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[54] **CONTROLLED RELEASE DRUG DELIVERY DEVICE**

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[63] Continuation of Ser. No. 165,437, Dec. 10, 1993, abandoned, which is a continuation-in-part of Ser. No. 52,435, Apr. 23, 1993, abandoned.

[51] **Int. Cl.**[6] **A61K 9/24**

[52] **U.S. Cl.** **424/473**; 424/468

[58] **Field of Search** 424/473, 468

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[57] **ABSTRACT**

A drug delivery device for delivering a drug either intermittently or to a pre-selected region of the gastro-intestinal tract, particularly to the colon, consists of an a solid core comprising an active agent coated with a delay jacket, then coated with a semi-permeable membrane which is optionally drilled to provide a release orifice, and then optionally further coated with an enteric material. The device delivers substantially all of the active agent to the targeted site.

23 Claims, No Drawings

CONTROLLED RELEASE DRUG DELIVERY DEVICE

This is a Continuation of Ser. No. 08/165,437, filed Dec. 10, 1993, now abandoned, which is a Continuation In Part of Ser. No. 08/052,435, filed on Apr. 23, 1993, now abandoned.

FIELD OF THE INVENTION

The present invention relates to tablets which are time-controlled to release active agent intermittently or at a pre-selected region of the gastro-intestinal tract, specifically the colon.

BACKGROUND OF THE INVENTION

Parametric drug delivery refers to drug release in synchrony with its temporal requirements or optimal absorption site, thereby maximizing therapeutic effect while simultaneously minimizing side-effects or in vivo degradation. An example of parametric drug delivery is delivery of a drag to a pre-selected region of the gastro-intestinal tract, such as the colon. Another example is delivery of a drug intermittently at pre-selected times such that the patient receives the drug when needed.

Delivery of a beneficial drug in the colon has been the goal of various research projects in the pharmaceutical industry. The reasons for this are multi-fold. To begin with, many drugs are rendered ineffective by the enzymes present in the fluids of the upper gastro-intestinal tract, particularly protein or peptide-like drugs. In addition, some drugs are more readily or more predictably absorbed by the colonic tissue than by that in the upper gastro-intestinal tract.

Delivery of a beneficial drug in the colon is also therapeutically indicated to treat diseased colonic tissue. In such circumstances, the drug should not be absorbed prior to localization in the colon lest its concentrations be diminished or even depleted prior to reaching the intended site of action. Such treatment would be beneficial for a variety of colonic diseases including inflammatory bowel disease, colitis ulcerosa, enteritis, regionalis Crohn, chronic nonspecific colitis, and diverticulitis.

Prior treatments have been attempted rectally using suppositories and enemas. Rectal administration, while often more effective than oral administration, is limited in that most rectally administrable dosage forms are capable of producing the intended result only in the immediate area, not reaching the upper portions of the colon. This is because the length of the colon reached is volume dependent, usually reaching only as far as the splenic flexure. In addition, rectal administration is messy and inconvenient, as well as not readily acceptable to the general patient population. Furthermore, if the patient suffers from severe inflammation of the rectum, he may experience difficulty with retention enemas.

Thus, an orally administrable dosage form to treat colonic diseases would usually be preferred and is often required. Orally administrable treatments, using tablets, capsules, and the like, have been attempted. However, to reach the colon intact, the dosage form must withstand the rigors of the transit through the gastro-intestinal tract. These rigors include at least a million-fold variation in hydrogen ion concentration, wide variations in osmotic pressure from the surrounding fluids, a variety of enzymes, and a strong mechanical grinding force.

Furthermore, most of these orally administered dosage forms result in delivery of the drug in the upper portion of the gastro-intestinal tract or, in the case of controlled release dosage forms, deliver drug throughout the entire length of the gastro-intestinal tract instead of concentrating delivery primarily within the colon. Thus, in either case, by the time the dosage form reaches the colon, the drug concentration is diminished or even depleted. In addition, the acidic and enzymatic environment of the stomach may inactivate a substantial mount of the drug, particularly protein or peptide-like drugs. Even if the drug is released from the stomach in its active state, such drugs frequently are metabolized or inactivated in the small intestine. Thus, little if any of the drug from these conventional dosage forms is available for producing a therapeutic result in the colon, especially if the dosage form reaches the colon essentially devoid of drug.

Drug delivery to the colon is difficult not only for the above mentioned facts, but also because of the uncertainty of the transit time from oral ingestion to arrival at this pre-selected site. The time of retention within the stomach is most variable, depending both on the size of the dosage form and the mount of food present at the time of ingestion. The drug delivery device may remain within the stomach from about 0.5 to about ten hours. The device then enters the small intestine where retention time is significantly more constant and less dependent upon the mount of food present. It takes from about three to about six hours to travel the length of the small intestine to the beginning of the colon. The device may then remain within the colon from about ten to about fourteen hours in a subject with normal motility.

Thus, the time span necessary to delay release of the drug from an orally administered dosage form until the beginning of the colon is wide. However, the time span can be considerably narrowed by measuring the time from arrival in the small intestine instead of from the time of ingestion. Drug delivery in the stomach may be prevented by the use of an enteric coating which is resistant to the gastric fluids. As such a coating is not soluble in fluids with an acidic pH, such as that of the stomach, application to the outside of the dosage form inhibits release prior to reaching the higher pH of the small intestine. Once the dosage form reaches the small intestine and the enteric coating dissolves, drug release needs to be delayed only an additional three to six hours to result in substantially no active agent being delivered before the colon.

Although some drug may reach the colon passively, conventional peroral dosage forms are not designed to deliver their contents specifically to the colon. Generally, they are formulated to be immediate release devices which disintegrate in the stomach, duodenum, or small intestine, allowing the drug to be immediately exposed to the local environment.

More recently, controlled release dosage forms, for example Orally Releasing Osmotic Systems or OROS® (Alza Corporation), have been developed (U.S. Pat. No. 3,845,770). Although the benefits of controlled release are significant, such as reduction in the number of doses and steady drug levels in the blood, they are generally no more effective than conventional tablets in delivering the active agent primarily to the colon.

Several delivery forms have been developed which attempt to deliver active agent primarily to the colon. These methods rely upon either the environmental conditions surrounding the system, particularly pH, bacterial count and/or time.

Wong, et at. (U.S. Pat. Nos. 4,627,851; 4,693,895; and 4,705,515) disclose a tri-laminated core in which the first

layer is composed of an insoluble, but semi-permeable composition, the second is a microporous combination of water insoluble polymer and osmotic solute, and the third contains an enteric composition. This dosage form has a delayed onset of delivery for a period of about two hours after it exits the stomach, after which only about 50% of the drug is released within twenty-four hours. This drug delivery time scheme is insufficient to insure that the bulk of the drug is delivered to the colon.

Theeuwes, et al. (U.S. Pat. No. 4,904,474) disclose a dosage form which has a two-layered internal compartment with a first layer of the drug in an excipient layer adjacent to an exit passageway and a second layer of a push component. The internal compartment is surrounded by a semi-permeable wall and then an enteric layer. Theeuwes's dosage form results in a delay of the onset of delivery in intestinal fluid for a period of about two hours. This represents a delay period too short, and a delivery rate too slow to insure the bulk of the drug is delivered to the colon.

Ring, et at. (WO 91/07949) disclose a tablet core coated with two laminates. The outer laminate is an erodible acrylic polymer and the inner laminate consists primarily of amylose in the glassy state which can only be degraded in the presence of fecal microflorae.

The instant parametric drug delivery devices can also be used to deliver a drug intermittently at pre-selected times such that the patient receives the drug when needed. This is of particular importance in treating diseases which have symptoms which do not remain constant throughout the day and night.

For example, blood pressure is known to follow a circadian rhythm during a 24-hour period. In some subjects the highest pressure occurs in the morning shortly after the individual awakes, suggesting that it would be appropriate to deliver an antihypertensive agent such as a β-blocker to such a patient sufficiently before awakening so as to mitigate the effects of the disease at the most appropriate time interval. In order to accomplish this without disturbing the patient's sleep, it is necessary to administer the drug in the evening in a form that is activated just before the patient arises.

Another example is the treatment of asthma with the agent theophylline. The drug has a rather narrow therapeutic index with minimum effective blood concentrations of 6–10 μg/ml and toxic levels of approximately 20 μg/ml. However, the serum theophylline concentrations required to produce maximum physiological benefit may fluctuate with the degree of bronchospasm present and are variable. Asthma often exhibits more serious symptoms in the evening, while theophylline absorption may change due to posture and changes in the circadian rhythm. This suggests that the nighttime dosing need not be identical to the daytime dosing regimen, and it is recommended that the extended release formulation not be given in the evening. Thus, a sustained acting dosage form for the day, with a bolus dose of theophylline at bedtime combined into a single peroral drug delivery system requiring once per day dosing in the evening is of possible benefit.

Many controlled release dosage forms are created by the use of special water insoluble membranes which either limit the flow of gastro-intestinal juices into the system, or modulate the release of dissolved substances out of the system. Application of such a membrane was initially accomplished by thin layer, spray application of lacquer coatings made with organic solvents. These processes allowed the manufacturer to achieve the desired membrane qualities in short time using few components. However, it was eventually realized that the processes were often dangerous in that excessive use of organic solvents were capable of causing irreversible harm to the environment and produced dosage forms which contained extraneous, undesirable residuals.

Whenever organic solvent is used in a pharmaceutical process, measures need to be taken to protect the operators who produce the dosage forms and the environment from overexposure to the hazardous, often teratogenic and carcinogenic materials. Additional precautions are necessary to protect personnel, equipment and facilities from harm due to the ignition of explosive vapors. Even if these immediate problems can be solved through engineering means, it is still possible for detectable levels of residual solvent to remain in the finished dosage form, the long term effects of which are either undesirable or not yet established.

Several manufacturers of coating equipment responded to the challenge of minimizing the dangers of using hazardous solvents by building machines which contained and controlled the exhaust vapors from organic solvent coating processes. Despite the capability of these machines to minimize the problems of explosion and exposure hazards, the equipment is complicated, costly to operate, and requires rather expensive maintenance even on a murine basis. It also does not address the problem of residual solvent remaining in the finished dosage form. This is ameliorated by storing the coated tablets in containers at high temperatures and humidities in order to draw the solvent out of the tablets; however, solvent extraction from finished dosage forms adds costs to the manufacturing process in additional capital equipment expenditures, processing time and analytical requirements.

The impetus for seeking new manufacturing techniques is obvious. The U.S. Food and Drug Administration and Environmental Protection Agency are continuously urging all manufacturers to reduce, and wherever possible, to eliminate the use of organic solvents in manufacturing.

Rather than pursuing costly engineering solutions to the problem, raw material suppliers were encouraged to develop aqueous dispersions of the materials most frequently employed to produce film coatings for tablets, pellets and particulate dosage forms. Aqueous dispersions allow utilization of existing equipment and familiar processes, thus avoiding the expenses of capital investments, maintenance, process validation and retraining of personnel.

SUMMARY OF THE INVENTION

It is accordingly an object of the present invention to provide a delivery device for the oral administration of a pharmaceutically acceptable active agent to a warm-blooded animal, either intermittently at pre-selected times or to a pre-selected region of the gastro-intestinal tract, particularly to the lower portion of the small intestine and/or the colon, more particularly to the colon.

It is another object of this invention to provide a dosage form for delivering substantially all of a therapeutic drug to the colon.

It is yet another object of this invention to provide a dosage form which comprises a core tablet coated with a delay jacket for delaying the delivery of the drug to insure the time required for the dosage form to travel through the small intestine.

It is still yet another object of this invention to provide a dosage form in which the semi-permeable membrane may be applied without the use of organic solvents, ie. aqueously, yet is still strong enough to resist the hydrostatic pressures of the ordinary osmotic core.

It is a further object of this invention to provide a dosage form which comprises an enteric coating over a semi-permeable wall for further delaying the delivery of the active agent during the time required for the dosage form to travel through the stomach.

It is still a further object of this invention to provide a dosage form which resists dissolution in gastric fluid for at least two hours, further delays initiation of active agent release for at least three hours, and releases at least 70% of its active agent within twenty-four hours.

It is yet still a further object of this invention to provide a delivery device which delivers drag intermittently at pre-selected times.

These, and other objects apparent to those skilled in the art from the following detailed description, am accomplished by the present invention which pertains to the delivery of a therapeutic drug to a pre-selected region of the gastro-intestinal tract, particularly the colon, by means of a drug delivery device. This drug delivery device comprises:

a) a solid core comprising an active agent;

b) a delay jacket coated over the core;

c) a semi-permeable membrane coated over the delay jacket, the membrane optionally having a release orifice; and optionally

d) an enteric coating over the semi-permeable membrane.

DETAILED DESCRIPTION OF THE INVENTION

This invention pertains to an osmotic delivery device for the oral administration of a pharmaceutically acceptable active agent to a warm-blooded animal, either intermittently at pre-selected times or to a pre-selected region of the gastro-intestinal tract, particularly to the lower portion of the small intestine and/or the colon, more particularly to the colon. This drug delivery device comprises:

a) a solid core comprising an active agent;

b) a delay jacket coated over the core;

c) a semi-permeable membrane coated over the delay jacket, the membrane optionally having a release orifice; and optionally

d) an enteric coating over the semi-permeable membrane.

Such device with an enteric coating thus resists dissolution in gastric fluid for at least two hours and thereafter limits the release of active agent in intestinal fluid to approximately ten percent or less for at least three hours after the device passes through the pylorus due to the delay jacket. The device thus allows for controlled continuous release of the active agent in the pre-selected region of the gastro-intestinal tract at a predetermined average rate, preferably at a rate of about 5 percent to about 25 percent by weight per hour. In addition, the device allows for substantially all of the active agent to be released at the pre-selected region of the gastro-intestinal tract, preferably 70–100% within twenty-four hours of ingestion.

Preferably, the basic device releases its active agent in vitro according to the following scheme, where time is hours from inception corresponding to in vivo release of active agent from time of ingestion:

Time (hrs.)	Fluid	Total Amount Released (%)
2	gastric	0–4
5	intestinal	0–10
6	intestinal	0–20
8	intestinal	0–50
10	intestinal	10–80
12	intestinal	20–100
18	intestinal	50–109
24	intestinal	70–115

Thus, the colonic delivery device would deliver from about 50% to about 100%, more particularly from about 60% to about 90%, most particularly from about 70% to about 80% of its active agent to the colon.

The solid core comprises an active agent and may optionally include other pharmaceutically acceptable excipients including osmotic agents, lubricants, glidants, wetting agents, binders, fillers, and suspending/thickening agents. Any core which would be suitable for an OROS-type system may be used in the present invention, including the various modifications currently known in the art such as MOCOS™ and push-pull OROS.

As used herein, MOCOS refers to a mono-compartmental system, such as that described in U.S. Pat. No. 4,857,336, hereby incorporated by reference, in which the elementary OROS has been modified in that the core comprises a hydrogel in addition to an active agent and an osmotic agent; and push-pull OROS refers to a system, such as that described in U.S. Pat. No. 4,111,202 (equivalent to Great Britain Patent 1,551,898), hereby incorporated by reference, in which the core has a drug layer immediately adjacent to the release orifice, a "push" layer consisting of hydrogels and osmotic agents beneath the drug layer, and an optional partition layer between the two.

Active agents useful in the present invention include, but are not limited to, proteins and peptides, antiasthmatics, antianginals, corticosteroids, 5-lipoxygenase inhibitors, antihypertensives, and leukotriene B_4 receptor antagonists. Proteins and peptides include, but are not limited to, transforming growth factors (TGF), immunoglobulin E (IgE) binding factors, interleukins, interferons (IFN), insulin-like growth factors (IGF), milk growth factors, anticoagulants, and parathyroid hormones (PTH). Specific active agents include, but are not limited to theophylline, IGF-I, PTH (1–34) and analogues thereof, TGF_{α},$TGF_{\beta 1}$, $TGF_{\beta 2}$,$TGF_{\beta 3}$, IFN_{α}, hybrid IFN_{α}, IFN_{γ}, hirudin, heparin, calcitonin, 5-aminosalicylic acid, CGS 23885, CGS 25019C, CGS 26529, Zileuton, ONO-LB 457, beclomethasone dipropionate, betamethasone-17-valerate, prednisolone metasulfobenzoate, tixocortol pivalate, budesonide, fluticasone, metoprolol fumarate, metoprolol tartrate, tetrahydroaminoacridine (THA), galanthamine, ursodiol, clomipramine hydrochloride, terbutaline sulfate, aminoglutethimide, deferoxamine mesylate, estradiol, isoniazid, methyltestosterone, metyrapone, and rifampin. Of particular importance are theophylline, IGF-I, PTH (1–34) and analogues thereof, TGF_{α},$TGF_{\beta 1}$, $TGF_{\beta 2}$,$TGF_{\beta 3}$,IFN_{α}, hybrid IFN_{α}, IFN_{γ}, hirudin, heparin, calcitonin, 5-aminosalicylic acid, CGS 23885, CGS 25019C, CGS 26529, Zileuton, ONO-LB 457, beclomethasone dipropionate, betamethasone-17-valerate, prednisolone metasulfobenzoate, tixocortol pivalate, budesonide, fluticasone, and metoprolol. Virtually any other active agent which is known to be colonically absorbable or used to topically treat the colon can be used as an active agent in the present invention as long as it is compatible with the system components.

As used herein, the active agents CGS 23885, 25019C, CGS 26529, Zileuton, ONO-LB 457 are defined as follows:

CGS 23885 refers to N-hydroxy-N-((6-phenoxy-2H-1-benzopyran-3-yl)methyl)-urea; CGS 25019C refers to 4-[5-[4-(aminoiminomethyl)phenoxy]pentoxy]-3-methoxy-N,N-bis(1-methylethyl)benzamide (Z)-2-butenedioate; CGS 26529 refers to N-[2-[[2-[[4-(4-fluorophenyl)phenyl]methyl]-1,2,3,4-tetrahydro-1-oxo-6-isoquinolinyl]oxo]ethyl]-N-hydroxyurea; Zileuton refers to 1-(1-benzo[b]thien-2-ylethyl)-1-hydroxyurea; ONO-LB 457 refers to 5-[2-(2-carboxyethyl)-3-{6-(para-methoxyphenyl)-5E-hexenyl}oxyphenoxy] valeric acid.

The core may include an osmotic agent if necessary or desirable to effect the desired release profile. The active agent, for example, metoprolol fumarate, may be sufficiently soluble to induce an internal hydrostatic pressure acceptable to eliminate the need for any additional osmotic agent. Typically, however, an additional compound will be included as the osmotic agent so as to promote the dissolution and release of the core active agent. The osmotic agent is a water-soluble compound which induces a hydrostatic pressure after water penetrates the semi-permeable membrane to drive out the active agent as a solution or a suspension. Suitable osmotic agents include any number of agents having a suitably high solubility and dissolution rate. The osmotic agent may be selected from any pharmaceutically acceptable chemical entity which is inert to the system. Suitable osmotic agents include pharmaceutically acceptable salts of inorganic and organic acids or nonionic organic acids of particularly high water solubility, e.g. carbohydrates such as sugar, or amino acids, or another active agent possessing suitable solubility.

Examples of such water-soluble compounds for inducing osmosis in the core include inorganic salts such as sodium, potassium or magnesium chloride, or sodium or potassium hydrogen or dihydrogen phosphate; salts of organic acids such as sodium alginate, sodium ascorbate, sodium benzoate, sodium citrate, edetate disodium, sodium fumarate, sodium or potassium acetate, or magnesium succinate; organic acids such as alginic acid, ascorbic acid, citric acid, edetic acid, malic acid, or sorbic acid; carbohydrates such as dextrates, sorbitol, xylitol, maltitol, mannitol, arabinose, ribose, xylose, glucose, dextrose, fructose, galactose, mannose, sucrose, maltose, lactose, or raffinose; water-soluble amino acids such as glycine, leucine, alanine or methionine; or miscellaneous others such as magnesium sulfate, magnesium carbonate, urea, saccharin, sodium saccharin, glycerin, hexylene glycol, polyethylene glycol, or propylene glycol; and mixtures thereof.

Additional core excipients may include tabletting lubricants, glidants, wetting agents to aid in dissolution of the components, binders, and suspending/thickening agents. Suitable lubricants include, but are not limited to, calcium stearate, glyceryl behenate, hydrogenated vegetable oils, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and zinc stearate. Suitable glidants include, but are not limited to, fused or colloidal silicon dioxide, calcium silicate, magnesium silicate, talc, and silica hydrogel. Suitable wetting agents include, but are not limited to, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docusate sodium, lecithin, nonoxynol 9, nonoxynol 10, octoxynol 9, poloxamer, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 50 stearate, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, sodium lauryl surfate, sorbitan esters, polyoxyethylene sorbitan fatty acid esters, and Tyloxapol (4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane). Suitable binders include, but are not limited to, acacia, alginic acid, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyethylene oxide, polymethylmethacylates, polyvinylpyrrolidone, pregelatinized starch, sodium alginate, syrup, and zein. Suitable suspending/thickening agents include acacia, agar, alginic acid, bentonite, carbomer, carboxymethylcellulose calcium, carageenan, carboxymethylcellulose sodium, corn starch, dextrin, gelatin, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, lecithin, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, pectin, poloxamer, polyethylene glycol alginate, polyethylene oxide, polyvinyl alcohol, polyvinylpyrrolidone, vinyl acetate, powdered cellulose, pregelatinized starch, propylene glycol alginate, silicon dioxide, sodium alginate, tragacanth, and xanthan gum.

The delay jacket is included to impede the dissolution and release of the active agent for the time necessary for the drug delivery device to travel through the small intestine. It comprises soluble materials, but may contain insoluble materials as well. The delay jacket must be capable of attracting water across the semi-permeable membrane while at the same time hindering the water from reaching the active core for the designated period of delay. Thus, the delay jacket will typically contain both water soluble, osmotically active components and insoluble and/or swellable components. The soluble osmotic agents leach out of the jacket and a suspension of at least some of the insoluble and/or swellable components remains. The active agent will later diffuse through this remaining suspension and thus the release of the active agent is dependent not only upon the composition of the inner core, but also upon the composition of the jacket.

The delay jacket typically comprises a binder, an osmotic agent, and a tablet lubricant. Suitable binders include, but are not limited to, acacia, alginic acid, carboxymethylcellulose sodium, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polyethylene oxide, polymethylmethacrylates, polyvinylpyrrolidone, pregelatinized starch, sodium alginate, syrup, and zein. Suitable osmotic agents include, but are not limited to, inorganic salts such as sodium, potassium or magnesium chloride, or sodium or potassium hydrogen or dihydrogen phosphate; salts of organic acids such as sodium alginate, sodium ascorbate, sodium benzoate, sodium citrate, edetate disodium, sodium fumarate, sodium or potassium acetate, or magnesium succinate; organic acids such as alginic acid, ascorbic acid, citric acid, edetic acid, malic acid, or sorbic acid; carbohydrates such as dextrates, sorbitol, xylitol, maltitol, mannitol, arabinose, ribose, xylose, glucose, dextrose, fructose, galactose, mannose, sucrose, maltose, lactose, or raffinose; water-soluble amino acids such as glycine, leucine, alaninc or methionine; or miscellaneous others such as magnesium sulfate, magnesium carbonate, urea, saccharin, sodium saccharin, glycerin, hexylene glycol, polyethylene glycol, or propylene glycol; and mixtures thereof. Suitable tablet lubricants include, but are not limited to, calcium stearate, glyceryl behenate, hydrogenated vegetable oils, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

Additional jacket excipients may include glidants and wetting agents. Suitable glidants include, but are not limited

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