modulates the release of the pharmaceutical active. Such agents can increase or decrease the permeability of the hydrocolloid to the intestinal fluid. This permeability affects the amount of intestinal fluid that contacts the core and leads to fragmentation. It is hypothesized that the fragments puncture the swellable coating upon fragmentation, thereby affecting the release of the pharmaceutical active. It is further believed that the openings created in the swellable coating provide conduits for the entry of additional intestinal fluid into the core, further accelerating fragmentation.

A third factor is the use of a disintegrant in the core. The employment of a disintegrant increases the rate of fragmentation of the core, which is thought to raise the frequency with which fragments create voids in the swellable coating. The sheer increase in fragments exiting through the swellable coating raises the rate of release of the pharmaceutical active. Additionally, the higher number of voids created in the swellable coating is believed to allow more water to enter the core, causing an even greater fragmentation of the active. Furthermore, the disintegrant may augment the force at which the core fragments impact the swellable coating, which may result in more fragments successfully creating voids in the swellable coating. These more forceful disintegrations further raise the rate of release of the pharmaceutical active by allowing a greater number of core fragments to pass through the swellable coating. Such disintegrants also produce additional openings for the intestinal fluid to hydrate and fragment the active, leading to additional release of the active

Although the rate of release of the pharmaceutical active can be modulated as set forth above, this invention does not have an objective of producing sustained release formulations whereby the pharmaceutical active is released at a controlled rate over an extended period of time, such as 12 or 24 hours. Rather, a feature of this invention is a delayed release of ingested pharmaceutical active until the dosage form has reached the intestinal tract, where the alkaline pH conditions will not affect an acid-sensitive pharmaceutical active, then facilitation of a rapid, essentially complete release of the pharmaceutical active for systemic absorption.

The following examples are provided to aid in understanding the invention, and are not intended, and should not be construed, to limit in any manner the invention as defined in the appended claims. In the examples, ingredients that are volatile during drying and therefore not present in the final product are not included in the tabular listings of ingredients; such ingredients, however, are mentioned as solvents, etc. in the preparation procedure discussions. Further, the weight added by printing information on a finished dosage form is insignificant and therefore is not included in the final cumulative weights. Percentages are expressed on a weight basis, unless the context clearly indicates otherwise.

EXAMPLE 1

Tablets containing either 20 or 40 mg of pantoprazole were prepared using the following components and procedure:

Ingredients	Quantity (mg) per 20 mg Tablet	Quantity (mg) per 40 mg Tablet
Core Tablet		
Dry Mixing		
Pantoprazole sodium	22.55	45.1
Mannitol (Pearlitol SD-200)	110.95	221.9
Crospovidone	8.25	16.5
Sodium carbonate	3.75	7.5
Granulation		
Sodium carbonate anhydrous	3.75	7.5
Hydroxypropyl cellulose (Klucel LF)	4	8
Lubrication		
Crospovidone	8.25	16.5
Talc	1.5	3
Calcium stearate	2	4
Total	165	330
Swellable Coating		
Zein F6000	2.07	4.13
Methacrylic acid copolymer (Eudragit L 100-55)	0.41	0.82
Cum. Total	167.48	334.95
Enteric Coating		
Methacrylic acid copolymer (Eudragit L 100-55)	9.25	18.49
Triethyl citrate	0.93	1.85
Titanium dioxide	1.83	3.65
Talc	1.41	2.81
Cum. Total	180.83	361.65
Film Coating		
Opadry Yellow OY-52945	4.52	9.04
Cum. Total	185.42	370.79
Printing		
Opacode Black S-1-8152 HV	q.s.	q.s.

Tablet cores were prepared by granulating a dry mix of pantoprazole sodium, mannitol, crospovidone and sodium carbonate with an aqueous solution of hydroxypropyl cellulose (Klucel LF) and sodium carbonate anhydrous. The granulates were dried using conventional drying techniques. The dried granules were then lubricated with crospovidone, talc and calcium stearate. The lubricated

granules were compressed into cores. The cores were subcoated with a mixture of zein, Eudragit L 100-55, water, and isopropyl alcohol, and dried. Enteric coating on top of the subcoat was performed using Eudragit L 100-55 with isopropyl alcohol as the solvent and triethyl citrate as the plasticizer. Talc and titanium dioxide were used as the lubricant and the opaquent, respectively. After drying, the enteric coated tablet was film-coated using Opadry Yellow OY-52945 and printed with Opacode Black S-1-8152 HV.

EXAMPLE 2

Tablets containing either 20 or 40 mg of pantoprazole were prepared using the following components and procedure.

Ingredients	Quantity (mg) per 20 mg Tablet	Quantity (mg) per 40 mg Tablet
Core Tablet		
Dry Mixing		
Pantoprazole potassium	22.55	45.1
Mannitol (Pearlitol SD-200)	110.95	221.9
Crospovidone	8.25	16.5
Sodium carbonate	3.75	7.5
Granulation		
Sodium carbonate anhydrous	3.75	7.5
Hydroxypropyl cellulose (Klucel LF)	4	8
Lubrication		
Crospovidone	8.25	16.5
Talc	1.5	3
Calcium stearate	2	4
Total	165	330
Swellable Coating		
Zein F6000	2.07	4.13
Methacrylic acid copolymer (Eudragit L 100-55)	0.41	0.82
Cum. Total	167.48	334.95
Enteric Coating		
Methacrylic acid copolymer (Eudragit L 100-55)	9.25	18.49
Triethyl citrate	0.93	1.85
Titanium dioxide	1.83	3.65
Talc	1.41	2.81
Cum. Total	180.83	361.65
Film Coating		
Opadry Yellow OY-52945	4.52	9.04
Cum. Total	185.42	370.79

Printing		
Opacode Black S-1-8152 HV	q.s.	q.s.

Tablet cores were prepared by granulating a dry mix of pantoprazole sodium, mannitol, crospovidone and sodium carbonate with an aqueous solution of hydroxypropyl cellulose (Klucel LF) and sodium carbonate anhydrous. The granulates were dried using conventional drying techniques. The dried granules were lubricated with crospovidone, talc and calcium stearate. The lubricated granules were then compressed into cores. The cores were subcoated with a mixture of zein, Eudragit L 100-55, water, and isopropyl alcohol. After drying, an enteric coating on top of the subcoat was performed using Eudragit L 100-55 with isopropyl alcohol as the solvent and triethyl citrate as the plasticizer. Talc and titanium dioxide were used as the lubricant and the opaquent, respectively. Then, the dried enteric coated tablet was film-coated using Opadry Yellow OY-52945 and printed upon with Opacode Black S-1-8152 HV.

EXAMPLE 3

Capsules containing 40 mg of omeprazole were prepared using the following components and procedure:

Ingredients	Quantity/Capsule (mg)
Core Pellets	
Omeprazole	40
Mannitol	236
Crospovidone	18
Hydroxypropyl methylcellulose, 5 cps	8
Poloxamer 407	5
Meglumine	3
Total	310
Swellable Coating	
Zein F 6000	6.2
Cum. Total	316.2
Enteric Coating	
Hydroxypropyl methylcellulose phthalate (HP 55)	63.24
Triethyl citrate	6.31
Talc	9.45
Cum. Total	395.25

Omeprazole core pellets were prepared by mixing omeprazole, mannitol, crospovidone, meglumine and polaxomer and granulating this mixture with hydroxypropyl methylcellulose as a binder. The granules thus obtained were subjected to extrusion and spheronization to produce spherical pellets. The pellets were then dried by conventional drying techniques. The pellets were coated with a swellable coating containing zein and sodium lauryl sulphate dissolved in a mixture of isopropyl alcohol and water, then dried. The enteric coat was prepared by dissolving hydroxypropyl methylcellulose phthalate and triethyl citrate in a mixture of isopropyl alcohol and acetone and dispersing talc in this solution, which was then layered upon the intermediate coating.

The coated pellets were measured into a gelatin capsule.

EXAMPLE 4

Tablets containing 40 mg of omeprazole were prepared using the following ingredients and procedure:

Ingredients	Quantity/Tablet (mg)
Core Tablet	
Omeprazole	40
Mannitol (Pearlitol SD-200)	231.3
Crospovidone	6
Meglumine	3
Poloxamer 407	5
Hydroxypropyl methylcellulose, 5 mPa·s	8
Magnesium stearate	3.8
Talc	3
Total	300
Swellable Coating	
Zein F 6000	2.73
Sodium lauryl sulphate	0.27
Cum. Total	303
Enteric Coating	
Hydroxypropyl methylcellulose phthalate (HP 55)	24
Triethyl citrate	2.4
Talc	3.6
Cum. Total	333

Omeprazole core tablets were prepared by mixing omeprazole, mannitol, crospovidone, meglumine and poloxmer and granulating the mixture with hydroxypropyl methylcellulose as a binder. The granules were dried in fluid bed drier and the dried granules were compressed into tablets or minitablets. These core tablets or minitablets were coated with intermediate coating solution containing zein and sodium lauryl sulphate dissolved in a mixture of isopropyl alcohol and water, then dried. The enteric coat was prepared by dissolving hydroxypropyl methylcellulose phthalate and triethyl citrate in a mixture of isopropyl alcohol and acetone and dispersing talc in this solution, which was then layered upon intermediate coating.

EXAMPLE 5

Tablets containing 40 mg of pantoprazole were prepared using the following components and procedure:

Ingredients	Quantity/Tablet (mg)
Core Tablet	
Pantoprazole sodium sesquihydrate	45
Mannitol (Pearlitol SD-200)	143.18
Mannitol (Pearlitol DC-400)	47.72
Crospovidone	16.5
Plasdone S-630	30
Sodium lauryl sulfate	2.5
Meglumine	3
Calcium stearate	6
Talc	6
Total	300
Swellable Coating	
Zein	4.5
Cum. Total	304.5
Enteric Coating	
Methacrylic acid copolymer (Eudragit L100-55)	16.81
Triethyl citrate	1.68
Titanium dioxide	3.39
Talc	2.51
Cum. Total	328.89

Core tablets were prepared by blending pantoprazole sodium sesquihydrate with mannitol, crospovidone, Plasdone S630, talc, and magnesium

stearate, and direct compressing into tablets. These core tablets were coated with a swellable coating solution containing zein and sodium lauryl sulphate dissolved in a mixture of isopropyl alcohol and water, then dried. The enteric coat was prepared by dissolving hydroxypropyl methylcellulose phthalate and triethyl citrate in a mixture of isopropyl alcohol and acetone and dispersing talc in this solution, which was then layered upon intermediate coating.

EXAMPLE 6

Capsules containing esomeprazole were prepared using the following components and procedure:

Ingredients	Quantity (g)
Pellets	
Esomeprazole magnesium trihydrate	178
Mannitol	938
Crospovidone	72
Sodium lauryl sulphate	20
Copovidone	32
Total	1240
Swellable Coating	
Zein	16.2
Sodium lauryl sulphate	1.62
Cum. Total	1257.82
Enteric Coating	
Methacrylic acid copolymer Type C	110
Triethyl citrate	11
Titanium dioxide	15.29
Talc	16.5
Cum. Total	1410.61

The core was prepared by mixing esomeprazole magnesium trihydrate, mannitol, crospovidone and sodium lauryl sulphate and granulating this mixture with an aqueous solution of copovidone. The granules were then subjected to extrusion and spheronization to obtain spherical pellets. The pellets were dried by conventional drying techniques. The dried pellets were coated with intermediate coating solution containing zein and sodium lauryl sulphate dissolved in a mixture of isopropyl alcohol and water, then dried. The enteric coat was prepared by dissolving Methacrylic Acid Copolymer Type C and triethyl citrate in isopropyl alcohol and dispersing talc and titanium dioxide in this solution.

Coated pellets are filled into gelatin capsules, giving 4000 capsules that each contain 40 mg of esomeprazole.

EXAMPLE 7

Esomeprazole tablets were prepared, using the following ingredients and procedure.

Ingredients	Quantity (mg/tablet)
Core Tablet	
Esomeprazole magnesium trihydrate	44.5
Magnesium oxide	20
Plasdone S-630	17.5
Crospovidone	10
Mannitol (Pearlitol SD 200)	227
Colloidal silicon dioxide	3.5
Sodium stearyl fumarate	17.5
Total	340
Swellable Coating	
Zein F6000	6.8
Cum. Total	346.8
Enteric Coating	
Eudragit L100-55	19.1
Triethyl citrate	1.9
Titanium dioxide	3.8
Talc	2.9
Cum. Total	374.5

Esomeprazole magnesium trihydrate, magnesium oxide, copovidone, crospovidone, mannitol, and silicon dioxide were blended, then sodium stearyl fumarate was added with further blending. This mixture was compressed into core tablets. The tablets were coated with an aqueous alcohol solution of zein, then dried. Finally, the enteric coating ingredients were dispersed in water and coated onto the zein-coated tablets, followed by a final drying.

EXAMPLE 8

Tablets containing rabeprazole sodium were prepared using the following components and procedure:

Ingredients	Quantity/Tablet (mg)
Core Tablet	
Rabeprazole sodium	20
Mannitol (Pearlitol SD 200)	97.2
Mannitol (Pearlitol DC 400)	28
Meglumine	5.1
Crospovidone	3.4
Plasdone S-630	10.5
Talc	3.4
Magnesium stearate	2.4
Total	170
Swellable Coating	
Zein F6000	4.25
Triethyl citrate	0.2
Cum. Total	174.45
Enteric Coating	
Methacrylic acid copolymer (Eudragit L 100-55)	12.26
Triethyl citrate	1.224
Talc	0.68
Cum. Total	188.614

Rabeprazole sodium, crospovidone, Plasdone S630 and mannitol (Pearlitol SD 200) were mixed with mannitol (Pearlitol DC 400) for 20 minutes. Talc and magnesium stearate were then added to the mixture and mixed for 5 minutes. This lubricated blend was then compressed into tablets. The core tablets were subcoated with a water-alcohol solution of zein (weight increase 2.5±0.5%) and dried. The subcoated tablets were coated with enteric coating solution (weight increase 8-9%).

EXAMPLE 9

Rabeprazole sodium tablets were prepared using the following components and procedure:

Ingredients	Quantity/Tablet (mg)
Core Tablet	
Rabeprazole sodium	20
Mannitol (Pearlitol SD-200)	97.01
Low substituted hydroxypropyl cellulose, LH21 ("L-HPC")	14.4
Magnesium oxide	40
Sodium lauryl sulfate	1.8

Hydroxypropyl methylcellulose, 5 mPa·s	3
Talc	1.54
Magnesium stearate	2.25
Total	180
Swellable Coating	
Zein 6000	4.9
Triethyl citrate	0.49
Cum. Total	185.39
Enteric Coating	
Eudragit L100-55	14.46
Triethyl citrate	1.44
Talc	0.79
Cum. Total	202.08
Film Coating	
Opadry Yellow OY-52945	5.05
Cum. Total	207.13
Printing	
Opacode Black	q.s.

Magnesium oxide was sifted through a 60 mesh sieve. Rabeprazole sodium, L-HPC, mannitol (SD 200) and the sifted magnesium oxide were sifted through a 40 mesh sieve. The materials were then mixed for 30 minutes in a Rapid mixer granulator. Sodium lauryl sulfate (SLS) was dissolved in purified water and hydroxypropylmethylcellulose (HPMC) was dissolved in warm purified water. The rabeprazole sodium mixture was mixed with the SLS and HPMC solutions. The wet mass was dried in a fluid bed drier and the dried granules were sifted through a 20 mesh sieve. The sifted granules were blended with L-HPC in a double cone blender for 5 minutes. Magnesium stearate (sifted through a 60 mesh sieve) was added to the blend and mixed for 5 minutes. The lubricated blend was then compressed into core tablets. The core tablets were coated with a water-alcohol zein coating solution (weight increase 2.5 ± 0.5%) and dried. The coated tablets were further coated with enteric coating solution (weight increase 8.0 ± 1.0%). The enteric coated tablets were additionally coated with Opadry solution until the weight increase was 2.0 ± 0.5%. Then, the film coated tablets were imprinted with Opacode black ink.

EXAMPLE 10

Pantoprazole sodium tablets, prepared according to Example 5, were tested according to Method 724 "Drug Release" of *The United States*

Pharmacopeia 24, United States Pharmacopeial Convention, Inc., Rockville, Maryland U.S.A., pp. 1944-1947, 2000, using Method B and Apparatus 1 (described in Method 711 "Dissolution," on page 1942). A tablet was first immersed in 0.1 N hydrochloric acid, with stirring, for two hours at 37°C. The tablet was then immersed in the pH 6.8 phosphate buffer, with stirring, and samples of the buffer solution were taken at intervals for analysis to determine the amount of drug released from the tablet.

Following are the data obtained from testing six tablets. The amount of drug released into the acid is not shown, but was small. In general, release of up to 10% of the drug into the acid is considered acceptable for enteric coated dosage forms. For purposes of this invention, a pharmaceutical active is considered to be substantially retained within the dosage form if less than about ten percent by weight is released into 0.1 N hydrochloric acid, under the conditions of the USP test.

Time (min.)	Percent Drug Released						
	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean
0	0	0	0	0	0	0	0
15	29	18	22	21	18	17	21
30	61	62	65	57	55	58	60
45	82	86	84	84	81	79	83
60	92	94	91	92	89	88	91

These results show that the drug was substantially completely released within sixty minutes at pH 6.8.

EXAMPLE 11

As in Example 10, tablets of rabeprazole sodium prepared according to Example 9 were tested by USP Drug Release Method 724. However, the alkaline solution for the second part of the test was a phosphate buffer adjusted to pH 8.0

and also containing 0.5 weight percent of sodium lauryl sulfate. Results were obtained, as follows.

Time (min.)	Percent Drug Released						
	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5	Tablet 6	Mean
0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0
30	18	37	12	43	0	28	23
45	82	94	74	94	93	92	88
60	91	91	92	90	92	92	91

These results show that the drug was substantially completely released within sixty minutes at pH 6.8.

EXAMPLE 12

Esomeprazole tablets were prepared using the following ingredients and the procedure described below.

Ingredients	Quantity/Tablet (mg)
Core Tablet	
Esomeprazole magnesium trihydrate	44.5
Magnesium oxide	20
Plasdone S-630	17.5
Mannitol (Pearlitol SD 200)	237
Colloidal silicon dioxide	3.5
Sodium stearyl fumarate	17.5
Total	340
Swellable Coating	
Zein F6000	6.8
Cum. total	346.8

Esomeprazole magnesium trihydrate, magnesium oxide, Plasdone S-630, silicon dioxide, and mannitol were sieved and blended, then sodium stearyl fumarate was added and the mixture blended, and finally tablets were formed by direct compression of the mixture. Zein was dissolved in aqueous alcohol and coated onto the tablets. The coated tablets were then dried.

Additional tablets were similarly prepared, further including either 7 mg or 10 mg of the disintegrant ingredient crospovidone in the core composition, with corresponding decreases in the amount of mannitol to maintain constant tablet weights. The tablets were tested for dissolution characteristics at pH 6.8, using the procedure of Example 10 (except that the acid contact step was omitted) and giving the following results.

Time (min.)	Percent Drug Released		
	No Disintegrant	7 mg Disintegrant	10 mg Disintegrant
15	0	0	61
30	0	1	80
45	0	3	86
60	0	6	89
90	0	-	88
120	1	-	-

For this particular formulation, 10 mg of disintegrant produced the desired rapid release of drug at pH 6.8. However, other formulations could exhibit the desired drug release with different disintegrant concentrations, depending on the identity of the various formulation components, the physical methods used to prepare cores (such as compression pressure for tablets), and the presence of additional coatings. Therefore, each proposed formulation should be tested using varying amounts of the selected disintegrant components, to identify the exact formulation that gives desired drug release characteristics.

CLAIMS:

1. A pharmaceutical dosage form comprising:
   a. a solid core comprising a pharmaceutical active and a disintegrant;
   b. a swellable coating comprising a prolamine surrounding the core; and
   c. an enteric coating surrounding the swellable coating.

2. The pharmaceutical dosage form of claim 1, wherein the core is a tablet.

3. The pharmaceutical dosage form of claim 1, comprising multiple coated cores contained in a capsule.

4. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical active is unstable in the presence of acid.

5. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical active is reactive with a component of the enteric coating.

6. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical active comprises a benzimidazole.

7. The pharmaceutical dosage form of claim 6, wherein the benzimidazole is one or more members selected from the group consisting of omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

8. The pharmaceutical dosage form of claim 1, wherein the disintegrant comprises one or more members selected from the group consisting of: starches; polyvinyl pyrrolidones; formaldehyde-casein compounds; resins; defatted soybean

extracts; alginic acid; agar-agar; calcium carbonate; calcium phosphate; sodium carbonate; and acrylic polymers.

9. The pharmaceutical dosage form of claim 1, wherein the swellable coating further comprises one or more hydrocolloid-forming members selected from the group consisting of: vinylpyrrolidone polymers; cellulose derivatives; starches; carboxyvinyl polymers; alginates; pectins; agar; and gums.

10. The pharmaceutical dosage form of claim 1, wherein the swellable coating comprises zein.

11. The pharmaceutical dosage form of claim 1, wherein the swellable coating further comprises a hydroxypropylmethyl cellulose.

12. The pharmaceutical dosage form of claim 1, wherein the swellable coating comprises an excipient that modulates release of pharmaceutical active from the core upon hydration.

13. The pharmaceutical dosage form of claim 12, wherein the excipient comprises one or more members selected from the group consisting of: plasticizers; water soluble surfactants; and enteric coating materials.

14. The pharmaceutical dosage form of claim 1, wherein the enteric coating comprises a component that is cellulose-based, methacrylate-based, polyvinyl acetate phthalate-based, or shellac-based.

15. The pharmaceutical dosage form of claim 1, wherein the enteric coating comprises a copolymer of methacrylic acid and ethyl acrylate.

16. The pharmaceutical dosage form of claim 1, wherein the core comprises at least about 50 percent of the weight of the dosage form.

17. The pharmaceutical dosage form of claim 1, wherein the swellable coating comprises about 0.1 to 10 percent of the weight of the dosage form.

18. The pharmaceutical dosage form of claim 1, wherein the enteric coating comprises about 0.1 to 30 percent of the weight of the dosage form.

19. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical active is substantially retained in the dosage form while the dosage form is present in the stomach, but is rapidly released after the dosage form enters a digestive system environment having a pH value at least about 5.

20. A pharmaceutical dosage form comprising:

a. a solid core comprising an acid-sensitive pharmaceutical active and a disintegrant;

b. a swellable coating comprising a prolamine, surrounding the core; and

c. an enteric coating surrounding the swellable coating.

21. The pharmaceutical dosage form of claim 20, wherein the acid-sensitive pharmaceutical active comprises a benzimidazole.

22. The pharmaceutical dosage form of claim 20, wherein the disintegrant comprises one or more members selected from the group consisting of: starches; polyvinyl pyrrolidones; formaldehyde-casein compounds; resins; defatted soybean extracts; alginic acid; agar-agar; calcium carbonate; calcium phosphate; sodium carbonate; and acrylic polymers.

23. The pharmaceutical dosage form of claim 20, wherein the hydrocolloid-forming component further comprises one or more members selected from the group consisting of: vinyl pyrrolidone polymers; cellulose derivatives; starches; carboxyvinyl polymers; alginates; pectins; agar; and gums.

24. The pharmaceutical dosage form of claim 20, wherein the enteric coating comprises a component that is cellulose-based, methacrylate-based, polyvinyl acetate phthalate-based, or shellac-based.

25. The pharmaceutical dosage form of claim 20, wherein the enteric coating comprises a copolymer of methacrylic acid and ethyl acrylate.

26. A pharmaceutical dosage form comprising:

a. a solid core comprising a benzimidazole and a disintegrant;

b. a swellable coating comprising a prolamine, surrounding the core; and

c. an enteric coating comprising a copolymer of methacrylic acid and ethyl acrylate, surrounding the swellable coating.

27. The pharmaceutical dosage form of claim 26, wherein the disintegrant comprises one or more members selected from the group consisting of: starches; polyvinyl pyrrolidones; formaldehyde-casein compounds; resins; defatted soybean extracts; alginic acid; agar-agar; calcium carbonate; calcium phosphate; sodium carbonate; and acrylic polymers.

28. The pharmaceutical dosage form of claim 26, wherein the swellable coating comprises zein.

29. The pharmaceutical dosage form of claim 26, wherein the swellable coating further comprises crospovidone.

30. The pharmaceutical dosage form of claim 26, wherein the swellable coating further comprises a hydroxypropyl cellulose.

31. A method of preparing a pharmaceutical dosage form, comprising the steps of:

a. combining components comprising a pharmaceutical active and a disintegrant, and forming a solid core;

b. coating the core with a swellable coating comprising a prolamine; and

c. applying an outer coating comprising an acid-resistant enteric substance.

32. The method of claim 31, wherein the solid core is formed as a tablet.

33. The method of claim 31, further comprising the step of filling multiple coated cores into a capsule.