Abstract:
The present invention relates to multilayered pharmaceutical compositions comprising at least one or more agents each selected from same or different classes having a low dose, comprising at least one polymer(s) or enteric polymer that predominantly controls or delays the release of at least one active agent(s) and optionally one or more pharmaceutically acceptable excipient(s).
MULTILAYERED PHARMACEUTICAL COMPOSITIONS AND PROCESSES THEREOF

FIELD OF THE INVENTION

The present invention relates to multilayered pharmaceutical compositions comprising at least one or more agents each selected from same or different classes having a low dose, comprising at least one polymer(s) or enteric polymer that predominantly controls or delays the release of at least one active agent(s) and optionally one or more pharmaceutically acceptable excipient(s). Particularly the multilayered pharmaceutical compositions comprise at least three layers wherein the first layer comprises a low-dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally along with one or more pharmaceutically acceptable excipient(s) in the immediate, extended or sustained or prolonged or delayed release form; a second (intermediate) lag time controlling layer entirely covering the first layer comprising at least one hydrophilic swellable polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and a third layer comprising at least one low dose active agent(s) which is same or different from the first low-dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally along with one or more pharmaceutically acceptable excipient(s) in the immediate, extended or sustained or prolonged or delayed release form such that the said third layer is a coated or compressed on to the second layer optionally coated with a film former or a coating having an active agent. The present invention also describes process for preparation of such compositions and method of using such compositions thereof.

BACKGROUND OF THE INVENTION

The inherent physicochemical properties of active(s) make it particularly difficult to formulate combinations of two biologically-active agents. Combining two or more actives as a fixed dose-pharmaceutical composition improves patient compliance is known in the art. It can be either in the form of two or more active ingredients in immediate release form or a combination of immediate release and modified release form. There are various techniques by which the combination of immediate release and modified release is formulated in single dosage form.

US Pat. No. 6,682,759 discloses an oral tablet containing a system of immediate-release of a drug including glimepiride and another drug including metformin hydrochloride, with
extended release. According to the procedure revealed in this document, glimepiride is formulated in a coating surrounding the core of metformin. US20030187074 discloses a release system consisting of a two-layered pharmaceutical form, one with a biguanide including metformin hydrochloride of controlled release depending on the pH environment, and the other layer of sulphonylurea such as glimepiride. US20070264331 claims a stable pharmaceutical composition in the form of a tablet comprising a core or matrix containing an extended-release biguanide; further comprising an insulating layer or coating comprising a hydrophobic polymer, and further comprising a coating containing an immediate-release sulphonylurea. WO9929314 discloses a combination of metformin (2:1) salts along with sulphonylureas such as glimepiride. WOO132158 describes a formulation comprising a low dose combination of metformin and at least one other agent such as glimepiride employed in substantially higher daily dosages as prescribed in generally accepted medical practice for first line therapy in treating diabetes. WO200412700 claims a dosage form of combination of high dose high solubility active ingredient such as metformin hydrochloride as modified release and low dose active ingredient such as glibenclamide as immediate release suitable for swallowing. WO200326637 claims a dosage form for the treatment of diabetes mellitus and conditions associated with it, comprising a compressible controlled release core composition comprising metformin or its pharmaceutically acceptable salt, two or more swellable polymers wherein at least one polymer is an anionic polymer, one or more pharmaceutically acceptable excipient(s) that improve the compressibility of the core composition, and optionally, a coat comprising one or more water insoluble polymer(s) surrounding the core; further comprising an immediate release long-acting sulphonylurea such as glibenclamide. WO200294285 claims a single-daily-dose oral pharmaceutical form comprising a biguanide and at least another active principle such as glibenclamide, wherein either of them is in the form of prolonged release compositions.

WO2004045622 (Ranbaxy Lab Ltd.) claims a solid pharmaceutical dosage form for oral administration, the dosage form comprising an extended release layer comprising a biguanide; and an immediate release layer comprising a sulphonylurea. The composition is in the form of a matrix comprising a mixture of the biguanide and one or more rate controlling polymers or the biguanide layered onto a pharmaceutically inert core or seed, along with an immediate release outer layer comprising a sulphonylurea.
US20040081697 describes a pharmaceutical composition which comprises an insulin sensitizer and another agent and a pharmaceutically acceptable carrier therefore, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitizer and the other agent. US 20030219482 claims a pharmaceutical composition for the once-a-day administration of drugs for the treatment of non-insulin dependent diabetes mellitus in humans, the composition comprising a core comprising a multiparticulate polyphasic system comprising a first particulate phase comprising a biguanide or pharmaceutically acceptable salt of the biguanide, a binding agent and a first hydrophilic water-swellable polymer; a second particulate phase comprising a sulfonylurea or pharmaceutically acceptable salt of the sulfonylurea, a wetting agent, a cyclodextrin polymer and a second hydrophilic water-swellable polymer; and a third phase comprising a third hydrophilic water-swellable polymer; and a coating on the core, wherein the coating has a rupture time of not more than about 1 hour. US 20040039031 discloses novel medicinal products consisting of a combination of a biguanide and a sulfonamide, at low doses, in combination or as a mixture with one or more inert, pharmaceutically acceptable excipients. US Pat. No. 6,099,862 claims a controlled release pharmaceutical tablet containing antihyperglycemic drug preferably biguanides and a hypoglycemic drug preferably sulfonylureas that does not contain an expanding or gelling polymer layer and comprising a core containing the antihyperglycemic drug and the hypoglycemic drug, a semipermeable coating membrane surrounding the core and at least one passageway in the membrane to allow the drugs to be released from the core. US Pat. No. 6,001,391 describes a process for producing solid combination tablets, which have at least two phases. The one of the two phases is processed by melt extrusion technique and contains a water soluble or swellable binder. US Pat. No. 6,238,699 describes a pharmaceutical dosage form of carbidopa and levodopa where both the active ingredients are present as immediate release and sustained release. The formulation is in the form of inlay tablet or bilayered tablet or a capsule containing pellets. US Pat. No. 6,372,254 discloses a press coated, pulsatile active ingredient delivery system which comprises a core of immediate release, enveloped by an extended release compartment.

However none of the prior art documents described hereinabove disclose multilayered pharmaceutical compositions which are highly safe and effective and are easy to
formulate as described in context of the present invention. A review of the prior art reveals that there still exists an unmet medical need for development of pharmaceutical compositions to provide treatment regimens that could alleviate the drawbacks associated with the prior art compositions that have so far plagued effective patient management. The present invention provides novel safe and effective compositions for the management of disease(s) which are particularly devoid of the associated side effects and therefore provides a significant advancement in the said field.

SUMMARY OF THE INVENTION

It is an objective of the present invention to provide multilayered pharmaceutical compositions comprising at least one or more low dose active agent(s) selected from same or different classes, at least one release rate controlling polymer(s) or enteric polymer that predominantly controls or delays the release of at least one low dose active agent(s) and optionally one or more pharmaceutically acceptable excipient(s).

It is a preferred objective of the present invention to provide multilayered pharmaceutical compositions comprising at least three layers wherein the first layer comprises a low dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally along with one or more pharmaceutically acceptable excipient(s) in the immediate, extended or sustained or prolonged or delayed release form optionally coated with a pH dependent or pH independent film former; a second layer entirely covering the first layer comprising at least one hydrophilic swellable polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and a third layer comprising at least one low dose active agent(s) which is same or different from the first low-dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally along with one or more pharmaceutically acceptable excipient(s) in the immediate, extended or sustained or prolonged or delayed release form such that the said third layer is a coated or compressed on to the second layer optionally coated with a film former or a coating having an active agent.

It is a preferred objective of the present invention to provide multilayered pharmaceutical compositions comprising at least three layers wherein the first layer comprises a low dose active agent with or without release rate controlling polymer(s) or
enteric polymer(s) optionally alongwith one or more pharmaceutically acceptable
excipient(s) in the immediate, extended or sustained or prolonged or delayed release form
optionally coated with a pH dependent or pH independent film former; a second layer
entirely covering the first layer comprising atleast one hydrophilic swellable polymer(s)
and optionally one or more pharmaceutically acceptable excipient(s); and a third layer
comprising at least one low dose active agent(s) which is same or different from the
first low-dose active agent with release rate controlling polymer(s) or enteric
polymer(s) optionally alongwith one or more pharmaceutically acceptable excipient(s)
in the immediate, extended or sustained or prolonged or delayed release form such that
the said third layer is a coated or compressed on to the second layer.

It is a preferred objective of the present invention to provide multilayered
pharmaceutical compositions comprising atleast three layers wherein the first layer
comprises a low dose active agent optionally alongwith one or more pharmaceutically
acceptable excipient(s) in the immediate release form; a second layer entirely covering
the first layer comprising atleast one hydrophilic swellable polymer(s) and optionally
one or more pharmaceutically acceptable excipient(s); and a third layer comprising at
least one low dose active agent(s) which is same or different from the first low-dose
active agent with release rate controlling polymer(s) or enteric polymer(s) optionally
alongwith one or more pharmaceutically acceptable excipient(s) in the immediate,
extended or sustained or prolonged or delayed release form such that the said third
layer is a coated or compressed on to the second layer.

In accordance with the present invention, the term "multilayered pharmaceutical
composition" as used herein refers to a composition wherein the dosage form have at
least two or more layers such as bilayered tablet or trilayered tablet wherein one layer is
exactly adjacent to the next layer and completely surrounded by the next layer. For
example, a bilayered coated tablet-in-tablet dosage form wherein first layer is in the
form of a compressed tablet surrounded by a second layer compressed on to the first
layer, and a third layer in the form of a coating such as film coating or sugar coating
over the second layer, wherein the first and the third layer comprises at least one active
agent. Alternatively the composition can be a trilayered tablet-in-tablet dosage form
wherein first layer is in the form of a compressed tablet surrounded by a second layer
compressed on to the first layer, and a third layer compressed on to the second layer, optionally further comprising a coating such as film coating or sugar coating over the third layer wherein the coat may or may not comprise an active agent.

It is also an objective of the present invention to provide a dosage form composition which comprises low dose active agent in two distinct fractions, wherein the said dosage form provides immediate or extended or sustained or prolonged or delayed release of first fraction of the low dose active agent from the first (innermost) layer; a second inert polymeric layer covering the first layer, and an immediate or extended or sustained or prolonged or delayed release of the second fraction of low dose active agent from the third layer (outermost), such that the gap or lag or interval or delay or difference between the release of first and second pulse of the active agent from the first (innermost) and third (outermost) layer is about 1 hour to about 10 hours after oral administration and wherein the said dosage form provides a sustained release of the first (innermost) layer for an extended period of time such as from 8-24 hours.

It is yet another objective of the present invention to provide process for preparation of such multilayered pharmaceutical compositions.

It is still another objective of the present invention to provide a method of using such composition which comprises administering to a subject an effective amount of the composition.

The compositions of the present invention provide effective prophylactic or therapeutic concentrations of active agent(s) for extended period of time.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides multilayered pharmaceutical compositions comprising at least one or more low dose active agent(s) each selected from same or different classes of agents, at least one release rate controlling polymer(s) or enteric polymer that predominantly controls or delays the release of at least one active agent(s) and optionally one or more pharmaceutically acceptable excipient(s).

In the context of the present invention, low dose active agents(s) can be defined as the
active agents having low dose which ranges from 0.01 mg to about 100 mg.

In context of the present invention, multilayered pharmaceutical compositions release the drug in a time controlled pulsatile manner such that a single dosage form provides an initial dose or pulse of the active agent followed by one release-free interval or lag-phase, after which second dose or pulse of the active agent is released. The pulsatile effect i.e., the release of the active agent as a "pulse" after a lag time has been designed in such a way that a complete and immediate or extended or sustained or prolonged or delayed release should follow the lag time. Such systems are also called time-controlled as the active agent release is independent of the surrounding micro gastrointestinal tract (GIT) environment.

In an embodiment, the present invention provides multilayered pharmaceutical compositions comprising at least three layers wherein the first layer comprises a low dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally along with one or more pharmaceutically acceptable excipient(s) in the immediate, extended or sustained or prolonged or delayed release form optionally coated with a pH dependent or pH independent film former; a second layer entirely covering the first layer comprising at least one hydrophilic swellable polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and a third layer comprising at least one low dose active agent(s) which is same or different from the first low-dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally along with one or more pharmaceutically acceptable excipient(s) in the immediate or extended or sustained or prolonged or delayed release form such that the said third layer is a coated or compressed on to the second layer optionally coated with a film former or a coating having an active agent.

In accordance with the present invention, the term "multilayered pharmaceutical composition" as used herein refers to a composition wherein the dosage form can have at least two or more layers such as bilayered tablet or trilayered tablet wherein one layer is exactly adjacent to the next layer and completely surrounded by the next layer. For example, a bilayered coated tablet-in-tablet dosage form wherein first layer is in the form of a compressed tablet surrounded by a second layer compressed on to the first layer, and a third layer in the form of a coating such as film coating or sugar coating.
over the second layer, wherein all the first and the third layer comprises at least one active agent. Alternatively the composition can be a trilayered tablet-in-tablet dosage form wherein first layer is in the form of a compressed tablet surrounded by a second layer compressed on to the first layer, and a third layer compressed on to the second layer, optionally further comprising a coating such as film coating or sugar coating over the third layer wherein the coat may or may not comprise an active agent.

In another embodiment, the present invention provides multilayered pharmaceutical compositions comprising atleast three layers wherein the first layer comprises a low dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally alongwith one or more pharmaceutically acceptable excipient(s) in the immediate, extended or sustained or prolonged or delayed release form optionally coated with a pH dependent or pH independent film former; a second layer entirely covering the first layer comprising atleast one hydrophilic swellable polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and a third layer comprising at least one low dose active agent(s) which is same or different from the first low-dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally alongwith one or more pharmaceutically acceptable excipient(s) in the immediate or extended or sustained or prolonged or delayed release form such that the said third layer is a coated or compressed on to the second layer.

In another embodiment, the present invention provides a dosage form composition which comprises low dose active agent in two distinct fractions, wherein the said dosage form provides immediate or extended or sustained or prolonged or delayed release of first fraction of the low dose active agent from the first (innermost) layer; a second inert polymeric layer covering the first layer, and an immediate or extended or sustained or prolonged or delayed release of the second fraction of low dose active agent from the third layer (outermost), such that the gap or lag or interval or delay or difference between the release of first and second pulse of the active agent from the first (innermost) and third (outermost) layer is about 1 hour to about 10 hours after oral administration and wherein the said dosage form provides a sustained release of the first (innermost) layer for an extended period of time such as from 8-24 hours after administration.

In an embodiment, the multilayered pharmaceutical compositions according to the
present invention are designed in such a manner so as to affect an immediate, extended or sustained or prolonged or delayed release of the first pulse of the first low dose active agent, followed by lag phase and thereafter followed by immediate, extended or sustained or prolonged or delayed release of the low dose active agent which is same or different from the first low dose active agent. The pharmaceutical compositions of the present invention provide a less frequent dosing of the medicament as is required by only a sustained release dosage form, increase the resultant patient compliance and provides a more sustained drug blood level response without any side effect(s). By providing a slow and steady release of a medicament over time, absorbed drug concentration spikes are mitigated or eliminated by affecting a smoother and more sustained blood level response. The compositions of the present invention can be made for once-a-day or twice-a-day administration. The compositions of the present invention result in a uniform and constant dissolution of the active agent from the pharmaceutical formulation and are thus effective for an extended period of time. Further, such a formulation is simple to make and the manufacturing process is reproducible.

In a preferred embodiment according to the present invention, the second (intermediate) inert or placebo layer comprises at least one hydrophilic swelling polymer(s) as the release rate controlling polymer. When the said layer is exposed to aqueous fluids in vivo, the said release rate controlling polymer swells forming a gel or a gel-like mass which prevents the entry of the fluid into the innermost layer comprising the active agent in an immediate release form for at least 1 hour to about 10 hours. Subsequently the said gel or gel-like mass erodes gradually thus leading to the contact of the in vivo fluids with the inner layer and its disintegration to release the second pulse of the low dose active agent same or different from the first active agent released from the outermost layer.

In another preferred embodiment according to the present invention, the second (intermediate) inert layer comprises hydrophilic swelling polymer such as hydroxypropyl methylcellulose (HPMC) as the release rate controlling polymer.

In another embodiment, the multilayered pharmaceutical compositions are able to provide efficient blood therapeutic levels of the active agent for extended duration. Also the first pulse of the active agent released almost immediately upon in vivo
administration helps to provide immediate relief against a disease/disorder and the subsequent sustained release of the second pulse of the active agent after a lag time of about 1 hour to about 10 hours provides a treatment for an extended duration of time besides ensuring that there is no substantial build-up of toxic levels of active agent in the blood at any point of time.

In another embodiment, the present invention provides multilayered pharmaceutical compositions comprising three layers wherein the first layer comprises a low dose active agent or its salts, esters, prodrugs, isomers, solvates, hydrates, or derivatives, with or without release rate controlling polymer(s) or enteric polymer(s) optionally alongwith one or more pharmaceutically acceptable excipient(s) in the immediate, extended or sustained or prolonged or delayed release form; a second layer entirely covering the first layer comprising atleast one hydrophilic swellable polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and a third layer which is in the form of a coating provided on the second layer wherein said coating comprises a low dose active agent which is same or different from the first active or its salts, esters, prodrugs, isomers, solvates, hydrates, or derivatives, alongwith with a film former and optionally one or more pharmaceutically acceptable excipient(s) which provides an immediate release of the agent.

In a preferred embodiment, the present invention provides multilayered pharmaceutical compositions wherein the said system releases the active agent(s) predominantly by erosion mechanism or combination of erosion and diffusion mechanisms, and which provides therapeutic concentrations of active agent(s) for extended periods of time.

In an embodiment, the low dose active agent according to the present invention is selected from but not limited to a group comprising of adrenergic agent; adrenocortical steroid; adrenocortical suppressant; aldosterone antagonist; amino acid; anabolic; analeptic; analgesic; anesthetic; anorectic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-anemic; anti-anginal; anti-arhritic; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholinergic; anticoagulant; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; anti-emetic; anti-epileptic; antifibrinolytic; antifungal; antihemorrhagic; antihistamine; antihyperlipidemia; antihypertensive; antihypotensive; anti-infective; anti-inflammatory; anti-pyretic; antimicrobial; antimigraine; antimitotic; antinociceptant, antineoplastic, antineutropenic,
antiparasitic; antiproliferative; antipsychotic; antirheumatic; antiseborrheic; antisecretory; antispasmodic; antithrombotic; anti-ulcerative; antiviral; appetite suppressant; blood glucose regulator; bone resorption inhibitor; bronchodilator; cardiovascular agent; cholinergic; depressant; diagnostic aid; diuretic; dopaminergic agent; estrogen receptor agonist; fibrinolytic; fluorescent agent; free oxygen radical scavenger; gastric acid suppressant; gastrointestinal motility effector; glucocorticoid; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; hormone; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; LHRH agonist; mood regulator, mucolytic; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol derivative; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; psychotropic; radioactive agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A1 antagonist; serotonin antagonist; serotonin inhibitor, serotonin receptor antagonist; steroid; anticancer compounds, antiparkinson agents, thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; amyotrophic lateral sclerosis agent; cerebral ischemia agent; Paget's disease agent; unstable angina agent; vasoconstrictor; vasodilator; wound healing agent; xanthine oxidase inhibitors, vitamins, minerals, nutritional supplements and the like, and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof, used either alone or in combination thereof.

In another embodiment, the release rate controlling polymer(s) of the present invention comprises a polymeric material selected from but not limited to the group comprising pH dependent polymers; pH independent polymers; swellable polymers; non-swellable polymers; hydrophilic polymers; hydrophobic polymers and/or one or more other hydrophobic materials; ionic polymers such as sodium alginate, carbomer, calcium carboxymethylcellulose or sodium carboxymethylcellulose; non-ionic polymers such as hydroxypropyl methylcellulose; synthetic or natural polysaccharide selected from the group comprising alkylcelluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitrocelluloses, dextrin, agar, carrageenan, pectin, furcellaran, starch and starch derivative, and mixtures thereof. The polymeric material used in the present invention is selected from but not limited to a group comprising cellulosic polymer, methacrylate polymer, methacrylate copolymer such as Eudragit® EPO, Eudragit® ElOO, Eudragit® E12.5 and the like or mixtures thereof, Polyvinylpyrrolidone (PVP), alginate,
polyvinylpyrrolidone-polyvinyl acetate (PVP-PVA) copolymer, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(alkyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(alkyl acrylate), poly(ocadecyl acrylate), poly(ethylene), poly(alkylene), poly(alkylene oxide), poly(alkylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) and polyurethane or a mixture thereof used either alone or in combination thereof.

In a further embodiment, the dosage form comprises a gum selected from but not limited to a group comprising xanthan gum, guar gum, gum arabic, carrageenan gum, karaya gum, locust bean gum, acacia gum, tragacanth gum, agar and the like or mixtures thereof.

In a further embodiment, the release controlling polymer(s) useful in the present invention is selected from but not limited to a group comprising carbopol; cellulosic polymers such as sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose; copolymers of methyl vinyl ether and maleic anhydride such as Gantrez®; enteric polymers; sodium hyaluronate; gums; alginates; polycarbophil; polyethylene oxide; starch; dextran; chitosan; and the like or mixtures thereof.

In an embodiment of the present invention, the pH independent polymer is selected from but not limited to a group comprising alkyl celluloses such as methyl cellulose, hydroxyalkyl alkyl celluloses such as hydroxypropyl methyl cellulose (HPMC, Methocel®), hydroxy alkyl celluloses such as hydroxypropyl cellulose (HPC, Klucel®) and hydroxy ethyl cellulose (HEC, Natrosol®), polyethylene glycols (PEG®, Lutrol®), copolymers of ethylene oxide with propylene oxide (Poloxamer®), gelatin, polyvinylpyrrolidones (PVP, Kollidon®), vinylpyrrolidones, vinyl acetates, polyvinylimidazoles, polyvinylpyridine N-oxides, copolymers of vinylpyrrolidone with long-chained alpha-olefins, copolymers of vinylpyrrolidone with vinylimidazole, poly(vinylpyrrolidone/dimethylaminoethyl methacrylates), copolymers of vinylpyrrolidone/dimethylaminopropyl methacrylamides, copolymers of vinylpyrrolidone/ dimethylaminopropyl acrylamides, quaternised copolymers of vinylpyrrolidones and dimethylaminoethyl methacrylates, terpolymers of vinylcaprolactam/vinylpyrrolidone/ dimethylaminoethyl methacrylates, copolymers of
vinylpyrrolidone and methacrylamidopropyl-trimethylammonium chloride, terpolymers of caprolactam/vinylpyrrolidone/dimethylaminoethyl methacrylates, copolymers of styrene and acrylic acid, polycarboxylic acids, polyacrylamides, polyvinyl alcohols (PVA, Mowiol®), optionally hydrolysed polyvinyl acetate, copolymers of ethyl acrylate with methacrylate and methacrylic acid, copolymers of maleic acid with unsaturated hydrocarbons and mixed polymerisation products of the said polymers, polysaccharide gums, both natural and modified (semi-synthetic), including but not limited to xanthan gum, veegum, agar, guar gum, locust bean gum, gum arabic, okra gum, alginic acid, other alginates (e.g. sodium alginate, propyleneglycol alginate), benitonite, arabinogalactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, and the like, or mixtures thereof.

The release rate controlling material(s) useful in the present invention preferably comprises a polymeric material selected from but not limited to the group comprising pH dependent polymers such as alginates, carbomers, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate or methacrylic acid polymers and the like or mixtures thereof.

In another embodiment of the present invention, the release rate controlling polymer(s) is present in an amount of not less than about 1.5% preferably not less than about 3% by weight of the composition. In another embodiment, the release rate controlling system comprises pH independent or dependent or mixtures thereof as rate controlling polymer(s) in an amount of not less than about 2% by weight of the composition. In an embodiment, the release rate controlling polymer is a cellulosic polymer and optionally used in combination with one or more other rate controlling agent(s).

In another preferred embodiment, multilayered pharmaceutical compositions delivers atleast one low dose active in two substantially distinct pulses, wherein one pulse is released in vivo almost immediately after ingestion and a second pulse is released after a gap of at least 3 hours, preferably after 5 hours. The total daily dose of low dose active is therefore divided into two fractions for release separately so as to avoid a high concentration of the low dose active beyond effective therapeutic levels.

In an embodiment, the dosage form compositions according to the present invention are
designed in the following manner:

i) A coating or a compressed layer of low dose active agent that is released almost immediately (first pulse) after the oral dosage form is exposed to medium either in-vivo or in vitro,

ii) An intermediate inert polymeric layer comprising at least one hydrophilic swellable polymer, and

iii) An inner tablet of low dose active agent same or different from the first active agent that provides a delayed or sustained release of the active agent (second pulse).

In an embodiment of the present invention is provided a process for the preparation of such multilayered pharmaceutical compositions according to the present invention. In an embodiment, the preparation of such composition comprises the following steps:

i) treating the low dose active agent(s) with one or more pharmaceutically acceptable excipient(s) and compressing it into a tablet,

ii) coating the tablet of step (i) with pH dependent and pH independent film forming material,

iii) compressing the inert polymeric material at least one hydrophilic swellable polymer on to the coated tablet of step (ii) to obtain a bilayered tablet,

iv) treating same or different low dose active agent(s) with a release rate controlling polymer or enteric polymer with one or more pharmaceutically acceptable excipient(s) and compressing the material thus obtained on to the tablet of step (iii) to obtain a trilayered tablet,

v) optionally coating the tablet obtained in step (iv).

In another embodiment, the preparation of such composition comprises the following steps:

i) treating the low dose active agent(s) with a release rate controlling polymer(s) or enteric polymer and optionally with one or more pharmaceutically acceptable excipient(s) and compressing it into a tablet,

ii) compressing the inert polymeric material at least one hydrophilic swellable polymer thus obtained on to the tablet of step (i) to obtain a bilayered tablet,

iii) preparing a coating composition comprising same or different low dose active agent(s) with a a release rate controlling polymer(s) or enteric polymer and
along with a film former and optionally one or more pharmaceutically acceptable excipient(s), and

iv) coating the tablet of step (ii) with the coating material of step (iii).

In an embodiment, the composition of the present invention comprises one or more pharmaceutically acceptable excipient(s) selected from but not limited to a group comprising diluents; disintegrants; binders; fillers; bulking agent; organic acid(s); colorants; stabilizers; preservatives; lubricants; glidants; chelating agents; vehicles; bulking agents; stabilizers; preservatives; hydrophilic polymers; solubility enhancing agents such as glycerine, various grades of polyethylene oxides, transcutol and glycofurol; tonicity adjusting agents; local anesthetics; pH adjusting agents; antioxidants; osmotic agents; chelating agents; viscosifying agents; acids; sugar alcohol; reducing sugars; non-reducing sugars and the like used either alone or in combination thereof. Certain excipients used in the present composition can serve more than one purpose. Suitable binders include for example starch, polyvinylpyrrolidone, hydroxypropyl methylcellulose, pregelatinised starch, hydroxypropylcellulose, or mixtures thereof. The disintegrants useful in the present invention include but not limited to a group comprising croscarmellose sodium (e.g. Primellose®), sodium starch glycollate, cross-linked sodium carboxymethyl cellulose (e.g. Ac-di-sol®, Solutab®, Vivasol®, starches, pregelatinized starch, celluloses, cross-linked carboxymethylcellulose, crospovidone, clays, alginates, gums and the like used either alone or in combination thereof. The diluents or fillers useful in the present invention are selected from but not limited to a group comprising lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate, calcium lactate, dextrose, dextran, dextrates, inositol, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, cellulose powder, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, glycine, or bentonites, and the like, or mixtures thereof. The lubricants useful in the present invention are selected from but not limited to a group comprising talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, hydrogenated vegetable oil, sodium stearyl fumarate, glyceryl behenate, waxes and the like used either alone or in combination thereof. The anti-adherents or glidants are selected from but not limited to a group comprising talc, corn starch, DL-leucine, sodium lauryl sulfate, magnesium stearate, calcium stearate, sodium stearate, colloidal silicon dioxide, and the like, or mixtures thereof. In an embodiment of the present invention, the
composition may additionally comprise a conventionally known antioxidant such as ascorbyl palmirate, butyl hydroxy anisole, butyl hydroxy toluene, propyl gallate, α-tocopherol, and the like or mixtures thereof. In another embodiment, the dosage form of the present invention additionally comprises at least one surfactant selected from a group comprising anionic surfactants, cationic surfactants, non-ionic surfactants, zwitterionic surfactants or mixtures thereof.

In a further embodiment, the composition of the present invention is preferably formulated as a solid dosage form such as layered tablets or layered minitablets filled into capsules. The tablets can be prepared by either wet granulation, direct compression, or by dry compression (slugging). The granulation technique is either aqueous or non-aqueous. The non-aqueous solvent used is selected from a group comprising acetone, ethanol, isopropyl alcohol or methylene chloride. In an embodiment, the compositions of the present invention are in the form of compressed tablets, moulded tablets, mini-tablets, compacts, pellets, granules or the like.

In yet another embodiment of the present invention is provided a method of using such novel compositions which comprises administering to a subject in need thereof an effective amount of the composition. In a further embodiment, the composition of the present invention may be useful for the management such as prophylaxis, amelioration or treatment of disease(s)/disorder(s) for extended time period.

Examples:

Example-1:

Part A: Inner Layer

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredient</th>
<th>Quantity (mg)/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core tablet composition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Ateenuooltooll</td>
<td>25</td>
</tr>
<tr>
<td>2.</td>
<td>Starch</td>
<td>1500</td>
</tr>
<tr>
<td>3.</td>
<td>Lactose</td>
<td>44</td>
</tr>
<tr>
<td>4.</td>
<td>Povidone K-30</td>
<td>2</td>
</tr>
<tr>
<td>5.</td>
<td>Crosspovidone</td>
<td>8</td>
</tr>
<tr>
<td>6.</td>
<td>Magnnessium Sheaarrattee</td>
<td>1</td>
</tr>
</tbody>
</table>
7. Isopropyl alcohol q.s. (lost in processing)

**Coating composition**

8. Ethyl cellulose 10
9. Distilled water q.s to 100 ml

5 Procedure:

i) Atenolol, Starch 1500, Lactulose, povidone K-30 and Crosspovidone were passed through #40 and mixed well.

ii) The material of step (i) was granulated with isopropyl alcohol and lubricated with magnesium stearate after drying.

iii) The material of step (ii) was compressed into tablets.

iv) A coating dispersion was prepared by dispersing ethyl cellulose in water.

v) The tablets of step (iii) were coated to build 7.5% build up with the dispersion material of step (iv) and dried.

15 Part B: Intermediate Polymeric Layer

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lactose</td>
<td>45</td>
</tr>
<tr>
<td>2.</td>
<td>Povidone K-30</td>
<td>6</td>
</tr>
<tr>
<td>3.</td>
<td>Sodium carboxymethyl cellulose (Sodium CMC)</td>
<td>96</td>
</tr>
<tr>
<td>4.</td>
<td>Hydroxypropyl methylcellulose (HPMC)</td>
<td>150</td>
</tr>
<tr>
<td>5.</td>
<td>Magnesium stearate</td>
<td>3</td>
</tr>
<tr>
<td>6.</td>
<td>Isopropyl alcohol q.s. (lost in processing)</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Ethyl cellulose (extra granular)</td>
<td>100</td>
</tr>
</tbody>
</table>

25 Procedure:

i) Lactose, Povidone K-30 and Sodium CMC were weighed and passed through #40 and mixed well.

ii) The blend of step (i) was granulated with isopropyl alcohol.

iii) The wet granules were dried completely.

iv) The granules of step (iii) were blended with Magnesium stearate

v) The material of step (iv) is compressed on to the tablets of step (v) (Part A) with the tablets of step (v) (Part A) within.

Part C: Outer Coating Layer
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredient</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Glimepiride</td>
<td>2</td>
</tr>
<tr>
<td>2.</td>
<td>Opadry II</td>
<td>8</td>
</tr>
<tr>
<td>3.</td>
<td>Dichloromethane: Isopropyl alcohol q.s.</td>
<td></td>
</tr>
</tbody>
</table>

5 Procedure:

i) Glimepiride and Opadry II, were added to dichloromethane: isopropyl alcohol mixture with continuous stirring to prepare a 10% dispersion.

ii) The tablets of step (v) (Part B) were coated with the material of step (i) (Part C) to obtain a trilayered tablet.

10 Dissolution profile

(1) Atenolol from inner tablet

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Time (Hours)</th>
<th>% cumulative drug released</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameters: USP Apparatus II, 75 rpm, temp. 37°C, pH 7.8 Phosphate Buffer for 2 hrs followed by pH 4.6 Phosphate buffer, Volume 900 ml, Replacement with 10 ml of media</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>3.</td>
<td>6</td>
<td>0.73</td>
</tr>
<tr>
<td>4.</td>
<td>8</td>
<td>4.93</td>
</tr>
<tr>
<td>5.</td>
<td>10</td>
<td>8.68</td>
</tr>
<tr>
<td>6.</td>
<td>12</td>
<td>23.55</td>
</tr>
<tr>
<td>7.</td>
<td>14</td>
<td>101.15</td>
</tr>
</tbody>
</table>

(ii) Glimepiride Coating Layer

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Time (Hours)</th>
<th>% cumulative drug released</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameters: USP Apparatus II, 75 rpm, temp. 37°C, pH 7.8 Phosphate Buffer for 2 hrs followed by pH 4.6 buffer, Volume 900 ml, Replacement with 10 ml of media</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 2:

Part A: Inner Layer

S. No. Ingredient Quantity (mg)

Core tablet composition

1. Glimepiride 1
2. Microcrystalline Cellulose 40.5
3. Polyvinyl pyrrolidone K-30 2.5
4. Sodium Starch Glycolate 5
5. Magnesium Stearate 1

Procedure:

i) Glimepiride, Microcrystalline Cellulose, Polyvinyl pyrrolidone K-30 and Sodium Starch Glycolate were passed through # 40 and mixed well.

ii) The material of step (i) was mixed and lubricated with magnesium stearate.

iii) The material of step (ii) was compressed into tablets.

Part B: Intermediate Polymeric Layer

S. No. Ingredients Quantity (nig)

1. Microcrystalline Cellulose 10
2. Povidone K-90 40
3. Sodium carboxymethyl cellulose (Sodium CMC) 80
4. Cetosteryl Alcohol 10
5. Hydroxypropyl methylcellulose (HPMC) 90
6. Magnesium stearate 5
7. Distilled water q.s

Procedure:
Microcrystalline Cellulose, Povidone K-90 and Sodium CMC were weighed and passed through #60 and mixed well.

The blend of step (i) was granulated with water.

The soft mass of step (ii) was passed through #10 and dried.

The semidried granules of step (iii) were passed through #16 followed by #24 and dried completely.

Cetosteryl Alcohol, Magnesium stearate and HPMC were weighed and passed through #40 and blended with the granules of step (iv).

The material of step (v) is compressed on to the tablets of step (iii) (Part A) with the tablets of step (iii) (Part A) within.

**Part C: Outer coating layer**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredient</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Glimepiride</td>
<td>1</td>
</tr>
<tr>
<td>2.</td>
<td>Opadry yellow</td>
<td>19</td>
</tr>
<tr>
<td>3.</td>
<td>Ethanol : Dichloromethane</td>
<td>q.s</td>
</tr>
</tbody>
</table>

**Procedure:**

Glimepiride and Opadry yellow were added to dichloromethane: ethanol mixture with continuous stirring to prepare a 10 % dispersion.

The tablets of step (vi) (Part B) were coated with the material of step (i) (Part C) to obtain a trilayered tablet to obtain 3.3% weight gain.

**Dissolution profile**

(1) Glimepiride from inner tablet

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Time (Hours)</th>
<th>% drug released</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameters: USP Apparatus III, 15 dpm, temp. 37°C, pH 7.8 Phosphate Buffer, Volume 250 ml</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>0.25</td>
<td>35.4</td>
</tr>
<tr>
<td>3.</td>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>4.</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>5.</td>
<td>4.5</td>
<td>0</td>
</tr>
</tbody>
</table>
Example-3:

Part A: Ate nnoollooll IInnnneerr LLaayyeerr

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredient</th>
<th>Quantity (mg)/unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Atenolol</td>
<td>25</td>
</tr>
<tr>
<td>2.</td>
<td>Starch 1500</td>
<td>20</td>
</tr>
<tr>
<td>3.</td>
<td>Lactose</td>
<td>50</td>
</tr>
<tr>
<td>4.</td>
<td>Povidone K-300</td>
<td>2</td>
</tr>
<tr>
<td>5.</td>
<td>Crosspovidone</td>
<td>2</td>
</tr>
<tr>
<td>6.</td>
<td>Magnesium Stearate</td>
<td>1</td>
</tr>
<tr>
<td>7.</td>
<td>Isopropyl alcohol q.s.</td>
<td>(lost in processing)</td>
</tr>
</tbody>
</table>

Procedure:
i) Atenolol, Starch 1500, Lactulose, povidone K-30 and Crosspovidone were passed through # 40 and mixed well,
ii) The material of step (i) was granulated with isopropyl alcohol and lubricated with magnesium stearate after drying,
iii) The material of step (ii) was compressed into tablets.

Part B: Intermediate Polymeric Layer

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Microcrystalline Cellulose</td>
<td>24</td>
</tr>
<tr>
<td>2.</td>
<td>Povidone K-90</td>
<td>48</td>
</tr>
<tr>
<td>3.</td>
<td>Sodium carboxymethyl cellulose (Sodium CMC)</td>
<td>96</td>
</tr>
<tr>
<td>4.</td>
<td>Cetosteryl Alcohol</td>
<td>62</td>
</tr>
<tr>
<td>5.</td>
<td>Hydroxypropyl methylcellulose (HPMC)</td>
<td>108</td>
</tr>
<tr>
<td>6.</td>
<td>Magnesium stearate</td>
<td>12</td>
</tr>
<tr>
<td>7.</td>
<td>Isopropyl alcohol q.s.</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

Procedure:
i) Microcrystalline Cellulose, Povidone K-90, Sodium CMC and Hydroxypropyl methylcellulose were weighed and passed through #40 and mixed well.

ii) The blend of step (i) was granulated with isopropyl alcohol and dried.

iii) Cetosteryl Alcohol was weighed and passed through #40 and blended with the granules of step (ii).

iv) The material of step (iii) was blended and mixed well with Magnesium stearate.

v) The material of step (iv) is compressed on to the tablets of step (iii) (Part A) with the tablets of step (iii) (Part A) within.

10

Part C: Outer coating layer

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredient</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Amlodipine</td>
<td>2.5</td>
</tr>
<tr>
<td>2.</td>
<td>Opadry yellow</td>
<td>7.25</td>
</tr>
<tr>
<td>3.</td>
<td>Ethanol : Dichloromethane</td>
<td>q.s</td>
</tr>
</tbody>
</table>

Procedure:

i) Amlodipine and Opadry yellow were added to dichloromethane: ethanol mixture with continuous stirring to prepare a 10% dispersion.

ii) The tablets of step (v) (Part B) were coated with the material of step (i) (Part C) to obtain a trilayered tablet.

Dissolution profile

(1) Atenolol from inner tablet

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Time (Hours)</th>
<th>% cumulative drug released</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parameters: USP Apparatus III, 10 dpm, temp. 37°C, 0.1 N HCl for 2 hrs followed by pH 4.5 Phosphate buffer, Volume 250 ml in each row</td>
</tr>
<tr>
<td>1.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3.</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4.</td>
<td>3</td>
<td>0.19</td>
</tr>
</tbody>
</table>
(ii) Amlodipine (2.5mg) coating composition

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Time (Hours)</th>
<th>% cumulative drug released</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parameters: USP Apparatus III, 10 dpm, temp. 37°C, 0.1 N HCl for 2 hrs followed by pH 4.5 Phosphate buffer, Volume 250 ml in each row</td>
</tr>
<tr>
<td>1.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>0.25</td>
<td>49.6</td>
</tr>
<tr>
<td>3.</td>
<td>0.5</td>
<td>84</td>
</tr>
<tr>
<td>4.</td>
<td>0.75</td>
<td>96.4</td>
</tr>
<tr>
<td>5.</td>
<td>1</td>
<td>96.7</td>
</tr>
</tbody>
</table>

Example-4:

Part A: Ondansetron hydrochloride (Sustained release)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredient</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ondansetron hydrochloride</td>
<td>17.85</td>
</tr>
<tr>
<td>2.</td>
<td>Anhydrous lactose</td>
<td>6.15</td>
</tr>
<tr>
<td>3.</td>
<td>Glyceryl behenate</td>
<td>100.00</td>
</tr>
<tr>
<td>4.</td>
<td>Alginic acid</td>
<td>35.00</td>
</tr>
<tr>
<td>5.</td>
<td>Polyvinylacetate and povidone copolymer (Kollidon®SR)</td>
<td>85.00</td>
</tr>
<tr>
<td>6.</td>
<td>Magnesium stearate</td>
<td>6.00</td>
</tr>
</tbody>
</table>

Procedure:

i) Ondansetron hydrochloride and Anhydrous lactose are mixed together.

ii) Glyceryl behenate and Kollidon®SR are mixed together followed by addition of Alginic acid and passed through #40 sieve.

iii) The blend of step (i) is mixed with the blend of step (ii).

iv) The material of step (iii) is mixed with a portion of #60 sieve passed Magnesium stearate followed by roller compaction to obtain compacts.

v) The compacts of step (iv) are passed through sieve #30 and retained on sieve
vi) The granules of step (v) were lubricated with remaining portion of #60 sieve passed Magnesium stearate.

vii) The material of step (vi) is compressed into tablets.

5

Part B: Intermediate Polymeric Layer

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Polyvinyl pyrrolidone</td>
<td>40.0</td>
</tr>
<tr>
<td>2.</td>
<td>Mannitol</td>
<td>10.0</td>
</tr>
<tr>
<td>3.</td>
<td>HPMC (Methocel® K100 CR)</td>
<td>90.0</td>
</tr>
<tr>
<td>4.</td>
<td>Glyceryl behenate</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Procedure:

i) Ingredients 1, 2 and 3 are weighed and passed through #40 and mixed well.

ii) The blend of step (i) is granulated with water.

iii) The wet granules are passed through #18 & dried.

iv) The semidried granules are passed through #20 and dried completely.

v) The granules of step (iv) are mixed with #40 passed Glyceryl behenate.

vi) The material of step (v) is compressed on to the tablets of step (vii) (Part A) with the tablets of step (vii) (Part A) within.

20

Part C: Ondansetron hydrochloride (Immediate release)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ondansetron hydrochloride</td>
<td>1.98</td>
</tr>
<tr>
<td>2.</td>
<td>Anhydrous lactose</td>
<td>113.02</td>
</tr>
<tr>
<td>3.</td>
<td>Polyvinylpyrrolidone (PVP K-30)</td>
<td>6.50</td>
</tr>
<tr>
<td>4.</td>
<td>Magnesium stearate</td>
<td>2.50</td>
</tr>
</tbody>
</table>

Procedure:

i) Ondansetron hydrochloride and Anhydrous lactose are mixed together.

ii) The mixture in step (i) is mixed with Polyvinylpyrrolidone and passed through #40 sieve.

iii) The blend in step (ii) is lubricated with a portion of #60 sieve passed Magnesium stearate followed by roller compaction to obtain compacts.

iv) The compacts of step (iii) are passed through sieve #30 and retained on sieve #60 to get granules.
v) The granules of step (iv) are lubricated with remaining portion of #60 sieve passed
Magnesium stearate.
vi) The material of step (v) (Part C) is compressed on to the tablets of step (vi) (Part B) to obtain a trilayered tablet.

5

Part D: Coating composition

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Quantity/ tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Opadry® II Pink</td>
<td>3.00</td>
</tr>
<tr>
<td>2.</td>
<td>Purified water</td>
<td>q.s. (lost in processing)</td>
</tr>
</tbody>
</table>

10 Procedure:
i) Opadry® II Pink is steadily added in Purified water with continuous stirring.
ii) The trilayered tablets of step (vi) (Part C) are coated with the film coating material of step (i) (Part D).

15 DETAILED DESCRIPTION OF THE DRAWINGS

Figure 1: The said figure shows the in-vitro release profile of the composition as mentioned hereinafter in Example-1, Part A.

Figure 2: The said figure shows the in-vitro release profile of the composition as mentioned hereinafter in Example-1, Part C.

Figure 3: The said figure shows the in-vitro release profile of the composition as mentioned hereinafter in Example-2

Figure 4: The said figure shows the in-vitro release profile of the composition as mentioned hereinafter in Example-3, Part A.

Figure 5: The said figure shows the in-vitro release profile of the composition as mentioned hereinafter in Example-3, Part C.

Figure 6: The said figure shows the diagrammatic representation of the present invention.

Figure 7: The said figure shows the diagrammatic representation of the present invention.

Figure 8: The said figure shows the diagrammatic representation of the present invention.
CLAIMS

1. Multilayered pharmaceutical compositions comprising at least one or more low dose active agent(s) each selected from same or different classes of agents, at least one release rate controlling polymer(s) or enteric polymer that predominantly controls or delays the release of at least one active agent(s) and optionally one or more pharmaceutically acceptable excipient(s).

2. The compositions according to claim 1, comprising atleast three layers wherein the first layer comprises a low dose active agent with or without at least one rate release controlling polymer or enteric polymer(s) optionally alongwith one or more pharmaceutically acceptable excipient(s) in the delayed release form optionally coated with a pH dependent or pH independent film former; a second layer entirely covering the first layer comprising atleast one hydrophilic swellable polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and a third layer comprising at least one low dose active agent(s) which is same or different from the first low-dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally alongwith one or more pharmaceutically acceptable excipient(s) in the immediate or extended or sustained or prolonged or delayed release form such that the said third layer is a coated or compressed on to the second layer optionally coated with a film former or a coating having an active agent.

3. The compositions according to claim 1, comprising atleast three layers wherein the first layer comprises a low dose active agent with or without release rate controlling polymer(s) or enteric polymer(s) optionally alongwith one or more pharmaceutically acceptable excipient(s) in the immediate, extended or sustained or prolonged or delayed release form optionally coated with a pH dependent or pH independent film former; a second layer entirely covering the first layer comprising atleast one hydrophilic swellable polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and a third layer comprising at least one low dose active agent(s) which is same or different from the first low-dose active agent with or without release rate controlling polymer(s) or enteric polymer(s)
optionally along with one or more pharmaceutically acceptable excipient(s) in the immediate or extended or sustained or prolonged or delayed release form such that the said third layer is a coated or compressed on to the second layer.

4. The compositions according to claims 1, wherein the compositions comprise low dose active agent in two distinct fractions, wherein the said dosage form provides immediate or extended or sustained or prolonged or delayed release of first fraction of the low dose active agent from the first (innermost) layer; a second inert polymeric layer covering the first layer, and an immediate or extended or sustained or prolonged or delayed release of the second fraction of the low dose active agent from the third layer (outermost), such that the gap or lag or interval or delay or difference between the release of first and second pulse of the active agent from the first (innermost) and third (outermost) layer is about 1 hour to about 10 hours after oral administration and wherein the said dosage form provides a sustained release of the first (innermost) layer for an extended period of time such as from 8-24 hours after administration.

5. The compositions according to claim 4, wherein the second (intermediate) inert or placebo layer comprises at least one hydrophilic swelling polymer(s) as the release rate controlling polymer, wherein when the said layer is exposed to aqueous fluids in vivo, the said release rate controlling polymer swells forming a gel or a gel-like mass which prevents the entry of the fluid into the innermost layer comprising the active agent in an immediate release form for atleast 1 hour to about 10 hours and subsequently the said gel or gel-like mass erodes gradually thus leading to the contact of the in vivo fluids with the inner layer and its disintegration to release the second pulse of the low dose active agent same or different from the first active agent released from the outermost layer.

6. The compositions according to claims 5, wherein the second (intermediate) inert layer comprises hydrophilic swelling polymer such as hydroxypropyl methylcellulose (HPMC) as the release rate controlling polymer.

7. The compositions according to claim 1, comprising three layers wherein the first layer comprises a low dose active agent or its salts, esters, prodrugs, isomers,
solvates, hydrates, or derivatives, optionally along with one or more pharmaceutically acceptable excipient(s) in the extended or sustained or prolonged or delayed release form; a second layer entirely covering the first layer comprising at least one hydrophilic swellable polymer(s) and optionally one or more pharmaceutically acceptable excipient(s); and a third layer which is in the form of a coating provided on the second layer wherein said coating comprises a low dose active agent which is same or different from the first active or its salts, esters, prodrugs, isomers, solvates, hydrates, or derivatives, along with a film former and optionally one or more pharmaceutically acceptable excipient(s) which provides an immediate release of the agent.

8. The compositions according to any one of the preceding claims, wherein the low dose active agent is selected from a group comprising: adrenergic agent; adrenocortical steroid; adrenocortical suppressant; aldosterone antagonist; amino acid; anabolic; analeptic; analgesic; anesthetic; anorectic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-anemic; anti-anginal; anti-arthritic; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholinergic; anticoagulant; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; anti-emetic; anti-epileptic; antifibrinolytic; antifungal; antihemorrhagic; antihistamine; antihyperlipidemia; antihypertensive; antihypotensive; anti-infective; anti-inflammatory; anti-pyretic; antimicrobial; antimigraine; antimitotic; antineoplastic; antineutropenic; antiparasitic; antiproliferative; antipsychotic; antirheumatic; antiseborrheic; antisecretory; antispasmodic; antithrombotic; anti-ulcerative; antiviral; appetite suppressant; blood glucose regulator; bone resorption inhibitor; bronchodilator, cardiovascular agent; cholinergic; depressant; diagnostic aid; diuretic; dopaminergic agent; estrogen receptor agonist; fibrinolytic; fluorescent agent; free oxygen radical scavenger; gastric acid suppressant; gastrointestinal motility effector; glucocorticoid; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; hormone; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; keratolytic; LHRH agonist; mood regulator; mucolytic; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol derivative; plasminogen activator; platelet activating factor.
antagonist; platelet aggregation inhibitor; psychotropic; radioactive agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A1 antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; steroid; anticancer compounds, antiparkinson agents, thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; amyotrophic lateral sclerosis agent; cerebral ischemia agent; Paget's disease agent; unstable angina agent; vasoconstrictor; vasodilator; wound healing agent; xanthine oxidase inhibitors, vitamins, minerals, nutritional supplements and the like, and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof, used either alone or in combination thereof.

9. A composition according to claim 8, wherein the low dose active agent is selected from a group comprising Glimepiride, Isotretinoin, Zafirlukast, rabeprazole sodium, Alvimopan, Amiloride, flucytosine, fenofibrate, Yominbine, hydralazine hydrochloride, exemestane, paroxetine mesylate, atenolol, carvedilol or their tautomeric forms, analogues, isomers, polymorphs, solvates, derivatives, or salts thereof used either alone or in combination thereof.

10. The compositions according to any one of the preceding claims, wherein the release rate controlling polymer(s) comprises a polymeric material selected from the group comprising pH dependent polymers; pH independent polymers; swellable polymers; non-swellable polymers; hydrophilic polymers; hydrophobic polymers and/or one or more other hydrophobic materials; ionic polymers such as sodium alginate, carbomer, calcium carboxymethylcellulose or sodium carboxymethylcellulose; non-ionic polymers such as hydroxypropyl methylcellulose; synthetic or natural polysaccharide selected from the group comprising alkylcelluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitrocelluloses, dextrin, agar, carrageenan, pectin, furcellaran, starch and starch derivative, and mixtures thereof.

11. The compositions according to claim 10, wherein the polymeric material is selected from a group comprising cellulosic polymer, methacrylate polymer, methacrylate copolymer such as Eudragit® EPO, Eudragit® E100, Eudragit® E12,5 and the like or mixtures thereof, Polyvinylpyrrolidone (PVP), alginate, polyvinylpyrrolidone-polyvinyl
acetate (PVP-PVA) copolymer, ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(alkyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(alkyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(alkylene), poly(alkylene oxide), poly(alkylene terephthalate), poly(vinyl isobutyl ether), polyvinyl acetate), polyvinyl chloride) and polyurethane or a mixture thereof used either alone or in combination thereof.

12. The compositions according to claim 10, wherein the dosage form comprises a gum selected from a group comprising xanthan gum, guar gum, gum arabic, carrageenan gum, karaya gum, locust bean gum, acacia gum, tragacanth gum, agar and the like or mixtures thereof.

13. The compositions according to claim 10, wherein the release controlling polymer(s) is selected from a group comprising carbopol; cellulosic polymers such as sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose; copolymers of methyl vinyl ether and maleic anhydride such as Gantrez®; enteric polymers; sodium hyaluronate; gums; alginates; polycarbophil; polyethylene oxide; starch; dextran; chitosan; and the like or mixtures thereof.

14. The compositions according to claim 10, wherein the pH independent polymer is selected from a group comprising alkyl celluloses such as methyl cellulose, hydroxyalkyl alkyl celluloses such as hydroxypropyl methyl cellulose (HPMC, Methocel®), hydroxy alkyl celluloses such as hydroxypropyl cellulose (HPC, Klucel®) and hydroxy ethyl cellulose (HEC, Natrosol®), polyethylene glycols (PEG®, Lutrol®), copolymers of ethylene oxide with propylene oxide (Poloxamer®), gelatin, polyvinylpyrrolidones (PVP, Kollidon®), vinylpyrrolidones, vinyl acetates, polyvinylimidazoles, polyvinylpyridine N-oxides, copolymers of vinylpyrrolidone with long-chained alpha-olefins, copolymers of vinylpyrrolidone with vinylimidazole, poly(vinylpyrrolidone/dimethylaminoethyl methacrylates), copolymers of vinylpyrrolidone/dimethylaminopropyl methacrylamides, copolymers of vinylpyrrolidone/ dimethylaminopropyl acrylamides, quaternised copolymers of
vinylpyrrolidones and dimethylaminoethyl methacrylates, terpolymers of vinylcaprolactam/vinylpyrrolidone/dimethylaminoethyl methacrylates, copolymers of vinylpyrrolidone and methacrylamidopropyl-trimethylammonium chloride, terpolymers of caprolactam/vinylpyrrolidone/dimethylaminoethyl methacrylates, copolymers of styrene and acrylic acid, polycarboxylic acids, polyacrylamides, polyvinyl alcohols (PVA, Mowiol®), optionally hydrolysed polyvinyl acetate, copolymers of ethyl acrylate with methacrylate and methacrylic acid, copolymers of maleic acid with unsaturated hydrocarbons and mixed polymerisation products of the said polymers, polysaccharide gums, both natural and modified (semi-synthetic), including xanthan gum, veegum, agar, guar gum, locust bean gum, gum arabic, okra gum, alginic acid, other alginates (e.g. sodium alginate, propyleneglycol alginate), benitonite, arabinogalactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, and the like, or mixtures thereof.

15. The compositions according to claim 10, wherein the release rate controlling material(s) comprises a polymeric material selected from the group comprising pH dependent polymers such as alginates, carbomers, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate or methacrylic acid polymers and the like or mixtures thereof.

16. The compositions according to any one of the preceding claims, wherein the release rate controlling polymer(s) is present in an amount of not less than about 1.5% not less than about 3% by weight of the composition.

17. The compositions according to any one of the preceding claims, wherein the release rate controlling system comprises pH independent or dependent or mixtures thereof as rate controlling polymer(s) in an amount of not less than about 2% by weight of the composition.

18. The compositions according to any one of the preceding claims, wherein the release rate controlling polymer is a cellulosic polymer and optionally used in combination with one or more other rate controlling agent(s).
19. The compositions according to claim 1, wherein compositions delivers at least one low dose active in two substantially distinct pulses, wherein one pulse is released in vivo almost immediately after ingestion and a second pulse is released after a gap of at least 3 hours, after 5 hours; the total daily dose of low dose active is therefore divided into two fractions for release separately so as to avoid a high concentration of the low dose active beyond effective therapeutic levels.

20. The compositions according to any one of the preceding claims, wherein the composition comprises one or more pharmaceutically acceptable excipient(s) selected from a group comprising diluents; disintegrants; binders; fillers; bulking agent; organic acid(s); colorants; stabilizers; preservatives; lubricants; glidants; chelating agents; vehicles; bulking agents; stabilizers; preservatives; hydrophilic polymers; solubility enhancing agents such as glycerine, various grades of polyethylene oxides, transcutol and glycofurol; tonicity adjusting agents; local anesthetics; pH adjusting agents; antioxidants; osmotic agents; chelating agents; viscosifying agents; acids; sugar alcohol; reducing sugars; non-reducing sugars and the like used either alone or in combination thereof.

21. The compositions according to any one of the preceding claims, wherein the composition is formulated as a solid dosage form such as layered tablets or layered minitablets filled into capsules; the tablets can be prepared by either wet granulation, direct compression, or by dry compression (slugging) wherein the granulation technique is either aqueous or non-aqueous.

22. The compositions according to any one of the preceding claims, wherein the compositions are in the form of compressed tablets, moulded tablets, minitablets, compacts, pellets, granules or the like.

23. A process of preparation of the multilayered pharmaceutical compositions according to claim 1, which comprises of the following steps:
i) A coating or a compressed layer of low dose active agent that is released almost immediately (first pulse) after the oral dosage form is exposed to medium either in-vivo or in vitro,

ii) An intermediate inert polymeric layer comprising at least one hydrophilic swellable polymer, and

iii) An inner tablet of low dose active agent same or different from the first active agent that provides a delayed or sustained release of the active agent (second pulse).

24. A process of preparation of the multilayered pharmaceutical compositions according to claim 1, which comprises of the following steps:

i) treating the low dose active agent(s) with one or more pharmaceutically acceptable excipient(s) and compressing it into a tablet,

ii) compressing the inert polymeric material at least one hydrophilic swellable polymer on to the tablet of step (i) to obtain a bilayered tablet,

iii) treating same or different low dose active agent(s) with one or more pharmaceutically acceptable excipient(s) and compressing the material thus obtained on to the tablet of step (ii) to obtain a trilayered tablet,

iv) optionally coating the tablet obtained in step (iii).

25. A process of preparation of the multilayered pharmaceutical compositions according to claim 1, which comprises of the following steps:

i) treating the low dose active agent(s) with a release rate controlling polymer(s) and optionally with one or more pharmaceutically acceptable excipient(s) and compressing it into a tablet,

ii) compressing the inert polymeric material at least one hydrophilic swellable polymer thus obtained on to the tablet of step (i) to obtain a bilayered tablet,

iii) preparing a coating composition comprising same or different low dose active agent(s) along with a film former and optionally one or more pharmaceutically acceptable excipient(s), and

iv) coating the tablet of step (ii) with the coating material of step (iii).
26. A method of using multilayered pharmaceutical compositions according to claim 1, which comprises administering to a subject in need thereof an effective amount of the composition.

27. The compositions according to claim 26, useful for the management such as prophylaxis, amelioration or treatment of disease(s)/disorder(s) for extended time period.

28. Use of a composition according to claim 1, for the preparation of a medicament for the management such as prophylaxis, amelioration or treatment of disease(s)/disorder(s) for extended time period.

29. The pharmaceutical compositions substantially as herein described and illustrated by the examples.

30. The processes for the preparation of pharmaceutical compositions substantially as herein described and illustrated by the examples.
Figure 1: In-vitro release profile of atenolol (Example 1)
Figure 2: In-vitro release profile of glimepiride (Example 1)
Figure 3: In-vitro release profile of glimepiride (Example 2)
Figure 4: In-vitro release profile of atenolol (Example 3)
Figure 5: In-vitro release profile of amlodipine (Example 3)
Figure 6:

Layer - I denotes Atenolol in IR form
Layer - II denotes lag-time controlling layer
Layer - III denotes Atenolol in IR form

Layer - I denotes Atenolol in SR form
Layer - II denotes lag-time controlling layer
Layer - III denotes Atenolol in SR form
Figure 7:

(A) Layer – I denotes Atenolol in IR form
Layer – II denotes lag-time controlling layer
Layer – III denotes Glimepiride in IR form

(B) Layer – I denotes Atenolol in IR form
Layer – II denotes lag-time controlling layer
Layer – III denotes Amlodipine in SR form
Figure 8:

Layer – I denotes Chlorthalidone in IR/SR form
Layer – II denotes pH dependent/pH independent film coating
Layer – III denotes lag-time controlling layer
Layer – IV denotes Atenolol in SR form
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 8: A61K 9/24; A61K 9/52
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)
IPC 8: A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2007/15305 A2 (COGENUS PHARMACEUTICALS INC) 11 October 2007 (11.10.2007) Claims 1, 7, 15-17, 19, 20; Description Paragraph [0102], [0103], [0106], [0107]</td>
<td>1-18, 20-22, 24, 25</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search: 22 July 2009 (22.07.2009)
Date of mailing of the international search report: 28 August 2009 (28.08.2009)

Name and mailing address of the ISA/AT

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**HUNGER U.**
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Continuation of first sheet

Observations where certain claims were found unsearchable
(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

Claims Nos.: 26 because they relate to subject matter not required to be searched by this Authority, namely.

Although a claim directed to a method of treatment is commonly searched on the basis of its alleged effects, claim 26 does not contain any concrete technical features; it was therefore excluded from the search.

Claims Nos.: 19, 23, 27-30 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 19 contains no technical feature and describes the composition exclusively in a function-oriented manner by describing the respective objective without presenting a solution. Claim 23 presents a process claim but contains exclusively product features. A process claim should contain the starting materials, the process steps and the final product. The claims 17 and 28 contain no concrete technical features. Neither the term "a disease(s)/disorder(s)" nor the term "for extended time period" in a first medical use claim or in a Swiss Type Claim are not appropriate medical indications or expressions needed in such claims.

The claims 29 and 30 contain a reference to the examples within the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.
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