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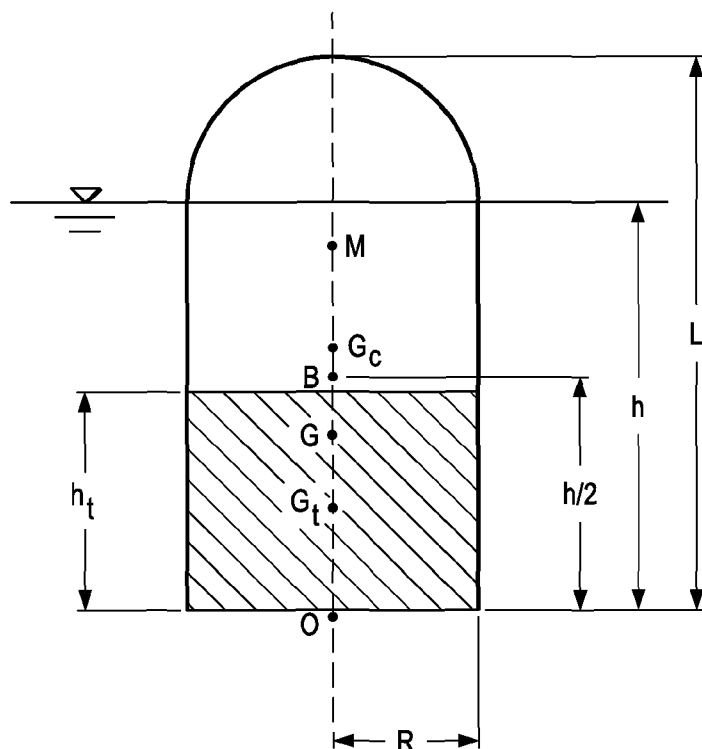
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(54) Title: MULTIPLE DOSING REGIMEN ORAL DRUG DELIVERY PLATFORM



(57) Abstract: The present invention includes compositions and methods of making a floating pharmaceutical reservoir for providing pulses release of at least one active pharmaceutical agent by coating a capsule with a water insoluble coating, an acid resistant coating or a water insoluble acid resistant coating; placing a flotation portion disposed in the capsule body, to maintain the buoyancy; depositing a first active agent into the capsule body; disposing a first lag-time layer in the capsule body adjacent to the one or more active agents to control the release of the first active agent after a predetermined lag time; and sealing the capsule body with a capsule cap.



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MULTIPLE DOSING REGIMEN ORAL DRUG DELIVERY PLATFORM

TECHNICAL FIELD OF THE INVENTION

The present invention relates in general to the field of drug delivery systems, and more particularly, to a floating and pulsatile drug delivery system.

BACKGROUND OF THE INVENTION

5 Without limiting the scope of the invention, its background is described in connection with a drug delivery system. There are many treatments that require the administration of a multiple dosing regimen to maintain prolonged therapeutic activity. Examples are antibacterials, cardiotonics, anticonvulsants, and hormones. A major obstacle to achieving the once-a-day dosing arises from the fact that a dosage form passes through the stomach and small intestine in a relatively short period of time, thus limiting the periodicity and/or extent of
10 drug absorption. Additionally, various diseases like asthma, arthritis, gastric distress, hypertension, heart failure, and stroke show circadian variation; demanding time-scheduled drug release, for the most effective and/or best tolerated dosing regimen. Therefore, pulsatile delivery systems are particularly useful for these diseases where a continuous release of drug is not ideal.

U.S. Patent Application No. 7,825,087 discloses a composition comprising a nanoparticulate cyclosporine
15 having improved bioavailability. The nanoparticulate cyclosporine particles of the composition have an effective average particle size of less than about 2000 nm in diameter and are useful in the prevention and treatment of organ transplant rejection and autoimmune diseases e.g., psoriasis, rheumatoid arthritis, and other related diseases. The invention also relates to a controlled release composition comprising a cyclosporine or a nanoparticulate cyclosporine that in operation delivers the drug in a pulsed or bimodal
20 manner for the prevention and treatment of organ transplant rejection and autoimmune diseases e.g., psoriasis, rheumatoid arthritis, and other related diseases.

U.S. Patent Application Publication No. 20070154547 entitled Gastric release pulse system for drug delivery discloses pharmaceutical products for providing pulses of at least one pharmaceutically active ingredient from a patient's stomach, or from a subsequent gastrointestinal site proximal thereto, for absorption thereof at
25 a site(s) more distal in the gastrointestinal tract than the patient's stomach, or than the subsequent gastrointestinal site proximal thereto. The product comprises first, second, and third pharmaceutical dosage forms, each of which comprises at least one pharmaceutically active agent and a pharmaceutically acceptable carrier. The product is formulated such that at least two of the first, second, and third pharmaceutical dosage

forms further comprise means for providing temporary gastric-retention of the at least two of the first, second, and third pharmaceutical dosage forms within the patient's stomach, or at the subsequent gastrointestinal site proximal thereto.

BRIEF SUMMARY OF THE INVENTION

5 The present invention provides pulsatile drug delivery systems to provide a pulsatile release of at least one active pharmaceutical agent including an impermeable capsule body comprising an open capsule end and a closed capsule end; an at least partially permeable capsule cap covering the open capsule end of the capsule body; a flotation portion disposed in the capsule body, to maintain the buoyancy of the impermeable capsule body; a first active agent disposed in the capsule body; one or more lag-time layers disposed in the capsule
10 body between the first active agent and the open capsule end; and a second active agent disposed in the capsule body between one or more lag-time layers and the open end of the capsule body, wherein the first active agent and the second active agent act as active agent reservoirs for a rapid bolus drug release after a predetermined lag time.

The present invention provides a pulsatile drug delivery composition to provide a pulsatile release of at least
15 one active pharmaceutical agent having a capsule body comprising an open capsule end and a closed capsule end; a capsule cap covering the open capsule end of the capsule body; a flotation portion disposed in the capsule body, to maintain the buoyancy of the water capsule body; one or more active agents disposed in the capsule body; and one or more lag-time layers disposed in the capsule body between the one or more active agent and the open capsule end, wherein the first active agent and the second active agent act as active agent
20 reservoirs for a rapid bolus drug release after a predetermined lag time.

The present invention provides a floating pharmaceutical reservoir for providing pulses release of at least one active pharmaceutical agent including an impermeable capsule body; a capsule cap connected to the capsule body, wherein the capsule cap soluble or at least partially permeable; one or more active agents disposed in the capsule body; one or more lag-time layers disposed in the capsule body adjacent to the one or more active
25 agents, wherein the one or more active agents act and one or more lag-time layers act as a reservoir for a rapid bolus drug release after a predetermined lag time; and a flotation portion disposed in the capsule body, to maintain the buoyancy.

The present invention provides a method of making a floating pharmaceutical reservoir for providing pulsed release of at least one active pharmaceutical agent by coating a capsule with a water insoluble coating, an
30 acid resistant coating or a water insoluble acid resistant coating; including a flotation portion disposed in the capsule body, to maintain the buoyancy; depositing a first active agent into the capsule body; disposing a first lag-time layer in the capsule body adjacent to the one or more active agents to control the release of the first

active agent after a predetermined lag time; and sealing the capsule body with a capsule cap.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

For a more complete understanding of the features and advantages of the present invention, reference is now made to the detailed description of the invention along with the accompanying figures and in which:

5 FIGURE 1 is an image of the stable position (i.e., the vertical position) of floating device which is made of impermeable capsule body with a tablet inside.

FIGURE 2 is an image of an assembled one-pulse platform without a cap of the present invention.

FIGURE 3 is an image of an assembled two-pulse platform of the present invention.

10 FIGURE 4 is a plot of the *in vitro* dissolution of two pulses of theophylline was performed and the time of 50% drug release of each pulse ($T_{50\%}$) was controlled using a 95 mg HPMC tablet.

FIGURE 5 is a plot of the *in vitro* dissolution of two pulses of theophylline was performed and the time of 50% drug release of each pulse ($T_{50\%}$) was controlled using a 110 mg HPMC tablet.

FIGURE 6 is a plot of the *in vitro* dissolution of two pulses of theophylline was performed and the time of 50% drug release of each pulse ($T_{50\%}$) was controlled using a 137 mg HPMC tablet.

15 FIGURE 7 is a plot of the *in vitro* dissolution and drug release in 0.1N HCl buffer solution (pH 1.2, $37 \pm 0.5^\circ\text{C}$) at paddle speed 50 rpm from two-pulse ciprofloxacin capsules.

FIGURE 8 is a plot of the *in vitro* dissolution Drug release in 0.1N HCl buffer solution (pH 1.2, $37 \pm 0.5^\circ\text{C}$) at paddle speed 50 rpm from three-pulse verapamil capsules.

FIGURE 9 is an image of an assembled two-pulse platform of the present invention.

20 FIGURE 10 is an image of an assembled three-pulse platform of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

While the making and using of various embodiments of the present invention are discussed in detail below, it should be appreciated that the present invention provides many applicable inventive concepts that can be embodied in a wide variety of specific contexts. The specific embodiments discussed herein are merely
25 illustrative of specific ways to make and use the invention and do not delimit the scope of the invention.

To facilitate the understanding of this invention, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the present invention. Terms e.g., “a”, “an” and “the” are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific embodiments of the invention, but their usage does not delimit the invention, except as outlined in the claims.

As used herein, the term “pharmaceutically acceptable salts” refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

As used herein, the term “modified release” denotes the coating or coating material or used in any other context, means release which is not immediate release and is taken to encompass controlled release, sustained release and delayed release.

As used herein, the term “immediate release” refers to describe a release profile to effect delivery of an active as soon as possible, that is, as soon as practically made available to an animal, whether in active form, as a precursor and/or as a metabolite. Immediate release may also be defined functionally as the release of over 80 to 90 percent (%) of the active ingredient within about 60, 90, 100 or 120 minutes or less. Immediate release as used herein may also be defined as making the active ingredient available to the patient or subject regardless of uptake, as some actives may never be absorbed by the animal. Immediate release formulations of the active on a carrier, such as rolled or compressed beads, may be formulated such that the surface area is maximized on beads and the active is exposed immediately. The immediate release formulations may also include effervescing agents that cause the disintegration of the structure integrity of the active and carrier such that release of the active is maximized. Various immediate release dosage forms may be designed readily by one of skill in art to achieve drug delivery to the stomach and small intestine, depending upon the choice of compression, adhesive materials and/or beading.

As used herein, the terms “extended release” and/or “delayed release” refers to a release profile to effect delivery of an active over an extended period of time, defined herein as being between about 60 minutes and about 2, 4, 6 or even 8 hours. Extended release may also be defined functionally as the release of over 80 to 90 percent (%) of the active ingredient after about 60 minutes and about 2, 4, 6 or even 8 hours. Extended release as used herein may also be defined as making the active ingredient available to the patient or subject regardless of uptake, as some actives may never be absorbed by the animal. Various extended release dosage forms may be designed readily by one of skill in art as disclosed herein to achieve delivery to both the small and large intestines, to only the small intestine, or to only the large intestine, depending upon the choice of coating materials and/or coating thickness.

As used herein, the terms “extended release” and/or “delayed release” refers to formulations that may be prepared and delivered so that release is accomplished at some generally predictable location in the lower intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. A method for delay of release is, e.g., a coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the lower gastrointestinal tract. Polymers and compatible mixtures thereof may be used to provide the coating for the delayed or the extended release of active ingredients, and some of their properties, include, but are not limited to: shellac, also called purified lac, a refined product obtained from the resinous secretion of an insect. This coating dissolves in media of pH >7.

As used herein, the term “time delay” denotes the duration of time between administration of the composition and the release.

As used herein, the term “erodible” refers to formulations which may be worn away, diminished, or deteriorated by the action of substances within the body.

As used herein, the term “diffusion controlled” denotes formulations which may spread as the result of their spontaneous movement, for example, from a region of higher to one of lower concentration.

As used herein, the term “osmotic controlled” denotes formulations which may spread as the result of their movement through a semipermeable membrane into a solution of higher concentration that tends to equalize the concentrations of the formulation on the two sides of the membrane.

Conventional frequent dosage regimes in which an immediate release dosage form is administered at periodic intervals typically give rise to a pulsatile plasma profile. In this case, a peak in the plasma drug concentration is observed after administration of each immediate release dose with troughs (regions of low drug concentration) developing between consecutive administration time points. Such dosage regimes (and their resultant pulsatile plasma profiles) have particular pharmacological and therapeutic effects associated with them.

The present invention further relates to a controlled release composition which in operation produces a plasma profile that eliminates the “peaks” and “troughs” produced by the administration of two or more immediate release dosage forms given sequentially if such a profile is beneficial. This type of profile can be obtained using a controlled release mechanism that allows for “zero-order” delivery.

Combinations of more than one surface stabilizer can be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic

pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include nonionic, anionic, cationic, ionic, and zwitterionic surfactants. Representative examples of surface stabilizers include hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers e.g., cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens; polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers; poloxamines; alkyl aryl polyether sulfonates; mixtures of sucrose stearate and sucrose distearate; p-isononylphenoxypoly-(glycidol); $C_{18}H_{37}CH_2(CON(CH_3)--CH_2(CHOH)_4(CH_2OH)_2$; decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulose, alginates, phospholipids, and nonpolymeric compounds, e.g., zwitterionic stabilizers, poly-n-methylpyridinium, anthryl pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide, hexyldesyltrimethylammonium bromide, and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, e.g., stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C12-15-dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl(ethenoxy)4

ammonium chloride or bromide, N-alkyl (C12-18)dimethylbenzyl ammonium chloride, N-alkyl (C14-18)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C12-14) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl
5 trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyltrimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C12-14) dimethyl 1-naphthylmethyl ammonium chloride and dodecyltrimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl
10 dimethyl ammonium bromide, C12, C15, C17 trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline
15 esters (e.g., choline esters of fatty acids), benzalkonium chloride, stearylkonium chloride compounds (e.g., stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, e.g., alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, e.g., lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt,
20 and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, e.g., poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Nonpolymeric surface stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic
25 organometallic compound, a quaternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quaternary ammonium compounds. Some compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride,
30 cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride (Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oleyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl

dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procaine hydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

Suitable gelling matrix polymers, which may be synthetic or natural, thus include polysaccharides, e.g., maltodextrin, xanthan, scleroglucan, dextran, starch, alginates, pullulan, hyaluronic acid, chitin, chitosan and the like; other natural polymers, e.g., proteins (albumin, gelatin etc.), poly-L-lysine; sodium poly(acrylic acid); poly(hydroxyalkylmethacrylates) (e.g., poly(hydroxyethylmethacrylate)); carboxypolymethylene; carbomer; polyvinylpyrrolidone; gums, e.g., guar gum, gum arabic, gum karaya, gum ghatti, locust bean gum, tamarind gum, gellan gum, gum tragacanth, agar, pectin, gluten and the like; poly(vinyl alcohol); ethylene vinyl alcohol; poly(ethylene oxide) (PEO); and cellulose ethers, e.g., hydroxymethylcellulose (HMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), methylcellulose (MC), ethylcellulose (EC), carboxyethylcellulose (CEC), ethyl hydroxyethylcellulose (EHEC), carboxymethyl hydroxyethylcellulose (CMHEC), hydroxypropylmethyl-cellulose (HPMC), hydroxypropylethylcellulose (HPEC) and sodium carboxymethylcellulose (Na CMC); as well as copolymers and/or (simple) mixtures of any of the above polymers. Certain of the above-mentioned polymers may further be crosslinked using standard techniques.

This invention relates to a floating and pulsatile drug delivery system applied to increase the gastric residence of the dosage form to act as a reservoir of a drug and have a rapid bolus drug release after predetermined lag times. The present invention provides a time-programmed therapeutic scheme releasing a specific amount of a drug at a specific time. The present invention provides a novel multiple dosing regimen platform for oral drug delivery that is capable of delivering specific doses of a drug from a specially designed floating delivery device to deliver drug at predetermined timed intervals.

The present invention provides a multiple drug dose composition, a reduced dosage frequency, improved patient compliance, compositions to suit circadian rhythms of body functions or diseases, composition for protection of mucosa from irritating drugs, drug targeting to specific sites within the gastrointestinal tract for local therapy and/or preferential drug absorption, a reduction in dose size and side effects.

The present invention describes a novel multiple dosing regimen platform that is capable of delivering specific doses of an active pharmaceutical ingredient (API) from a specially designed floating reservoir device at predetermined intervals. A floating device act as a reservoir, not to deliver a steady concentration of an API over time, but to deliver multiple doses of an API which may or may not need to be protected from

the harsh environment of the stomach. The device comprises a capsule body consisting of a water insoluble outer shell and is also impervious to stomach acid (e.g. ethyl cellulose) and a capsule cap. The contents of the device consist of API containing components (which can be small tablets, miniature capsules, or pellets), lag-time layers, and gas space (e.g. air). In one example, the first dose of an API is placed in the capsule cap
5 whereas other doses of the API alternated with lag time layer are placed in the opening of the ethyl cellulose capsule body and an air space are taken on the bottom part of the ethyl cellulose capsule body to allow it to remain upright and buoyant. The present invention relates more particularly to a pulsatile release profile which can deliver a first dose of API immediately followed by pulsatile delivery of subsequent doses while the device floats and is retained in the stomach.

10 As used herein, the term “active ingredient(s),” “pharmaceutical ingredient(s),” “active agents” and “bioactive agent” are defined as drugs and/or pharmaceutically active ingredients. The present invention may be used to encapsulate, attach, bind or otherwise be used to affect the storage, stability, longevity and/or release of any of the following drugs as the pharmaceutically active agent in a composition.

Non-limiting examples of active agents include, but are not limited to, antibiotics, analgesics, vaccines,
15 anticonvulsants; antidiabetic agents, antifungal agents, antineoplastic agents, antiparkinsonian agents, antirheumatic agents, appetite suppressants, biological response modifiers, cardiovascular agents, central nervous system stimulants, contraceptive agents, dietary supplements, vitamins, minerals, lipids, saccharides, metals, amino acids (and precursors), nucleic acids and precursors, contrast agents, diagnostic agents, dopamine receptor agonists, erectile dysfunction agents, fertility agents, gastrointestinal agents, hormones,
20 immunomodulators, antihypercalcemia agents, mast cell stabilizers, muscle relaxants, nutritional agents, ophthalmic agents, osteoporosis agents, psychotherapeutic agents, parasympathomimetic agents, parasympatholytic agents, respiratory agents, sedative hypnotic agents, skin and mucous membrane agents, smoking cessation agents, steroids, sympatholytic agents, urinary tract agents, uterine relaxants, vaginal agents, vasodilator, anti-hypertensive, hyperthyroids, anti-hyperthyroids, anti-asthmatics and vertigo agents.

25 In certain embodiments, the one or more therapeutic compounds are water-soluble, poorly water-soluble drug or a drug with a low, medium or high melting point. The therapeutic compounds may be provided with or without a stabilizing salt or salts.

Active Agents. One or more of the following active agents may be combined with one or more carriers and the present invention (which may itself be the carrier): Analgesic anti-inflammatory agents such as,
30 acetaminophen, aspirin, salicylic acid, methyl salicylate, choline salicylate, glycol salicylate, 1-menthol, camphor, mefenamic acid, fluphenamic acid, indomethacin, diclofenac, aleclofenac, ibuprofen, ketoprofen, naproxene, pranoprofen, fenoprofen, sulindac, fenbufen, clidanac, flurbiprofen, indoprofen, protizidic acid, fentiazac, tolmetin, tiaprofenic acid, bendazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone,

clofezone, pentazocine, mepirizole, and the like.

Drugs having an action on the central nervous system, for example sedatives, hypnotics, antianxiety agents, analgesics and anesthetics, such as, chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, amobarbital, cydobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, nicotine, and the like.

Antihistaminics or antiallergic agents such as, diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripeleminamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, chlorpheniramine, and the like. Anti-allergens such as, antazoline, methapyrilene, chlorpheniramine, pyrilamine, pheniramine, and the like.

Decongestants such as phenylephrine, ephedrine, naphazoline, tetrahydrozoline, and the like. Antipyretics such as aspirin, salicylamide, non-steroidal anti-inflammatory agents, and the like. Antimigraine agents such as, dihydroergotamine, pizotyline, and the like. Acetonide anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprofen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like.

Steroids such as, androgenic steroids, such as, testosterone, methyltestosterone, fluoxymesterone, estrogens such as, conjugated estrogens, esterified estrogens, estropipate, 17- β estradiol, 17- β estradiol valerate, equilin, mestranol, estrone, estriol, 17 β ethinyl estradiol, diethylstilbestrol, progestational agents, such as, progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17- α hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and the like.

Respiratory agents such as, theophylline and β_2 -adrenergic agonists, such as, albuterol, terbutaline, metaproterenol, ritodrine, carbutole, fenoterol, quinterenol, rimeterol, solmefamol, soterenol, tetroquinol, and the like. Sympathomimetics such as, dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine, arecoline, and the like. Local anesthetics such as, benzocaine, procaine, dibucaine, lidocaine, and the like.

Antimicrobial agents including antibacterial agents, antifungal agents, antimycotic agents and antiviral agents; tetracyclines such as, oxytetracycline, penicillins, such as, ampicillin, cephalosporins such as, cefalotin, aminoglycosides, such as, kanamycin, macrolides such as, erythromycin, chloramphenicol, iodides,

nitrofrantoin, nystatin, amphotericin, fradiomycin, sulfonamides, purrolnitrin, clotrimazole, miconazole chloramphenicol, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; clarithromycin; and other anti-infectives including nitrofurazone, and the like.

5 Antihypertensive agents such as, clonidine, α -methyldopa, reserpine, syrosingopine, rescinnamine, cinnarizine, hydrazine, prazosin, and the like. Antihypertensive diuretics such as, chlorothiazide, hydrochlorothiazide, bendoflumethazide, trichlormethiazide, furosemide, tripamide, methylclothiazide, penfluzide, hydrothiazide, spironolactone, metolazone, and the like. Cardiotonics such as, digitalis, ubidecarenone, dopamine, and the like. Coronary vasodilators such as, organic nitrates such as,
10 nitroglycerine, isosorbitol dinitrate, erythritol tetranitrate, and pentaerythritol tetranitrate, dipyridamole, dilazep, trapidil, trimetazidine, and the like. Vasoconstrictors such as, dihydroergotamine, dihydroergotamine, and the like. β -blockers or antiarrhythmic agents such as, timolol pindolol, propranolol, and the like. Humoral agents such as, the prostaglandins, natural and synthetic, for example PGE1, PGE2 α , and PGF2 α , and the PGE1 analog misoprostol. Antispasmodics such as, atropine, methantheline, papaverine,
15 cinnamedrine, methscopolamine, and the like.

Calcium antagonists and other circulatory organ agents, such as, aptopril, diltiazem, nifedipine, nicardipine, verapamil, bencyclane, ifenprodil tartarate, molsidomine, clonidine, prazosin, and the like. Anti-convulsants such as, nitrazepam, meprobamate, phenytoin, and the like. Agents for dizziness such as, isoprenaline, betahistine, scopolamine, and the like. Tranquilizers such as, reserprine, chlorpromazine, and antianxiety
20 benzodiazepines such as, alprazolam, chlordiazepoxide, clorazepate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam, diazepam, and the like.

Antipsychotics such as, phenothiazines including thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperracetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, and other major tranquilizers such as, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and
25 molindone, as well as, those agents used at lower doses in the treatment of nausea, vomiting, and the like. Muscle relaxants such as, tolperisone, baclofen, dantrolene sodium, cyclobenzaprine.

Drugs for Parkinson's disease, spasticity, and acute muscle spasms such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, bztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, dantrolene, and the like. Respiratory agents such as,
30 codeine, ephedrine, isoproterenol, dextromethorphan, orciprenaline, ipratropium bromide, cromglycic acid, and the like. Non-steroidal hormones or antihormones such as, corticotropin, oxytocin, vasopressin, salivary hormone, thyroid hormone, adrenal hormone, kallikrein, insulin, oxendolone, and the like. Vitamins such as, vitamins A, B, C, D, E and K and derivatives thereof, calciferols, mecobalamin, and the like for

dermatologically use. Enzymes such as, lysozyme, urokinase, and the like. Herb medicines or crude extracts such as, Aloe vera, and the like. Antitumor agents such as, 5-fluorouracil and derivatives thereof, krestin, picibanil, ancitabine, cytarabine, and the like. Anti-estrogen or anti-hormone agents such as, tamoxifen or human chorionic gonadotropin, and the like. Miotics such as pilocarpine, and the like.

- 5 Cholinergic agonists such as, choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, arecoline, and the like. Antimuscarinic or muscarinic cholinergic blocking agents such as, atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, eucatropine, and the like.

- Mydriatics such as, atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine,
10 hydroxyamphetamine, and the like. Psychic energizers such as 3-(2-aminopropyl)indole, 3-(2-aminobutyl)indole, and the like.

Antidepressant drugs such as, isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, trazodone, and the like. Anti-diabetics such as, insulin, and anticancer drugs such as, tamoxifen, methotrexate, and the like.

- 15 Anorectic drugs such as, dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, phentermine, and the like. Anti-malarials such as, the 4-aminoquinolines, alpha-aminoquinolines, chloroquine, pyrimethamine, and the like. Anti-ulcerative agents such as, misoprostol, omeprazole, enprostil, and the like. Antiulcer agents such as, allantoin, aldioxa, alcloxa, N-methylscopolamine methylsulfate, and the like. Antidiabetics such as insulin, and the like. For use with
20 vaccines, one or more antigens, such as, natural, heat-killed, inactivated, synthetic, peptides and even T cell epitopes (e.g., GADE, DAGE, MAGE, etc.) and the like.

The drugs mentioned above may be used in combination as required. Moreover, the above drugs may be used either in the free form or, if capable of forming salts, in the form of a salt with a suitable acid or base. If the drugs have a carboxyl group, their esters may be employed.

- 25 The acid mentioned above may be an organic acid, for example, methanesulfonic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, acetic acid, or an inorganic acid, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid. The base may be an organic base, for example, ammonia, triethylamine, or an inorganic base, for example, sodium hydroxide or potassium hydroxide. The esters mentioned above may be alkyl esters, aryl esters, aralkyl esters, and the like.

- 30 When a drug different than an anesthetic agent is used the solvent selected is one in that the drug is soluble. In generally the polyhydric alcohol may be used as a solvent for a wide variety of drugs. Other useful solvents are those known to solubilize the drugs in question.

There are no other devices found that function in this unique way. There are reservoir-type delivery systems based on the expansion of the core that have been evaluated for both floating delivery systems having a lower density than gastrointestinal fluids, and for pulsatile systems in which the core expansion based on an osmotic agent (Schultz and Kleinebudde, 1997) and effervescent agent (Krogel and Bodmeier, 1999b) causes rupturing of the coating consisting of acrylic or cellulosic polymer to allow rapid drug release. However, in order to allow continuous floating in stomach over a long period of time special design features need to be included, previous inventions do not maintain the structural integrity required to perform the functional aspects of this current invention.

There are also disadvantages of previously reported floating drug delivery systems that base their functionality on gas generation, including the control of *in situ* acid base reaction and the subsequent drug release (Singh and Kim, 2000). Low density porous calcium silicate used as drug carrier system included alginate to function as a time delaying agent for drug release in floating-pulsatile drug delivery system (Sharma and Pawar, 2006). Reduction of the alginate to calcium silicate ratio increased the release time of the drug. However, this system showed drug release in acidic medium before a pulse drug release occurred in simulated intestinal fluid.

A tablet formulation consisting of drug core tablet, an erodible outer shell containing METHOCEL[®] E15 and a top layer of buoyant material, e.g., METHOCEL[®] K4M, CARBOPOL[®] 934P and NaHCO₃ showed the *in vitro* floating onset time less than 1 min and the floating duration more than 12 hours (Zou, et al., 2008). *In vivo* study the tablet was found to increase the gastric retention time over 4 hours and the mean lag time was 4.4 ± 0.4 hours, this was consistent with the corresponding *in vitro* lag time (4.4 ± 0.4 hours). Another system consisting of a drug tablet placed within an impermeable capsule body closed with an erodible plug and floating material (hydrogenated castor oil or hexadecanol) filled at the bottom also has been developed (Zou, et al., 2007). *In vitro* study of the capsule indicated that it floated over a 12 hours period, but its ability to remain buoyant was insufficient *in vivo*: gastric retention time was found to be 4 hours after dinner, with *in vivo* lag time of 5 hours after administration which was longer than the corresponding *in vitro* time of 1 hour.

Multiple pulse systems have also been developed under the floating-pulsatile concept. As described in U.S. Patent Application Publication No. US 2007/0154547A1, the multipulse of a drug can be achieved by manufacturing different beads or pellets, that may be further processed by compressing into a tablet or filling into a capsule (Flanner, et al., 2007). Essentially, the combination of different types of pellets can be combined to achieve multiple pulsed release times. The first type of pellet can be a core pellet containing a drug for the first pulse quick A second pellet comprising the core pellet coated with an expanding layer and pH independent layer for a second pulse quick release of drug after a predetermined lag time. A third type of pellet may comprise the core pellet coated with the expansion layer and an enteric layer (with an optional

muco adhesive layer applied in order to achieve dose from retention in stomach) could provide a third pulsed release. This system has a disadvantage of complexity in manufacturing and further *in vitro* and *in vivo* studies have to confirm its functionality.

Another swelling system has also been used for two pulse deliveries as described in WO/2009/017716 (Cowles, et al., 2009). A dosage form comprised of a first dose of a drug that is immediately release after oral administration, and a second dose of drug that is contained in a hydrophilic polymer that swells by imbibing water present in gastric fluid to a size sufficient to achieve retention in a stomach and released the drug 2-6 hours after ingestion.

Many kinds of devices to house the pulsatile dose have been developed. The most extensive device is coated gelatin capsule by the strategy of coating method. The film formers used to coat the gelatin capsule are insoluble and either water-impermeable e.g., ethyl cellulose which been used in the PULSINCAPTM device (McNeill, et al., 1994) and alternative version of PULSINCAPTM (Mohamad and Dashevsky, 2006; Ross, et al., 2000) or semi-permeable e.g., cellulose acetate in PORT[®] system (Crison, et al., 1995). However, the critical part of coating method is the area around the mouth of the capsule and the region of the uncoated gelatin inside the capsule. This would be easy for water to penetrate into the capsule and this make gelatin hydrate and lose its structural integrity and eventually results in premature release of pulsatile doses. The other type of pulsatile devices is the polypropylene tube. However, the coated gelatin capsule with ethyl cellulose is considered to be more pharmaceutically acceptable than polypropylene tubes (Krogel and Bodmeier, 1999a). To overcome the critical part of coating method, a dipping process (modified hard gelatin capsule dipping process) and followed by dissolving gelatin out were introduced in the present invention.

The present invention has a distinct objective to make it feasible to deliver a variety of active pharmaceutical ingredients as part of a multiple dosing regimen by the means of floating device with pulsatile release pattern. The pulsatile dosage form of drug can be in the form of tablets, pellets, or beads and the lag-time layer sandwiches the active layers.

The present invention provides a simple and practical way to maintain the buoyancy (upward force that keeps the present device floating vertically) using a gas compartment concentrated on the bottom part of an insoluble capsule body. The overall mass distribution inside the device and low density of the device due to the gas pocket allow it to remain upright and buoyant (both key components in its functionality).

For the buoyancy theory the device floats when the total force F acting vertically on the device is positive (Timmermans and Moes, 1990). This means the buoyancy force is more than gravity force (weight of device). Therefore, the suitable mass of device can be precisely determined by using the following equation:

$$F = F_{\text{buoyancy}} - F_{\text{gravity}}$$

$$F_{\text{buoyancy}} > F_{\text{gravity}} = Mg$$

$$d_f gV > Mg$$

$$M < d_f V$$

5 where, F is the total vertical force, g is the acceleration due to gravity, d_f is the fluid density, M is the device mass, and V is the volume of the device. For example, M must be less than 726.9 mg for the device which is the capsule size No.0 ($V = 0.7256$ ml) to float in 0.1N HCl buffer (density = 1.0018 g/ml).

It is known that the specific gravity of gastric juices is from 1.0010-1.0100 (Hammarsten, 1911) and, accordingly, the floating device of the present invention will float on gastric fluids within that range.
 10 Consequently, the above equation can be used to design the maximum weight of the floating device and contents which are incorporated into a capsule of any given size.

There are many treatments that require the administration of a multiple dosing regimen to maintain prolonged therapeutic activity. Examples are antibacterials, cardiotonics, anticonvulsants, and hormones. Ideally, to optimize clinical effectiveness drug plasma concentrations must be maintained within the therapeutic
 15 window (e.g., above the minimum effective concentration and below the minimum toxic concentration) without excessive fluctuation and/or drug accumulation (which might take it outside of the therapeutic window).

Standard oral controlled release system show a typical pattern of drug release (zero order) in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensured
 20 sustained therapeutic action. This dosage form offer many advantages, e.g., nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance (Bussemer, et al., 2001). However, a continuous release pattern of oral controlled release systems is not suitable for diseases which show circadian rhythms in their pathophysiology (Ohdo, 2007). Migraine headache has the onset in the time of awakening from
 25 nighttime. Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug well after the time of administration (during morning hours), would be ideal in this case. The same is true for preventing the symptoms of rheumatoid arthritis, allergic and infectious rhinitis, incidences of angina, myocardial infarction, sudden cardiac death, and thrombotic and hemorrhagic stroke during the initial hours
 30 of daytime, pain and gastric distress in the late evening and early morning, epilepsy seizures around sleep onset at night and offset in the morning, symptoms of congestive heart failure in the middle of the night, and potential asthma attacks during nighttime. Therefore, the administration of drugs at time at which they are most effective and/or best tolerated is one approach to increase the efficiency of pharmacotherapy. This also

has implications for the minimization of side effects as targeting to a specific rhythm of a disease and result in the reduction of dosage of a specific drug. As a result those side effects associated with the drug are also reduced. In addition targeting rhythms may also prevent the interaction of certain drugs and so a wider treatment regime may become available when treating multiple ailments.

5 There are many diseases that would benefit from a sustained and constant plasma level for extended periods. For example, a typical course of antibiotic therapy is most effect when the drug is taken at regularly spaced intervals so as to maintain a plasma level above the minimum inhibitory concentration of the pathogen (typically a dose every 8 hours may be prescribed). Common causes of antibiotic misuse may include a failure to take the entire prescribed course of the antibiotic, or a departure from fairly precise daily dosing
10 intervals. Both of these areas of misuse potentially exacerbate the development of drug resistance in bacterial populations. In this case a precisely timed multiple dosing regimen taken orally, that could significantly reduce the burden placed on the patient to “get it right”, would of course improve both compliance and efficacy.

However, the major obstacle to achieving the multiple dosing regimen platform arises from the fact that most
15 dosage forms pass through the stomach and small intestine in a relatively short period of time, thus limiting the exposure time of the drug to different segments of the gastrointestinal (GI) tract. Regardless of whether the in vivo release of the drug formulations is constant, the extent of drug absorption will be related to the residence time the dosage form spends within each segment of the gut. After intake of various dosage forms it reaches the stomach, where it is normally transported after 0.5-3 hours into the small intestine (Chawla, et
20 al., 2003). The time to pass through the small intestine is usually 3-5 hours. The result of this is that absorption of the active ingredient must be complete within about 3-5 hours because most active ingredients are absorbed in the colon to only a negligible extent or not at all. It is therefore possible to adjust a longer release-slowing period only with difficulty. The bioavailability of active ingredients that are not completely absorbed in this period decreases because part of the dose is lost. An additional factor is that certain active
25 ingredients have an absorption window, which is very quickly passed through with conventional dosage forms, in the small intestine.

A system of the present invention remains in the stomach for a longer time and continuously releases active ingredient thus it avoid these disadvantages, since the active ingredient would continuously pass through the pylorus in dissolved form and could be taken up in the small intestine. It is possible in this way on the one
30 hand to extend the bioavailability but also, on the other hand, to extend the duration of action, for example of a drug product.

There are several key therapeutic advantages that can be deemed useful when considering a reservoir of drug in the stomach. Firstly, an API might have the potential to be locally active in the stomach. For example,

misoprostol, antacids, or antibiotics may be locally effective against *H. pylori* (Arora, et al., 2005; Garg and Gupta, 2008). While a standard dosing regimen may be used to provide the required regimen, a single dose with the floating device could potentially provide multiple doses within a predetermined period.

There may be a narrow absorption window in the stomach or in the upper small intestine. For example this occurs with drugs e.g., levodopa, metformin, furosemide, riboflavin, or p-aminobenzoic acid (Arora, et al., 2005; Garg and Gupta, 2008). This window almost precludes the formulation of those drugs into conventional controlled release dosage forms that, in order to function effectively, must traverse a wide ranging environment within the GI tract. Thus having a floating reservoir of drug that pulses a controlled amount of drug for rapid absorption in the small intestinal area would be an obvious advantage to taking multiple tablets in order to achieve that same type of bioavailability.

To achieve improved therapeutic efficacy, the inventors of the present invention have designed a novel multiple dosing regimen platform combining the advantages of floating and pulsatile drug delivery systems. This will have the effect of increasing the gastric residence of the dosage form to act as a reservoir of a drug and have a rapid bolus drug release after a predetermined lag time, not to deliver a steady concentration of drug over time, but to deliver multiple dose of a drug. This is a time-programmed therapeutic scheme releasing the right amount of drug at the right time.

There are several advantages over current technologies of this invention, e.g., the ability to reach and maintain a plateau of dosing via the oral route since this multiple dosing plateau is normally reserved for intravenous administration dosing regimens, precluding its use by an out-patient population; the ability to provide single timely administrations of drugs to coincide with the peak onset of symptoms exhibited by some disease states; the ability to provide a delivery platform to aide in the targeting of specific sites within the GI tract for local therapy, and/or preferential drug absorption; the ability to promote the completion of dosing regimens that are difficult for patients to follow, which may in the worst cases lead to the emergence of pathogen drug resistance.

EXAMPLE 1: Preparation of Ethyl Cellulose Impermeable Capsule Bodies by Dipping Process. A coating solution is prepared using the component of the Table below:

COMPONENT	AMOUNT
Ethocel [®] Standard 100 Premium	38 g
Triethyl citrate	2 g
Acetone	250 ml
Propan-2-ol	250 ml

The gelatin capsule body was dipped into coating solution for 10 seconds per dipping time every 10 minutes for four cycles. The capsule bodies were then placed in the oven at 40°C to remove all the solvent for 12 hours. The resultant capsule bodies were then further processed by simply immersing in water to remove the gelatin layer, yielding a completely impermeable capsule body with the mean weight of 56 mg.

5 EXAMPLE 2: Buoyancy and Stability of Floating Devices. Various tablet weights of HPMC tablets were prepared and incorporated in the impermeable capsule body prepared in Example 1 and left the space for the air concentrated at the bottom of the capsule body for buoyancy study (FIGURE 1). The powder of METHOCEL[®] K 100 Premium LV 20% w/w and lactose monohydrate 79.2% w/w were sieved through a 600-μm sieve and then blended for 15 min in an orbital-mixer followed by the addition of 0.8% w/w
10 magnesium stearate and further blending for 5 min. The HPMC tablets were prepared by direct compression with a single punch press equipped with a 7 mm diameter flat plain punch and die set (Natoli Engineering Company, Inc., St.Charles, MO) which will contribute the consistency of dissolution/erosion controlling rate of lag-time layer.

FIGURE 1 is an image of the stable position (i.e., the vertical position) of floating device, which is made of
15 impermeable capsule body with HPMC tablet inside. Then the in vitro floating behavior of devices was performed in a USP dissolution type II apparatus by placing them in 900 ml 0.1N HCl buffer (37±0.5°C, 50 rpm). To determine the optimal loading capacity of the floating capsule body that maintains a good vertical-floating stability (FIGURE 1), the capsule body floats in 0.1N HCl buffer of density, d_f , with a depth of immersion, h . The center of buoyancy is B, and G_c and G_t are the center of gravity of the capsule body and
20 tablet, respectively. The center of gravity of whole device is G and its metacenter is M. The masses of the capsule body and tablet, m_c and m_t , were measured. The parameter to evaluate the stability of floating device is metacentric height (GM) as shown in the equation below:

$$h = (m_c + m_t) / \pi R^2 d_f$$

$$OG = (OG_c m_c + OG_t m_t) / (m_c + m_t) = (m_c (L/2) + m_t (h_t/2)) / (m_c + m_t)$$

$$25 \quad GM = BM + BG = BM + OB - OG = (R^2/4h) + (h/2) - OG$$

For stability, the metacentric height (GM) must be positive. Stability (restoring force) increases with increasing GM. The floating device was always floating on the surface. The buoyancy and stability of devices were determined by visual observation as shown in the Table below:

Sample No.	m_{tot} (mg)	m_c (mg)	L (cm)	D (cm)	R (cm)	m_t (mg)	GM (cm)	Float /Sink	Vertical	Remark	Density of device (mg/ml)
1	184.7	54.7	1.8012	0.7394	0.3697	130.0	-0.0594	Float	No	-	256.2
2	307.4	54.8	1.7635	0.7475	0.3738	252.6	0.0432	Float	No	-	427.2
3	405.7	54.8	1.7744	0.7482	0.3741	350.9	0.0870	Float	No	-	559.1
4	517.7	55.2	1.8181	0.7421	0.3711	462.5	0.1404	Float	No	almost	706.1

										vertical	
5	518.2	55.6	1.8222	0.7404	0.3702	462.6	0.1410	Float	Yes	Stable	708.2
6	549.6	55.3	1.7670	0.7421	0.3711	494.3	0.1505	Float	Yes	Stable	772.9
7	649.0	55.4	1.7632	0.7427	0.3714	593.6	0.1817	Float	Yes	Stable	913.4
8	698.7	55.1	1.8034	0.7427	0.3714	643.6	0.1956	Float	Yes	Stable	959.8
9	700.5	55.6	1.8178	0.7383	0.3692	644.9	0.2057	Float	Yes	Stable	965.1
10	702.1	55.4	1.8021	0.7401	0.3701	646.7	0.2041	Float	Yes	Stable	971.8
11	708.7	55.3	1.8211	0.7386	0.3693	653.4	0.2017	Float	Yes	Stable	973.7
12	710.9	57.6	1.8255	0.7396	0.3698	653.3	0.1995	Float	Yes	Stable	971.7
13	715.1	54.9	1.8103	0.7447	0.3724	660.2	0.1887	Float	Yes	almost sink	973.3
14	720.8	55.2	1.8283	0.7432	0.3716	665.6	0.1813	Float	Yes	almost sink	974.4
15	722.1	55.2	1.7981	0.7406	0.3703	666.9	-	Sink	Yes	-	1000.5
Mean	-	55.3	1.8011	0.7420	0.3710	-	-	-	-	-	-
CV (%)	-	1.24	1.29	0.40	0.40	-	-	-	-	-	-

The results from the stability of floating devices are shown in the Table with the vertical floating stable range 462.6-653.3 mg for optimal loading capacity and 518.2-710.9 mg for total weights of floating capsule body.

- 10 In the stable floating range metacentric height GM were positive. This data can be used to design the suitable mass range inside the floating capsule bodies for remaining buoyant in a good vertical stability position. In addition, placebo tablets will be chosen to adjust the mass inside the floating capsule body to control the stability during buoyancy.

- 15 EXAMPLE 3: Preparation of 460 mg Placebo Tablets by Dry Blend-Direct Compression. A placebo tablet is prepared using the component of the Table below:

COMPONENT	AMOUNT (per tablet)
Lactose monohydrate	351.9 mg
Prosolv SMCC® 90	92.0 mg
Croscarmellose sodium	13.8 mg
Magnesium stearate	2.3 mg
Total	460.0 mg

All powdered ingredient were passed through a 600 µm sieve before use for deagglomeration and tumble mixed for 15 min. Magnesium stearate was added and tumbled mixed for 5 min. The powders were fed manually to the die of a single punch tableting machine equipped with non-beveled flat faced punch of 7-mm diameter and compressed.

- 20 EXAMPLE 4: Preparation of Theophylline Tablets by Dry Blend-Direct Compression. A theophylline tablet is prepared using the component of the Table below:

COMPONENT	AMOUNT (per tablet)
Theophylline anhydrous	5.0 mg
Lactose monohydrate	71.5 mg
Prosolv SMCC® 90	20.0 mg
Croscarmellose sodium	3.0 mg
Magnesium stearate	0.5 mg
Total	100.0 mg

All powdered ingredient were passed through a 600 µm sieve before use for deagglomeration and tumble mixed for 15 min. Magnesium stearate was added and tumbled mixed for 5. The powders were fed manually to the die of a single punch tabletting machine equipped with non-beveled flat faced punch of 7-mm diameter and compressed at 7 kp.

- 5 EXAMPLE 5: Physical Characterizations of Theophylline Tablets. Weight, hardness, and thickness were evaluated as shown in the Table below:

Sample No.	Weight (mg)	Hardness (kp)	Thickness (mm)
1	103	7.6	1.872
2	100	7.4	1.839
3	99	6.9	1.819
4	104	7.2	1.880
5	100	7.3	1.828
Mean ± SD	101.2 ± 2.17	7.3 ± 0.26	1.848 ± 0.027

EXAMPLE 6: Preparation of 95 mg Lag-Time Tablet Using METHOCEL® K100 Premium LV 20% w/w by Dry Blend-Direct Compression. A lag-time tablet comprising METHOCEL® K100 Premium LV 20% w/w is prepared using the component of the Table below:

COMPONENT	AMOUNT (per tablet)
METHOCEL® K100 Premium LV	19.00 mg
Lactose monohydrate	75.24 mg
Magnesium stearate	0.76 mg
Total	95.00 mg

- 10 EXAMPLE 7: All powdered ingredient were passed through a 600 µm sieve before use for deagglomeration and tumble mixed for 15 min. Magnesium stearate was added and tumbled mixed for 5 min. The powders

were fed manually to the die of a single punch tableting machine equipped with flat faced punch of 7-mm diameter and compressed.

EXAMPLE 8: Device Assembly of Delayed Release of Theophylline. FIGURE 2 is an image of the assembled two-pulse platform of an active agent, e.g., theophylline: (a) lag-time tablet 10; (b) second dose of theophylline tablet 12; (c) placebo tablet 14; (d) air 16; (e) impermeable capsule body 18. Assembly of the delayed pulse from floating-pulsatile release device proceeded as follows (FIGURE 2): (i) a 460 mg placebo tablet was filled into the impermeable capsule body prepared in Example 1 to adjust the mass inside the capsule body device and remain the stability of floating device; (ii) the second dose of theophylline tablet was placed next to the placebo tablet; (iii) a 95 mg lag-time tablet was inserted into the mouth of the impermeable capsule body and positioned flush with the end of the impermeable capsule body. The air compartment was concentrated at the bottom of the impermeable capsule body.

EXAMPLE 9: FIGURE 3 is an image of the assembled two-pulse platform of an active agent, e.g., theophylline. The first dose of theophylline tablet was placed onto the 95 mg lag-time tablet and covered with gelatin cap. FIGURE 3 illustrates assembled two-pulse release of theophylline: (a) lag-time tablet 10; (b) second dose of theophylline tablet 12; (c) placebo tablet 14; (d) air 16; (e) impermeable capsule body 18; (f) first dose of theophylline tablet 20; (g) gelatin cap 22.

EXAMPLE 10: Preparation of 440 mg Placebo Tablets by Dry Blend-Direct Compression. A placebo tablet is prepared using the component of the Table below:

COMPONENT	AMOUNT (per tablet)
Lactose monohydrate	336.6 mg
Prosolv SMCC [®] 90	88.0 mg
Croscarmellose sodium	13.2 mg
Magnesium stearate	2.2 mg
Total	440.0 mg

All powdered ingredient were passed through a 600 μ m sieve before use for deagglomeration and tumble mixed for 15 minutes. Magnesium stearate was added and tumbled mixed for 5 minutes. The powders were fed manually to the die of a single punch tableting machine equipped with flat faced punches of 7-mm diameter and compressed.

EXAMPLE 11: Preparation of 110 mg Lag-Time Tablet Using METHOCEL[®] K100 Premium LV 20% w/w by Dry Blend-Direct Compression. A lag-time tablet comprising METHOCEL[®] K100 Premium LV 20% w/w is prepared using the component of the Table below:

COMPONENT	AMOUNT (per tablet)
Methocel [®] K100 Premium LV	22.00 mg
Lactose monohydrate	87.12 mg
Magnesium stearate	0.88 mg
Total	110.00 mg

All powdered ingredient were passed through a 600 μ m sieve before use for deagglomeration and tumble mixed for 15 minutes. Magnesium stearate was added and tumbled mixed for 5 minutes. The powders were fed manually to the die of a single punch tabletting machine equipped with flat faced punch of 7-mm diameter and compressed.

- 5 EXAMPLE 12: Device Assembly of Delayed Pulse of Theophylline. Assembly of the delayed pulse from floating-pulsatile release device proceeded as follows (FIGURE 2): (i) a 440 mg placebo tablet was filled into the impermeable capsule body prepared in Example 1 to adjust the mass inside the capsule body device and remain the stability of floating device; (ii) the second dose of theophylline tablet prepared in was placed next to the placebo tablet; (iii) a 110 mg lag-time tablet prepared in was inserted into the mouth of the
10 impermeable capsule body and positioned flush with the end of the impermeable capsule body. The air compartment was concentrated at the bottom of the impermeable capsule body.

EXAMPLE 13: Device Assembly of Two Pulses of Theophylline. The first dose of theophylline tablet was placed onto the lag-time tablet and covered with gelatin cap (FIGURE 3).

EXAMPLE 14: Preparation of 405 mg Placebo Tablets by Dry Blend-Direct Compression. A placebo tablet is prepared using the component of the Table below:

COMPONENT	AMOUNT (per tablet)
Lactose monohydrate	309.8 mg
Prosolv SMCC® 90	81.0 mg
Croscarmellose sodium	12.2 mg
Magnesium stearate	2.0 mg
Total	405.0 mg

All powdered ingredient were passed through a 600 µm sieve before use for deagglomeration and tumble mixed for 15 min. Magnesium stearate was added and tumbled mixed for 5 min. The powders were fed manually to the die of a single punch tableting machine equipped with flat faced punch of 7-mm diameter and compressed.

EXAMPLE 15: Preparation of 137 mg Lag-Time Tablet Using METHOCEL® K100 Premium LV 20% w/w by Dry Blend-Direct Compression. A lag-time tablet comprising METHOCEL® K100 Premium LV 20% w/w is prepared using the component of Table 9:

COMPONENT	AMOUNT (per tablet)
Methocel® K100 Premium LV	27.400 mg
Lactose monohydrate	108.504 mg
Magnesium stearate	1.096 mg
Total	137.000 mg

All powdered ingredients were passed through a 600 µm sieve before use for deagglomeration and tumble mixed for 15 min. Magnesium stearate was added and tumbled mixed for 5 min. The powders were fed manually to the die of a single punch tableting machine equipped with flat faced punch of 7-mm diameter and compressed.

EXAMPLE 16: Device Assembly of Delayed Pulse of Theophylline. Assembly of the delayed pulse from floating-pulsatile release device proceeded as follows (FIGURE 2): (i) a 405 mg placebo tablet was filled into the impermeable capsule body prepared in Example 1 to adjust the mass inside the capsule body device and remain the stability of floating device; (ii) the second dose of theophylline tablet was placed next to the placebo tablet; (iii) a 137 mg lag-time tablet was inserted into the mouth of the impermeable capsule body

and positioned flush with the end of the impermeable capsule body. The air compartment was concentrated at the bottom of the impermeable capsule body.

EXAMPLE 17: Device Assembly of Two Pulses of Theophylline. The first dose of theophylline tablet prepared in Example 5 was placed onto the lag-time tablet of Example 15 and covered with gelatin cap (FIGURE 3).

EXAMPLE 18: In Vitro Dissolution Study. The drug dissolution study was performed in a USP type II apparatus (Hanson SR-Plus™ Dissolution Test Station, Hanson Research Corporation, Chatsworth, CA) (n=2). The dissolution medium was 0.1N HCl (500 mL, pH 1.2, 37±0.5°C). The rate of agitation of the paddle was 50 rpm. The theophylline concentration from the dissolution test was automatically measured at 270 nm by UV/VIS spectrophotometer (Agilent, Santa Clara, CA).

EXAMPLE 19: *In Vitro* Dissolution Study of Example 9. FIGURE 4 is a plot of the in vitro dissolution of two pulses of theophylline was performed and the time of 50% drug release of each pulse (T_{50%}) was be calculated as shown in the Table below:

Sample No.	T _{50%} (hours)	
	1 st dose	2 nd dose
1	0.099	6.760
2	0.105	6.596
Mean	0.102	6.678

FIGURE 5 is an image of the in vitro dissolution study of two pulses of theophylline.

EXAMPLE 20: *In Vitro* Dissolution Study of Example 13. The in vitro dissolution study of two pulses of theophylline was performed as shown in FIGURE 5 and the time of 50% drug release of each pulse (T_{50%}) was be calculated as shown in the Table below:

Sample No.	T _{50%} (hours)	
	1 st dose	2 nd dose
1	0.090	8.415
2	0.092	8.250
Mean	0.091	8.333

EXAMPLE 21: *In Vitro* Dissolution Study of Example 17. FIGURE 6 is a plot of the *in vitro* dissolution study of two pulses of theophylline was performed as shown in Fig. 6. and the time of 50% drug release of each pulse (T_{50%}) was be calculated as shown the Table below:

Sample No.	T _{50%} (hours)	
	1 st dose	2 nd dose
1	0.096	11.266
2	0.098	11.093
Mean	0.097	11.179

EXAMPLE 22: Two-pulse platform of ciprofloxacin

A two-pulse platform of ciprofloxacin was assembled by inserting a thick spacer tablet into an impermeable capsule body followed by the second dose of ciprofloxacin tablet, a thin spacer tablet, and a lag-time tablet, respectively. The position of the lag-time tablet was flush with the mouth of the impermeable capsule body. A relatively air-tight seal was therefore created in the innermost portion of the impermeable capsule body. Finally, the first dose of ciprofloxacin tablet was placed onto the lag-time tablet and then covered with a water soluble gelatin cap. Drug release in 0.1N HCl buffer solution (pH 1.2, 37 ± 0.5°C) at paddle speed 50 rpm from two-pulse ciprofloxacin capsules (mean ± SD, n = 6) is shown in Figure 7.

EXAMPLE 23: Three-pulse platform of verapamil

A three-pulse platform of verapamil was assembled by inserting a thick spacer tablet into an impermeable capsule body followed by the third dose of verapamil tablet, thin spacer tablet, the second lag-time tablet, the second dose of verapamil tablet, thin spacer tablet, and the first lag-time tablet. The position of the first lag-time tablet was flush with the open end the impermeable capsule body. A relatively air-tight seal was created in the innermost portion of the impermeable capsule body. Finally, the first dose of verapamil tablet was placed onto the first lag-time tablet and covered with a gelatin cap. Drug release in 0.1N HCl buffer solution (pH 1.2, 37 ± 0.5°C) at paddle speed 50 rpm from three-pulse verapamil capsules (mean ± SD, n = 6) is shown in Figure 8.

The present invention provides an impermeable capsule body for the duration of the dosing. (See Examples 1 and 2). The present invention provides a swellable erodible polymer containing tablet that can seal the impermeable capsule body upon exposure to aqueous fluids. (see Example 3). The present invention provides a capsule that must float in a stable vertical position, having a positive metacentric height and must contain a gas (see Examples 3). The present invention provides a capsule that contains at least 2 internal layers (tablets in this example) with varying compositions (see Examples 3, 4, and 6). The present invention provides a drug containing tablet incorporated into the device to have a suitable therapeutic concentration (e.g., the example shown contains theophylline as a model drug, which is at a concentration less than a therapeutic dose) (see Example 4). The present invention provides internal tablets separated by a lag time

layer, which contains a swellable erodible polymer (see Example 6). The present invention provide devices includes an outer capsule body, a swellable erodible polymer containing layer erodible, a drug containing layer, a filler layer (placebo tablet in this case), and a gas layer to enable a positive metacentric height that enables vertical buoyancy (see Example 8). The present invention provides one orientation of a two pulsed delivery device that can contain two drug layers, one with immediate release (e.g., outside of the first erodible polymer containing layer), and the second drug containing layer inside the first erodible polymer containing layer (see Example 9). The present invention provide a filler layer (identified as the placebo tablet) is of variable thickness its function is to fill the capsule to a suitable depth such that a specific volume of gas is present in the device to allow the formation of a positive metacentric height during floating that will maintain the capsule device in a vertical orientation (see Example 10). The present invention provides a suitable polymer containing layer to delay drug release can comprise 20% HPMC (see Example 11). An example of capsule assembly for a single pulse capsule (see Example 12). The floating capsule device can be made to have one or more pulsed releases of a single or a combination of drugs (see Examples 13). The filler layer can be varied to adjust the internal gas volume (see Example 14). Delayed release time can be controlled by adjusting the thickness of the erodible polymer containing layer (proportional to tablet weight) (see Example 15). A dissolution test method is described (see Example 18). Dissolution test results are shown for a 2 pulse system, with an immediate pulsed release of theophylline followed by a second pulsed release of theophylline 6.5 hours later (see Example 19). Dissolution test results are shown for a 2 pulse system, with an immediate pulsed release of theophylline followed by a second pulsed release of theophylline 8 hours later (see Example 20). Dissolution test results are shown for a 2 pulse system, with an immediate pulsed release of theophylline followed by a second pulsed release of theophylline 11 hours later (see Example 21).

Drug release characteristics of multiple dose platforms (mean $\pm$ SD, n=6).

Platforms	Lag time (h)		T _{50%} (h)		
	1 st lag time	2 nd lag time	1 st dose	2 nd dose	3 rd dose
Two-pulse platform	12.3 $\pm$ 0.3	—	0.3 $\pm$ 0.0	12.8 $\pm$ 0.1	—
Three-pulse platform	8.0 $\pm$ 0.0	16.8 $\pm$ 0.3	0.3 $\pm$ 0.0	8.5 $\pm$ 0.2	17.0 $\pm$ 0.2

Dissolution study: 900 mL of 0.1N HCl buffer (pH 1.2, 37 $\pm$ 0.5°C) at paddle speed 50 rpm.

Two-pulse platform of an active agent. A two-pulse platform of ciprofloxacin was assembled by inserting a thick spacer tablet into an impermeable capsule body followed by the second dose of ciprofloxacin tablet, a thin spacer tablet, and a lag-time tablet, respectively (Figure 9). The position of the lag-time tablet was flush with the mouth of the impermeable capsule body. A relatively air-tight seal was therefore created in the innermost portion of the impermeable capsule body. Finally, the first dose of ciprofloxacin tablet was placed

onto the lag-time tablet and then covered with a water soluble gelatin cap. The release profile is shown in Figure 7.

Three-pulse platform of an active agent. A three-pulse platform of verapamil was assembled by inserting a thick spacer tablet into an impermeable capsule body followed by the third dose of verapamil tablet, thin
5 spacer tablet, the second lag-time tablet, the second dose of verapamil tablet, thin spacer tablet, and the first lag-time tablet. The position of the first lag-time tablet was flush with the open end the impermeable capsule body. A relatively air-tight seal was created in the innermost portion of the impermeable capsule body. Finally, the first dose of verapamil tablet was placed onto the first lag-time tablet and covered with a gelatin cap (Figure 10). The release profile is shown in Figure 8.

10 It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method, kit, reagent, or composition of the invention, and vice versa. Furthermore, compositions of the invention can be used to achieve methods of the invention.

It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various
15 embodiments without departing from the scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

All publications and patent applications mentioned in the specification are indicative of the level of skill of
20 those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,”
25 and “one or more than one.” The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.” Throughout this application, the term “about” is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

30 As used in this specification and claim(s), the words “comprising” (and any form of comprising, e.g., “comprise” and “comprises”), “having” (and any form of having, e.g., “have” and “has”), “including” (and any form of including, e.g., “includes” and “include”) or “containing” (and any form of containing, e.g.,

“contains” and “contain”) are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

The term “or combinations thereof” as used herein refers to all permutations and combinations of the listed items preceding the term. For example, “A, B, C, or combinations thereof” is intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, CBA, BCA, ACB, BAC, or CAB. Continuing with this example, expressly included are combinations that contain repeats of one or more item or term, e.g., BB, AAA, MB, BBC, AAABCCCC, CBBAAA, CABABB, and so forth. The skilled artisan will understand that typically there is no limit on the number of items or terms in any combination, unless otherwise apparent from the context.

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention.

All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

What is claimed is:

1. A pulsatile drug delivery system to provide a pulsatile release of at least one active pharmaceutical agent comprising:
 - an impermeable capsule body comprising an open capsule end and a closed capsule end;
 - a flotation portion disposed in the capsule body, to maintain the buoyancy of the impermeable capsule body;
 - 5 a first active agent;
 - one or more lag-time layers disposed in the capsule body between the first active agent and the open capsule end; and
 - additional active agent(s) disposed in the capsule body between one or more lag-time layers and the open end of the capsule body, wherein the first active agent and the additional active agent(s) act as active agent(s) reservoirs for a rapid bolus drug release after a predetermined lag time.
- 10 2. A pulsatile drug delivery composition to provide a pulsatile release of at least one active pharmaceutical agent comprising:
 - a capsule body comprising an open capsule end and a closed capsule end;
 - 15 a capsule cap covering the open capsule end of the capsule body;
 - a flotation portion disposed in the capsule body, to maintain the buoyancy of the water capsule body;
 - one or more active agents disposed in the capsule body; and
 - one or more lag-time layers disposed in the capsule body between the one or more active agent and the open capsule end, wherein the first active agent and the additional active agent(s) act as active agent reservoirs for a rapid bolus drug release after a predetermined lag time.
- 20 3. The composition of claim 2, wherein the capsule body is impermeable to gastric fluids
4. The composition of claim 2, wherein the capsule cap comprises gelatin.
5. The composition of claim 2, wherein the flotation portion comprises a gas reservoir positioned in the closed capsule end.
- 25 6. The composition of claim 2, wherein one or more lag-time layers each have different lag times.
7. The composition of claim 2, wherein each of the one or more active agents have different rates of release.

8. The composition of claim 2, further comprising a second one or more active agents disposed in the capsule body between the one or more lag-time layers and the open capsule end.
9. The composition of claim 2, further comprising a second one or more lag-time layers disposed in the capsule body between the one or more active agents and the open capsule end.
- 5 10. The composition of claim 2, further comprising an enteric coating over at least a portion of the capsule cap.
11. A floating pharmaceutical reservoir for providing pulses release of at least one active pharmaceutical agent comprising:
- An impermeable capsule body;
- 10 a capsule cap connected to the capsule body, wherein the capsule cap is at least partially permeable;
- one or more active agents disposed in the capsule body;
- one or more lag-time layers disposed in the capsule body adjacent to the one or more active agents, wherein the one or more active agents act and one or more lag-time layers act as a reservoir for a rapid bolus drug release after a predetermined lag time; and
- 15 a flotation portion disposed in the capsule body, to maintain the buoyancy.
12. A method of making a floating pharmaceutical reservoir for providing pulses release of at least one active pharmaceutical agent comprising the steps of:
- coating a capsule with a water insoluble coating, an acid resistant coating or a water insoluble acid resistant coating;
- 20 placing a flotation portion disposed in the capsule body, to maintain the buoyancy;
- depositing a first active agent into the capsule body;
- disposing a first lag-time layer in the capsule body adjacent to the one or more active agents to control the release of the first active agent after a predetermined lag time; and
- sealing the capsule body with a capsule cap.
- 25 13. The method of claim 12, wherein the capsule body comprises an erodible coating, a water insoluble coating, an acid resistant coating or a water insoluble acid resistant coating.
14. The method of claim 12, wherein the capsule cap comprises gelatin.
15. The method of claim 12, wherein the flotation portion comprises a gas reservoir positioned in the closed capsule end.

16. The method of claim 12, wherein the one or more active agents have different rates of release.
17. The method of claim 12, wherein the one or more lag-time layers each have different lag times, different rates of release.
18. The method of claim 12, further comprising the step of positioning a second active agent in the capsule body on the lag-time layer.
19. The method of claim 18, further comprising the step of positioning a second lag-time layer in the capsule body on the second active agent.
20. The method of claim 19, further comprising the step of positioning a third active agent in the capsule body on the second lag-time layer.
21. The method of claim 19, wherein the one or more lag-time layers each have different lag times.
22. The method of claim 19, wherein the one or more active agents are released from a patient's stomach, or from a subsequent gastrointestinal site proximal thereto, for absorption thereof at a site more distal in the gastrointestinal tract than said patient's stomach, e.g., the duodenum, the jejunum, the small intestine, the small intestine and colon, the ileum.
23. A pulsatile drug delivery systems to provide a pulsatile release of at least one active pharmaceutical agent comprising:
- a water insoluble acid resistant capsule body comprising an open capsule end and a closed capsule end, wherein at least a portion of the water insoluble acid resistant capsule body maintains buoyancy;
 - a first active agent disposed in the capsule body;
 - one or more lag-time layers disposed in the capsule body between the first active agent and the open capsule end; and
 - a second active agent disposed in the capsule body between one or more lag-time layers and the open end of the capsule body, wherein the first active agent and the second active agent act as active agent reservoirs for a rapid bolus drug release after a predetermined lag time.

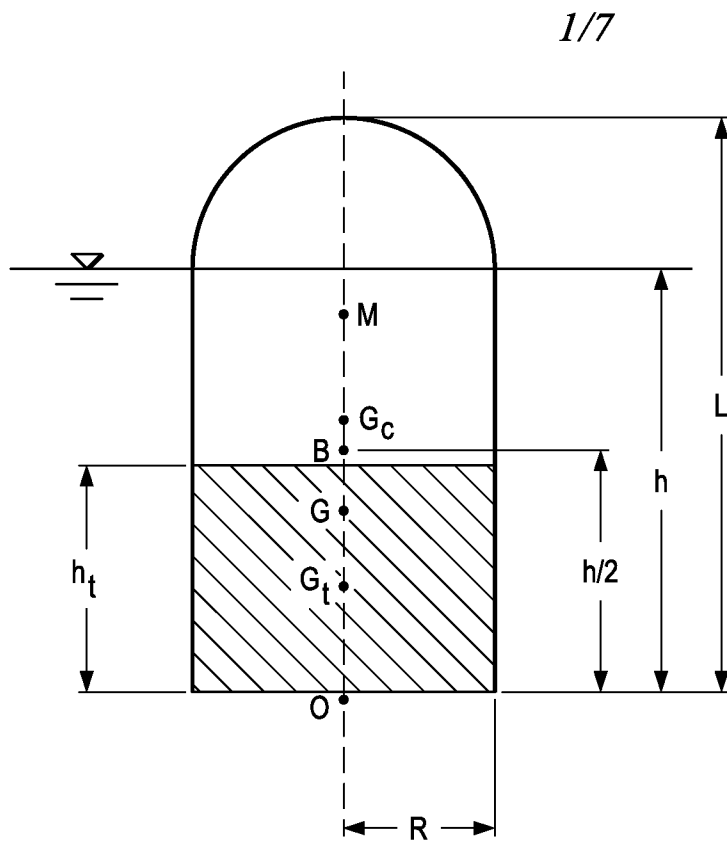


FIG. 1

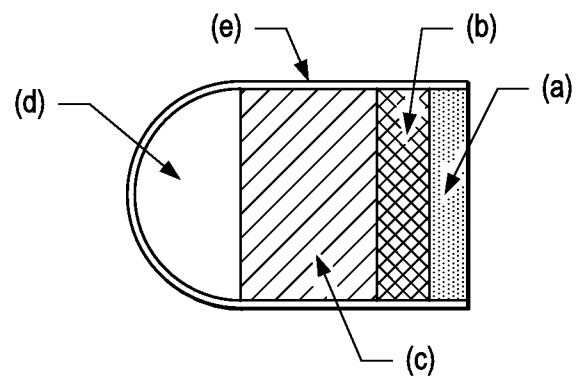


FIG. 2

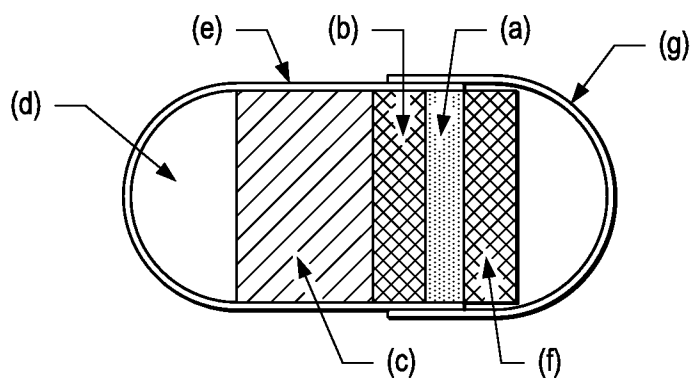
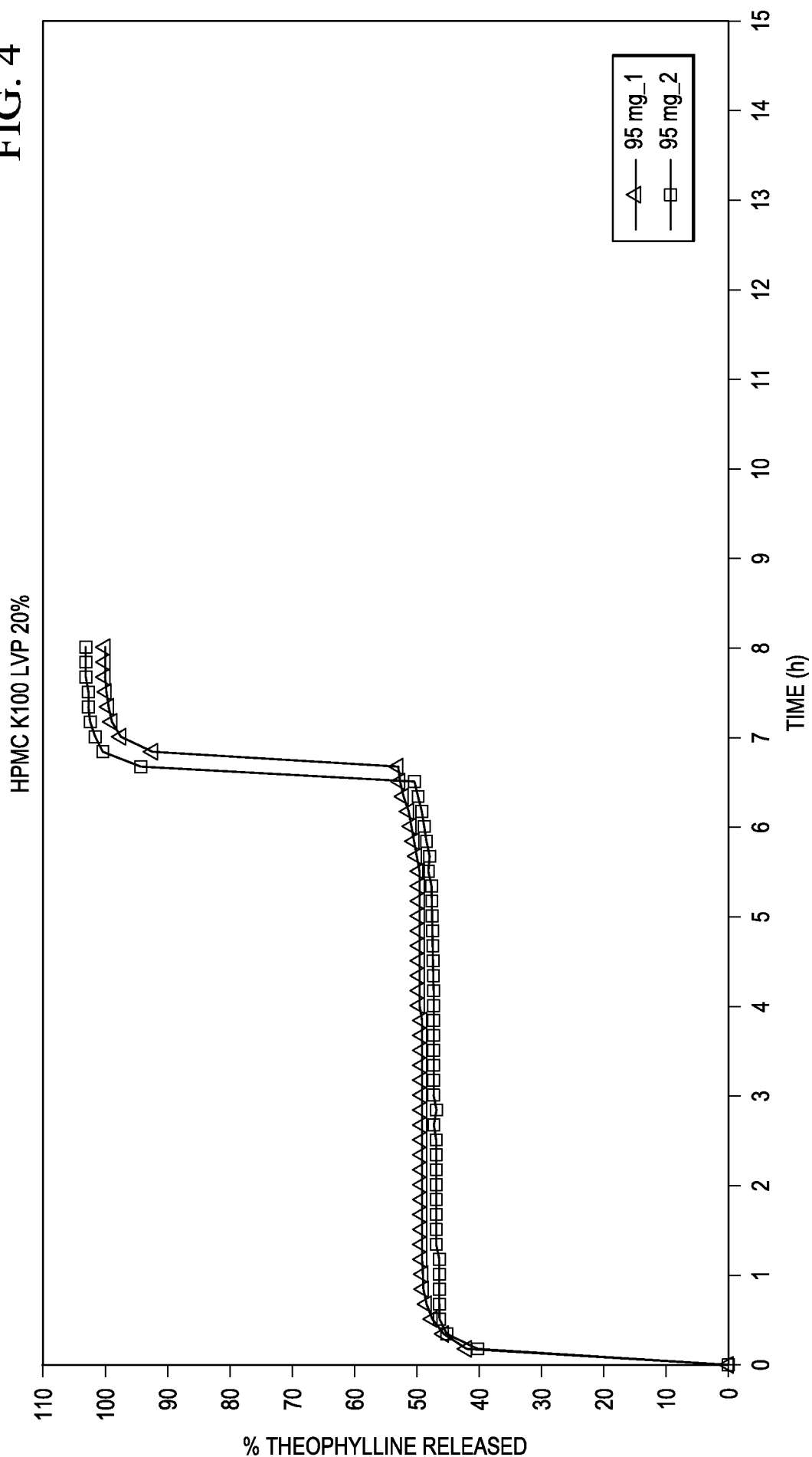


FIG. 3

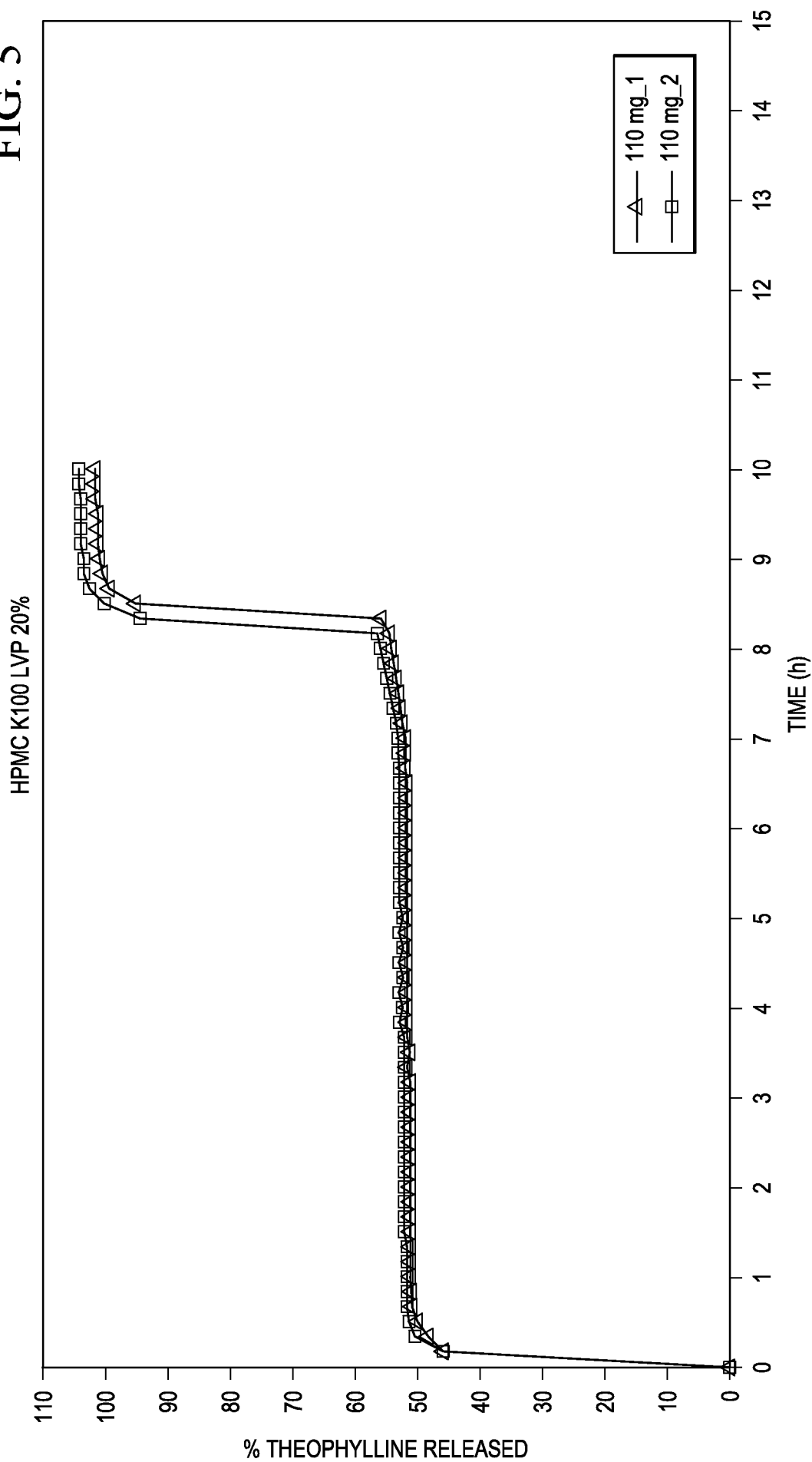
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FIG. 4



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FIG. 5



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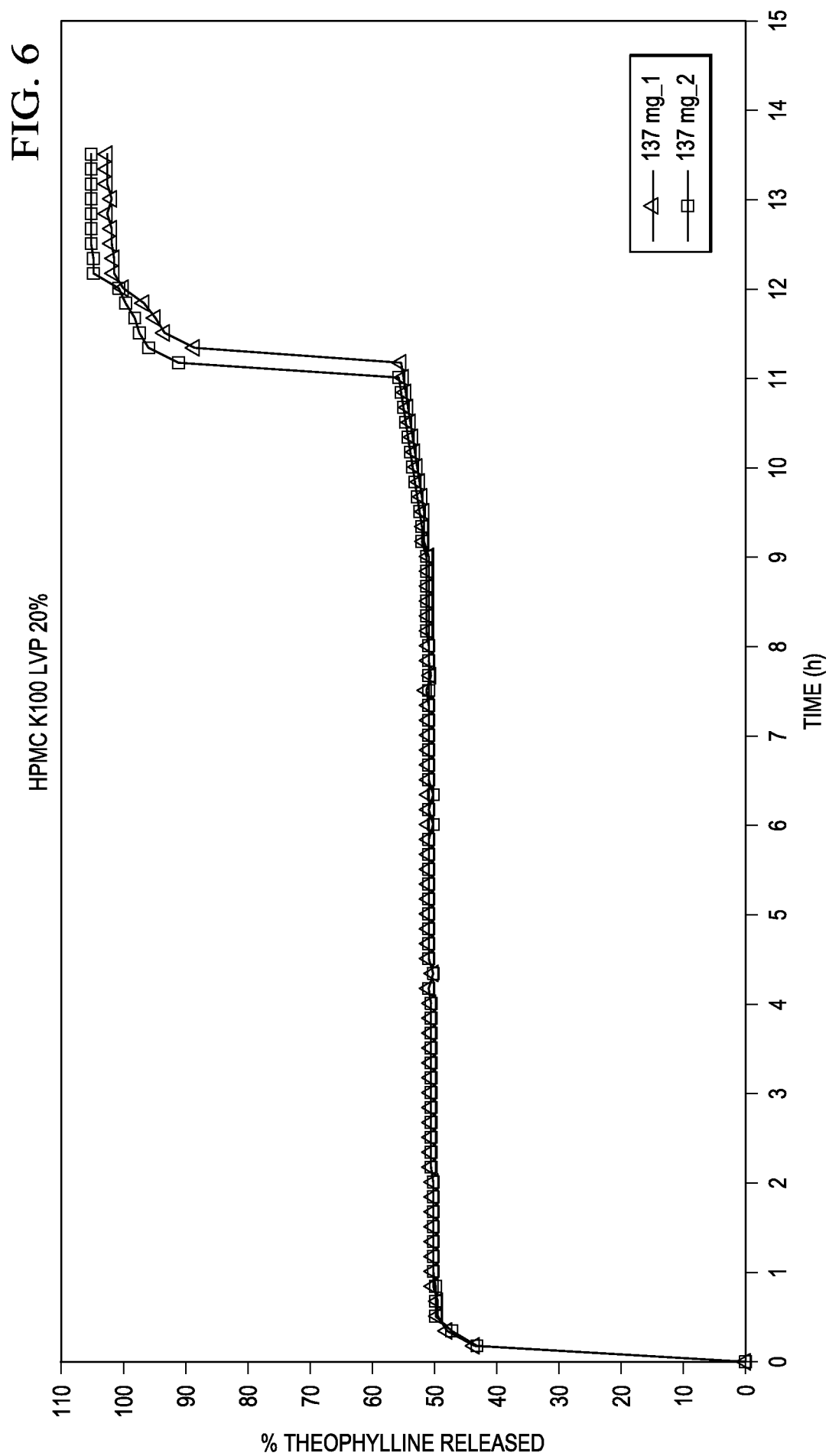
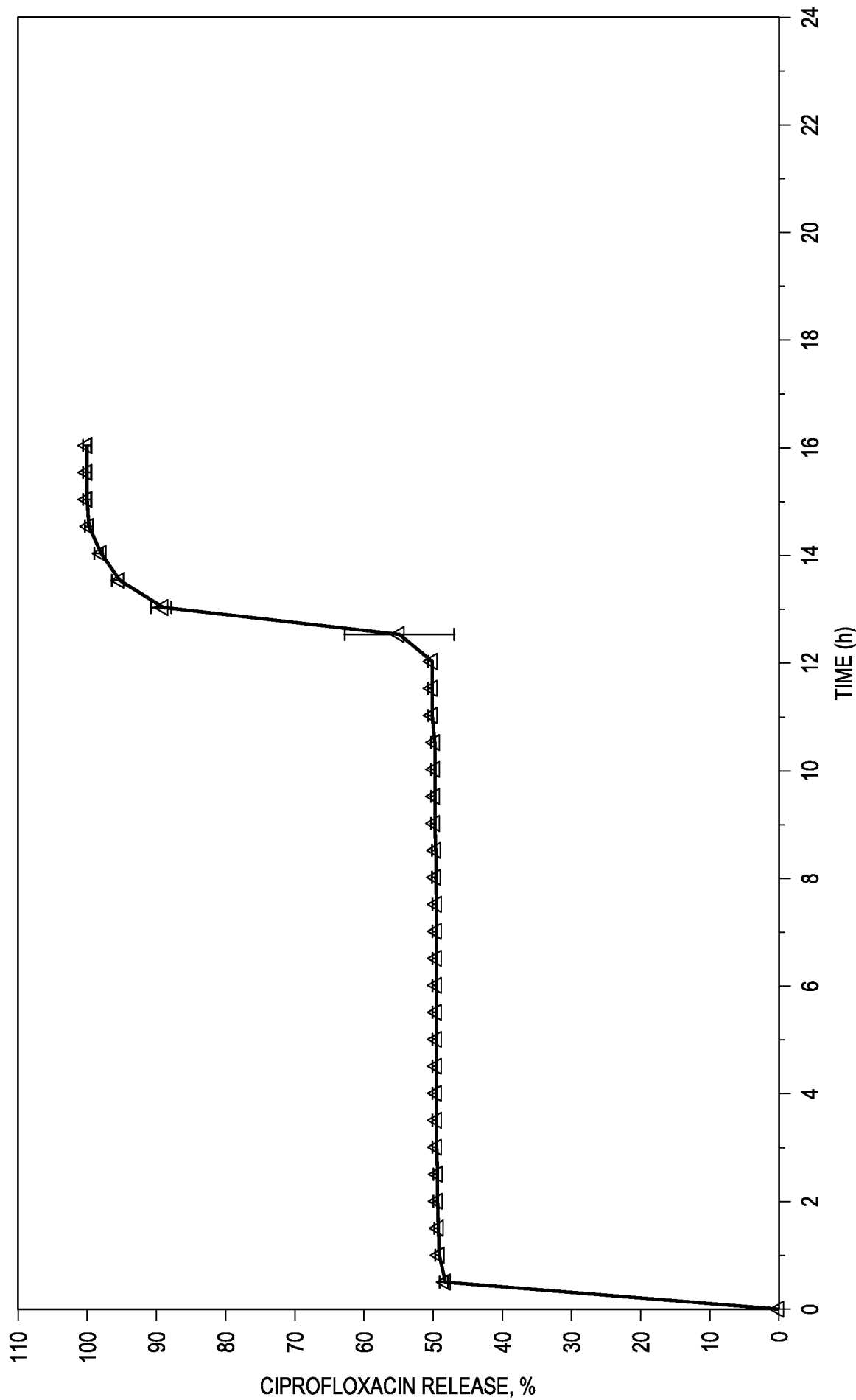
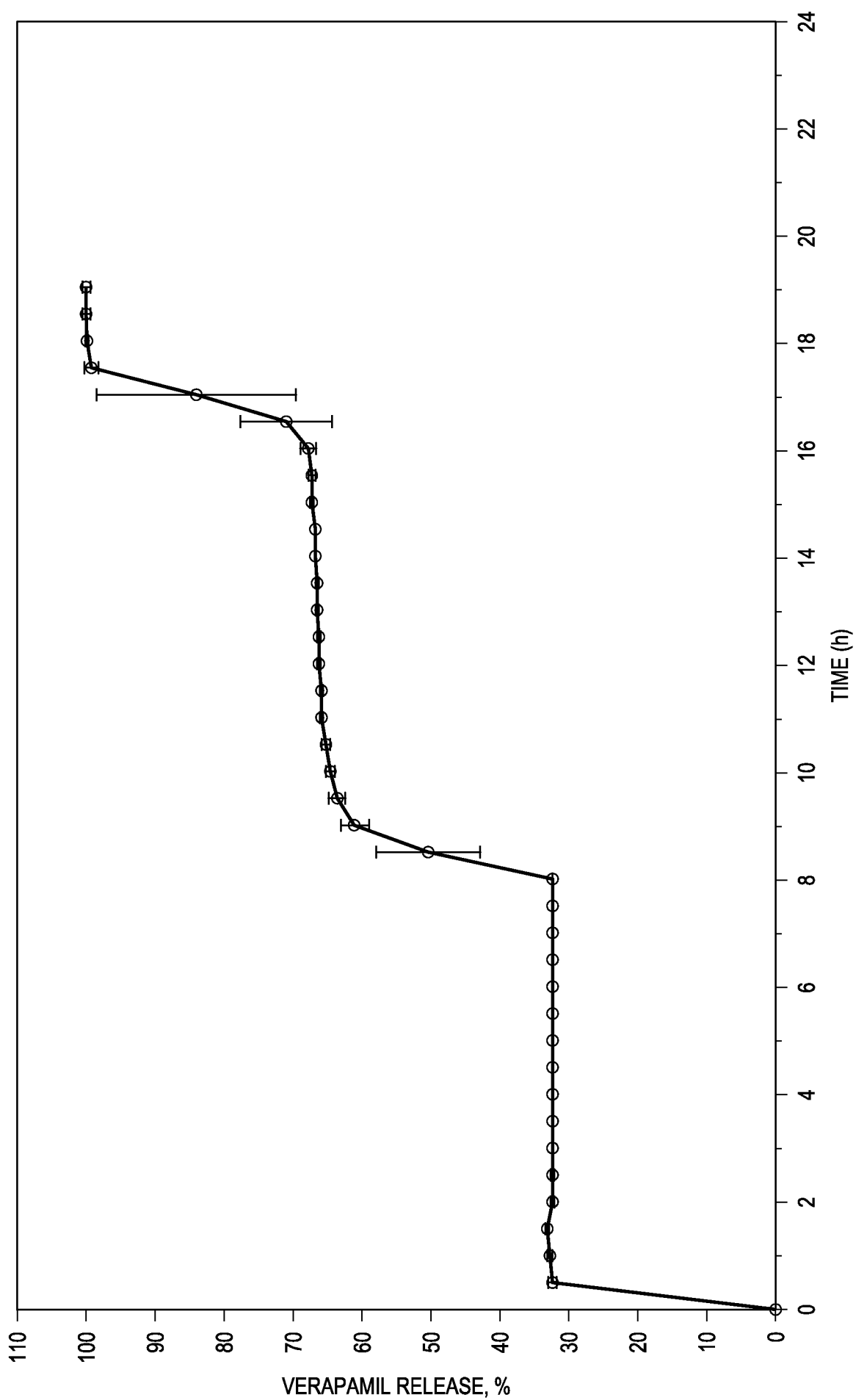


FIG. 7



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FIG. 8



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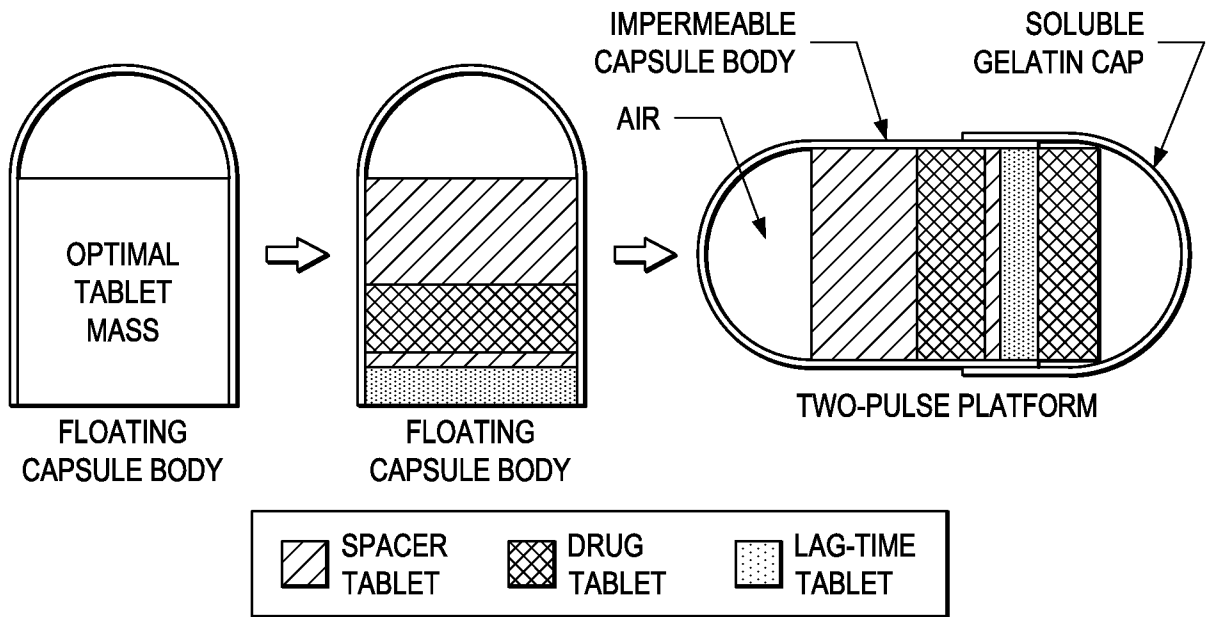


FIG. 9

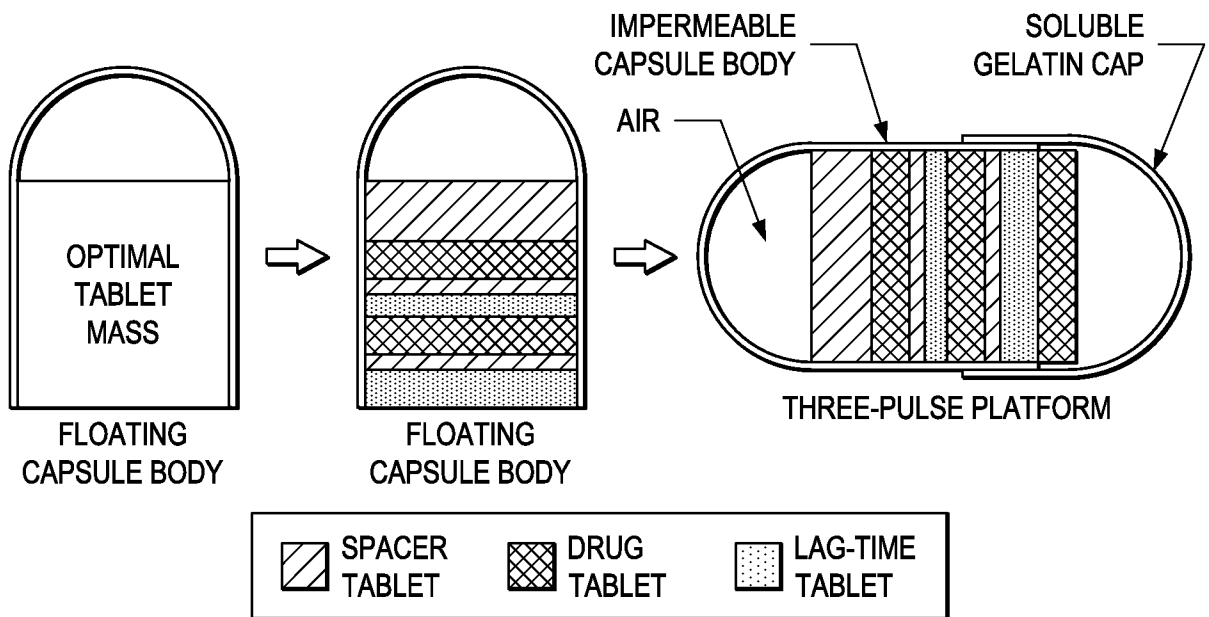


FIG. 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038690**A. CLASSIFICATION OF SUBJECT MATTER****A61K 9/48(2006.01)i, A61K 47/30(2006.01)i**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 9/48; A61K 9/22; A61K 31/165; A61K 9/50; A61K 9/28

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: pulsatile, impermeable capsule body, floating, buoyancy, lag-time layer, capsule cap

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	H. ZOU et al., "Design and gamma-scintigraphic evaluation of a floating and pulsatile drug delivery system based on an impermeable cylinder", Chemical & Pharmaceutical Bulletin, April 2007, Vol. 55, No. 4, pp 580-585. See abstract, page 580 and Figures 1-2.	1-11, 13-24
Y	R. LOBENBERG et al., "Pharmacokinetics of an immediate release, a controlled release and a two pulse dosage form in dogs", European Journal of Pharmaceutics and Biopharmaceutics, May 2005 (Available on-line 16 February 2005), Vol. 60, No. 1, pp. 17-23 See abstract, page 18 and Figure 1.	1-11, 13-24
A	B. LI et al., "A novel system for three-pulse drug release based on "tablets in capsule" device", International Journal of Pharmaceutics, 20 March 2008 (Available on-line 4 November 2007), Vol. 352, No. 1-2, pp. 159-164 See abstract, pages 1-2 and Figure 1.	1-11, 13-24
A	US 2007-0128276 A1 (R. JAIN et al.) 07 June 2007 See abstract and claims 1, 8, 12, 19, 20, 27, 29, 30.	1-11, 13-24

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

23 OCTOBER 2012 (23.10.2012)

Date of mailing of the international search report

23 OCTOBER 2012 (23.10.2012)

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Authorized officer

LEE, SUN HWA

Telephone No. 82-42-481-5606



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/038690

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007-0154547 A1 (H. H. FLANNER et al.) 05 July 2007 See abstract, paragraphs [0025], [0034], [0061], [0062], and Figure 5.	1-11,13-24
A	WO 2010-103367 A1 (COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH) 16 September 2010 See claims 1, 20, 21.	1-11,13-24
PX	S. THITINAN et al., "Development of a gastroretentive pulsatile drug delivery platform", Journal of Pharmacy and Pharmacology, April 2012, Vol. 64, No. 4, pp. 505-516 See pages 506-508, 512, 515, and Figure 1.	1-11,13-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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