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DESCRIPTION

Field of invention

[0001] In one aspect, the present invention is concerned with a treatment where it is desired that an active agent is designed to be released in a pulse at a time point some time after administration of the active agent. The present invention is particularly suited to administering an agent which may be released whilst a subject is sleeping. As well as treating certain conditions by a particular regime, the invention also provides novel formulations for a delayed, followed by a pulsed release of drug.

Background to the invention

[0002] Time-dependent release mechanisms of drugs have been described in the literature for tablet, pellet and capsule formulation utilising a wide range of physicochemical and physicomechanical strategies. The common feature of all such formulations is that they are activated by contact with fluids following ingestion by the patient and the drug will be released at the predetermined time after administration. Only after the formulations come into contact with gastric fluids does the 'clock' start. Drug release subsequently takes place at a predicted time, although it will be appreciated that since the dosage unit will be travelling through the GI tract during the lag period, drug release will necessarily be at some unknown GI tract site. Using such formulation strategies, it will be possible to design delivery systems capable of releasing drugs according to chronotherapeutic principles and targeting release to the circadian rhythm of disease states (Stevens HNE, Chronopharmaceutical Drug Delivery. J Pharm Pharmac., 50 (s) 5 (1998) and Ghimire M , European Journal of Pharmaceutics and Biopharmaceutics, 67 (2007)). However, many of the formulations in the art rely on complex structures which can add to the cost of the manufacture of the drug and/or can be subject to malfunction leading to incorrect/inappropriate administration of the drug.

[0003] It is amongst the objects of the present invention to obviate and/or mitigate at least one of the aforementioned disadvantages.

[0004] It is amongst the objects of the present invention to provide a formulation which may be easily and/or cheaply manufactured and which allows for an active agent to be administered in a short pulse, following a period of delay following administration.

Summary of invention

[0005] The present inventors recognised a need to be able to administer, for example, a pharmaceutically active agent to a subject in a manner such that a delayed release of the

pharmaceutically active ingredient could be achieved, followed by a pulsed delivery of the agent. This problem has been solved by a tablet formulation as defined by claims 1-9. Although this may have been possible using prior device/methods known in the art, many such devices/methods were highly complex and there is distinct advantage in providing a simpler press-coated tablet formulation.

[0006] One particularly preferred embodiment relates to treating subjects who wake during the night, but have no or little difficulty in initially falling asleep, commonly termed sleep maintenance insomnia. In a preferred embodiment therefore, the formulations of the present invention are for treating sleep maintenance insomnia. Such formulations therefore comprise a pharmaceutically active agent for inducing and/or facilitating sleep. Typically this may be a sedative or hypnotic agent, such as a benzodiazepine, chloral hydrate, melatonin and analogues thereof, zolpidem, zopiclone or zaleplon.

[0007] Thus, in a first aspect, the present invention provides a sleep inducing and/or maintaining formulation agent such as a sedative or hypnotic agent, formulated as a component of a press-coated tablet for treating sleep maintenance insomnia, wherein the formulation is intended to be administered immediately prior to a subject going to sleep (i.e. when a subject goes to bed at night for a prolonged period of sleep, such as 6-10 hours and hence is distinguished over shorter sleeping periods) and wherein the hypnotic agent is substantially not released from the formulation for a period between 1.5-8 hours after administration of the formulation to the subject and thereafter the agent is released from the formulation as a pulse such that at least 70-90%, for example 80% of the agent within the formulation is released within 5-80 mins, such as 10-45, or 10-30 mins.

[0008] In a further aspect there is provided a method of treating sleep maintenance insomnia, the method comprising administering a press-coated tablet comprising a sleep inducing agent, such as a sedative or hypnotic agent to a subject, immediately before the subject intends sleeping, wherein the formulation substantially delays release of the drug for 1.5 - 8 hours following administration of the formulation and thereafter the drug is released in a pulse over a period of 5-80 mins, such as 10-45 or 10-30 mins. The delayed release of the active agent is achieved by providing a press-coated tablet comprising a delayed release layer surrounding a core comprising the active agent. The delayed release layer comprises a wax and a low-substituted hydroxypropyl cellulose (L-HPC), which is LH-11. The present invention provides a press-coated tablet formulation for a delayed, followed by a pulsed release of an active agent, the tablet comprising

1. (a) a core comprising the active agent(s) together with an excipient(s); and
2. (b) a delayed release layer surrounding the core and comprising a wax and LH-11 in a ratio of 40:60 to 60:40 w/w; wherein the delayed release layer substantially delays release of the active agent within the core for 1.5 - 8 hours after administration of the tablet by a subject and thereafter a pulsed release of the active agent from the core occurs, such that at least 70% of the active agent in the core is released within 5-80 mins, such as 10-40 or 10-30 mins.

[0009] The active agents of the above aspect include any active agent for which delayed followed by pulsed release is desirable. In a preferred embodiment of the invention, the active agent is a pharmaceutically acceptable active agent and includes pharmaceutical and veterinary active agents (often referred to as drugs). In other embodiments, the active agent includes agrichemical agents (such as fertilizers, herbicides, pesticides and fungicides), active agent used in the exterminating industry (such as toxins and poisons), and active agents used in industrial manufacturing (such as catalysts or catalytic quenchers).

[0010] The press-coated tablets of the present invention may be used to treat one or more of the following conditions/disorders or diseases:

Central Nervous System disorders, e.g. Neurogenic pain, stroke, dementia, Alzheimer's disease, Parkinson's disease, neuronal degeneration, meningitis, spinal cord injury, cerebral vasospasm, amyotrophic lateral sclerosis

Cardiovascular disease, hypertension, atherosclerosis, angina, arterial obstruction, peripheral arterial disease, myocardial pathology, Arrhythmia, Acute Myocardial Infarction, Angina, Cardiomyopathy, Congestive heart failure, Coronary artery disease (CAD), Carotid artery disease, Endocarditis, Hypercholesterolemia, hyperlipidemia, Peripheral artery disease (PAD)

Genitourinary Disorders; erectile dysfunction, urinary organ diseases benign prostatic hypertrophy (BPH), Renal tubular acidosis, diabetic nephropathy, glomerulonephritis, glomerulosclerosis, urinary tract infection, faecal incontinence

Ocular disease glaucoma, blephartitis, ocular hypertension, retinopathy, conjunctivitis, scleritis, retinitis, keratitis, corneal ulcer, iritis, Chorioretinal inflammation, macular edema, Xerophthalmia

Pulmonary disease asthma, pulmonary hypertension, acute respiratory distress syndrome, COPD, emphysema, pneumonia, tuberculosis, bronchitis, Acute Bronchitis, Bronchiectasis, Bronchiolitis, Bronchopulmonary Dysplasia, Byssinosis, Coccidioidomycosis (Cocci), Cystic Fibrosis, Influenza, Lung Cancer, Mesothelioma

Metabolic diseases; Hypercalciuria, Hyperglycemia, Hyperinsulinemic hypoglycemia, Hyperinsulinism, Hyperlysinuria, Hypoglycemia

Exocrine and Endocrine; Addison's disease, Hypoaldosteronism, cushing's syndrome, diabetes, Goitre, Hyperthyroidism, Hypothyroidism, Thyroiditis, pancreatitis

Hepatic disorders, Hepatitis, Non-alcoholic fatty liver disease, cirrhosis, hepatic cancer, Primary sclerosing cholangitis, primary biliary cirrhosis, Budd-Chiari syndrome,

Autoimmune and Inflammatory diseases, multiple sclerosis rheumatoid arthritis, psoriasis, diabetes, sarcoidosis, Addison's Disease, Alopecia areata, Amyotrophic Lateral Sclerosis,

Ankylosing Spondylitis, polyarticular Arthritis, Atopic allergy, topic Dermatitis, Autoimmune hepatitis, Celiac disease, Chagas disease, Coeliac Disease, Cogan syndrome, Crohns Disease, Cushing's Syndrome, Diabetes mellitus type 1, Endometriosis, Eosinophilic fasciitis, Fibromyalgia/Fibromyositis, Gastritis, Glomerulonephritis, Graves' disease. Guillain-Barré syndrome (GBS), Hashimoto's encephalitis, Hashimoto's thyroiditis, Haemolytic anaemia, Idiopathic Inflammatory Demyelinating Diseases, Idiopathic pulmonary fibrosis, interstitial cystitis, Juvenile idiopathic arthritis, Juvenile rheumatoid arthritis, Kawasaki's Disease, Lichen sclerosus, Lupus erythematosus, Ménière's disease, Myasthenia gravis, myositis, Narcolepsy, Pernicious anaemia, Perivenous encephalomyelitis, Polymyalgia rheumatica, Primary biliary cirrhosis, Psoriatic Arthritis, Reiter's syndrome, Rheumatoid fever, Sarcoidosis, Schizophrenia, Sjögren's syndrome, Spondyloarthropathy, Ulcerative Colitis

Musculoskeletal disorders: osteoarthritis, osteoporosis, Osteonecrosis, Arthritis, Paget's Disease Bursitis, Costochondritis, Tendonitis

Skin disorders; Acne, alopecia, candidiasis, cellulilitis, dermatitis, eczema, epidermolysis bullosa, erythrasma, herpes, erysipelas, Folliculitis, impetigo, ringworm, scabies, Tinea, Trichomycosis

ENT disorders; Otitis, sinusitis, laryngitis, pharyngitis, laryngitis, meniere's disease, labyrinthitis,

Others: acute and chronic pain, viral infection, cancer, laryngitis, mastoiditis, myringitis, otitis media, rhinitis, sinusitis, Sialadenitis, Retropharyngeal Abscess, Tonsillopharyngitis,

Gastro-intestinal disorders

[0011] Irritable bowel syndrome (IBS) necrotizing entercolitis (NEC) non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstructioduodenogastric reflux, gastroesophageal reflux disease, ileus inflammation, gastroparesis, heartburn, constipation - (e.g. constipation associated with use for medications such as opioids), colorectal cancer, colonic polyps, diverticulitis, colorectal cancer, Barretts Esophagus, Bleeding in the Digestive Tract, Celiac Disease, Colon Polyps, Constipation, Crohns Disease, Cyclic Vomiting Syndrome, Delayed Gastric Emptying (Gastroparesis), Diarrhea, Diverticulosis, Duodenal Ulcers, Fecal Incontinence, Gallstones, Gas in the Digestive Tract , Gastritis, Gastroesophageal Reflux Disease (GERD), Heartburn, Hiatal Hernia, Hemochromatosis, Hemorrhoids, Hiatal Hernia, Hirschsprung's Disease, Indigestion, Inguinal Hernia, Lactose Intolerance, Peptic Ulcers, Polyps, Porphyria, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Proctitis, Rapid Gastric Emptying, Short Bowel Syndrome, Stomach Ulcers, Ulcerative Colitis, Ulcers, Whipples Disease

[0012] Exemplary active agents for use in the pharmaceutical and veterinary applications of

the invention include analgesics, anaesthetics, anticonvulsants, antidiabetic agents, antihistamines, anti-infectives, antineoplastics, antiparkinsonian agents, antirheumatic agents, appetite stimulants, appetite suppressants, blood modifiers, bone metabolism modifiers, cardiovascular agents, central nervous system depressants, central nervous system stimulants, decongestants, dopamine receptor agonists, electrolytes, gastrointestinal agents, immunomodulators, muscle relaxants, narcotics, parasympathomimetics, sympathomimetics, sedatives, and hypnotics.

Said active agent or agents may be selected from the following:

Gastro Drugs

[0013]

Antacids - aluminium hydroxide, magnesium carbonate, magnesium trisilicate, hydrotalcite, simeticone alginates,

Antispasmodics - atropine sulphate, dicycloverine hydrochloride, hyoscine butylbromine, propantheline bromide, alverine citrate, mebeverine hydrochloride,

Motility stimulants - metoclorpramide, domperidone

H2 - Receptor antagonists - Cimetidine, famotidinenizatidine, ranitidine **Antimuscarinics -** pirenzepine

Chelates - Tripotassium dicitratbismuthate, sucralfate,

Prostaglandin analogues- misoprostol

Aminosalicylates - balsazide sodium, mesalazine, olsalazine, sulphasalazine

Corticosteroids - beclometasone dipropionate, budenoside, hydrocortisone, pednisolone,

Affecting immune response - ciclosporin, mercaptopurine, methotrexate, adalimumab, infliximab

Stimulant Laxatives - bisacodyl, dantron, docusate, sodium picosulfate,

Drugs affecting biliary composition and flow - ursodeoxycholic acid

Bile acids sequestrants - colestyramine,

Oxyphencyclimine, Camylofin, Mebeverine, Trimebutine, Rociverine, Dicycloverine, Dihexyverine, Difemerine, Piperidolate Benzilone, Mepenzolate, Pipenzolate, Glycopyrronium, Oxyphenonium, Penthienate, Methantheline, Propantheline, Otilonium bromide, Tridihexethyl, Isopropamide, Hexocyclium, Poldine, Bevonium, Diphemanil, Tiemonium iodide, Prifinium

bromide, Timepidium bromide, Fenpiverinium Papaverine, Drotaverine, Moxaverine 5-HT3 antagonists (Alosetron, Cilansetron), 5-HT4 agonists (Mosapride, Prucalopride, Tegaserod) Fenpiprane, Diisopromine, Chlorbenzoxamine, Pinaverium, Fenoverine, Idanpramine, Proxazole, Alverine, Trepibutone, Isometheptene, Caroverine, Phloroglucinol, Silicones, Trimethyldiphenylpropylamine Atropine, Hyoscyamine Scopolamine (Butylscopolamine, Methylscopolamine), Methylatropine, Fentonium, Cimetropium bromide primarily dopamine antagonists (Metoclopramide/Bromopride, Clebopride, Domperidone, Alizapride), 5-HT4 agonists (Cinitapride, Cisapride),

Proton pump inhibitors Omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole sodium,

opioids and opioid receptor antagonists -e.g. codeine, morphine, loperamide, diphenoxylate, methylnaltrexone bromide

Analgesic

[0014] Acetaminophen, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Meclofenamate, Mefenamic, Acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Phenylbutazone, Piroxicam, Sulindac, Tolmetin, Celecoxib, Buprenorphine, Butorphanol, Codeine, Hydrocodone, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone, Oxymorphone, Pentazocine, Propoxyphene, Tramadol, codeine

Sleep drugs

[0015] Hypnotics - Nitrazepam, Flurazepam, Loprazolam, Lormetazepam, Temazepam, Zaleplon, Zolpidem, Zopiclone, Chloral Hydrate, Triclofos, Clomethiazole, Quazepam, triazolam Estazolam Clonazepam, Alprazolam, Eszopiclone, Rozerem, Trazodone, Amitriptyline Doxepin, Benzodiazepine drugs, melatonin, diphenhydramine and herbal remedies such as Valerian

Cardiovascular medicines

[0016]

Cardiac glycosides - Digoxin, digitoxin,

Phosphodiesterase Inhibitors - enoximone, milrinone

Thiazides and related diuretics - bendroflumethiazide, chlortalidone, cyclopenthiazide, inapamide, metolazone, xipamide

Diuretics - furosemide, bumetanide, torasemide,

Potassium sparing diuretics and aldosterone antagonists - amiloride hydrochloride, triamterene, weplerenone, spironolactone,

Osmotic diuretics - mannitol

Drugs for arrhythmias - adenosine, amiodarone hydrochloride, disopyramide, flecainide acetate, propafenone hydrochloride, lidocaine hydrochloride,

Beta adrenoreceptor blocking drugs - propanalol, atenolol, acebutolol, bisprolol fumarate, carvedilol, celiprolol, esmolol, lebatolol, metoprolol tartrate, nadolol, nebivolol, oxprenolol, pindolol, solatol, timolol,

Hypertension - ambrisentan, bosentan, diazoxide, hydralazine, iloprost, minoxidil, sildenafil, sitaxentan, sodium nitroprusside, clonidine, methyldopa, moxonidine, guanethidine monosulphate, doxazosin, indoramin, prazosin, terazosin, phenoxybenzamine, phentolamine mesilate,

Drugs affecting the renin-angiotensin system - Captropril, Cilazapril, Enalapril Maleate, Fosinopril, Imidapril, Lisinopril, Moexipril, Perindopril Erbumine, Quinapril, Ramipril, Trandolapril, Candesartan Cilexetil, Eprosartan, Irbesartan, Losartan, Olmesartan Medoxomil, Telmisartan, Valsartan, Aliskiren.

Nitrates, calcium channel Blockers and antianginal drugs - Glyceryl trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Amlodipine, Diltiazem, Felodipine, Isradipine, Lacidipine, Lercanidipine, Nicardipine, Nifedipine, Nimodipine, Verapamil, Ivabradine, Nicorandil, Ranolazine,

Peripheral Vasodilators and related drugs - Cilostazol, Inositol Nicotinate, Moxisylyte, Naftidrofuryl Oxalate, Pentoxifylline,

Sympathomimetics - Dopamine, Dopexamine, Ephedrine, Metaraminol, Noradrenaline Acid Tartrate, Norephidrine Bitartrate, Phenylephidrine,

Anticoagulants and Protamine - Heparin, Bemiparin, Dalteparin, Enoxaparin, Tinzaparin, Danaparoid, Bivalirudin, Lepirudin, Epoprostenol, Fondaprinux, Warfarin, Acenocoumarol, Phenindione, Dabigatran Etexilate, Rivaroxaban, Protamine Sulphate,

Antiplatelet Drugs - Abciximab, Asprin, Clopidogrel, Dipyridamole, Eptifibatide, Prasugrel, Tirofiban,

Fibrinolytic and antifibrinolytic Drugs - Alteplase, Reteplase, Streptokinase, Tenecteplase, Urokinase, Etamsylate, Tranexamic Acid,

Lipid Regulating Drugs - Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin, Simvastatin,

Colesevam, Colestyramine, Colestipol, Ezetimibe, Bezafibrate, Ciprofibrate, Fenofibrate, Gemfibrozyl, Acipmox, Nictotinic Acid, Omega three fatty acid compounds, Ethanolamine Oleate, Sodium Tetradecyl Suphate.

[0017] CNS Drugs - Benperidol, Chlorpromazine, Flupentixol, Haloperidol, Levomepromazine, Pericyazine, Perphenazine, Pimozide, Prochlorperazine, Promazine, Sulpiride, Trifluoperazine, Zuclopenthixol, Amisulpride, Aripiprazole, Clozapine, Olanzapine, Paliperidone, Quetiapine, Riperidone, Sertindole, Zotepine, Flupentixol, Fluphenazine, Olanzapine Embonate, Pipotiazine Palmitate, Risperidone, Zuclopenthixol Decanoate, Carbamazepine, Valproate, Valproic acid, Lithium Carbonate, Lithium Citrate, Amitriptyline, Clomipramine, Dosulepin, Imipramine, Lofepramine, Nortriptyline, Trimipramine, mianserin, Trazodone, Phenelzine, Isocarboxazid, Tranylcypromine, Moclobemide, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Agomelatine, Duloxetine, Flupentixol, Mirtazapine, Reboxetine, Trytophan, Venflaxine, Atomoxetine, Dexametamine, Methylphenidate, Modafinil, Eslicarbazepine, Ocarbazepene, Ethosuximide, Gabapentin, Pregabalin, Lacosamide, Lamotrigine, Levetiracetam, Phenobarbital, Primidone, Phenytoin, Rufinamide, Tiagabine, Topiramate, Vigabatrin, Zonisamide, ropinirole, Rotigotine, Co-Beneldopa, Levodopa, Co-Careldopa, Rasagiline, Selegiline, Entacapone, Tolcapone, Amantidine, Orphenadrine, Procyclidine, Trihexyphenidyl, Haloperidol, Piracetam, Riluzole, Tetrabenazine, Acamprosate, Disulfiram, Bupropion, Vareniciline, Buprenorphine, Lofexidine, Donepezil, Galantamine, Memantine, Rivastigimine.

[0018] Anti-Infectives - Benzylpenicillin, Phenoxymethylpenicillin, Flucloxacillin, Temocillin, Amoxicillin, Ampicillin, Co-Amoxiclav, Co-Fluampicil, Piperacillin, Ticarcillin, Pivmecillinam, Cephalosporins, Cefaclor, Cefadroxil, Cefalexin, Cefixime, Cefotaxime, Cefradine, Ceftazidime, Cefuroxime, Ertapenem, Imipenem, Meropenem, Aztreonam, Tetracycline, Demeclocycline, Doxocycline, Lymecycline, Minocycline, Oxytetracycline, Tigecycline, Gentamicin, Amikacin, Neomycin, Tobramycin, Erythromycin, Azithromycin, Clarithromycin, Telithromycin, Clindamycin, Chloramphenicol, Fusidic Acid, Vancomycin, Teicoplanin, Daptomycin, Linezolid, Quinupristin, Colistin, Co-Trimoxazole, Sulpadiazine, Trimethoprim Capreomycin, Cycloserine, Ethambutol, Isoniazid, Pyrazinamide, Rifabutin, Rifampicin, Streptomycin, Dapsone, Clofazimine, Metronidazole, Tinidazole, Ciproflaxacin, Levoflaxacin, Moxifloxacin, Nalidixic Acid, Norflaxine, Orflaxacin, Nitrofurantoin, Methenamine Hippurate, Amphotericin, Anidulafungin, Caspofungin, Fluconazole, Flucytosine, Griseofluvin, Itraconzole, Ketoconazole, Micafungin, Nystatin, Posaconazole, Terbinafine, Voriconazole, Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir Disoproxil, Zidovudine, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinair, Nelfinavir, Ritonavir, Saquinavir, Tipranavir, Efavirenz, Etravirine, Nevarapine, Enfuvirtide, Maraviroc, Raltegravir, Aciclovir, Famciclovir, Inosine Pranobex, Valaciclovir, Cidofovir, Gangciclovir, Foscarnet, Valgangciclovir, Adefovir Dipivoxil, Entecavir, Telbivudine, Amantadine, Oseltamivir, Zanamivir, Palivizumab, Ribavirin, Artemether, Chloroquine, MefloquinePrimaquine, Proguanil, Pyrimethamine, Quinine, Doxycyclin, Diloxanide Furoate, Metronidaziole, Tinidazole, MepacrineSodium Stibogluconate,

Atovaquone, Pentamidine Isetionate, Mebendazole, Piperazine,

Other:

[0019] Benztropiprocyclidine biperiden, Amantadine Bromocriptine Pergolide Entacapone Tolcapone Selegeline Pramipexole, budesonide, formoterol, quetiapine fumarate, olanzapine, pioglitazone, montelukast, Zoledromic Acid, valsartan, latanoprost, Irbesartan, Clopidogrel, Atomoxetine, Dexamfetamine, Methylphenidate, Modafinil, Bleomycin, Dactinomycin, Daunorubicin, Idarubicin, Mitomycin, Mitoxantrone, Azacitidine, Capecitabine, Cladribine, Clofarabine, Cytarabine, Fludarabine, Flourouracil, Gemcitabine, mercaptopurine, methotrexate, Nelarabine, Pemetrexed, Raltitrexed, Thioguanine, Apomorphine, Betamethasone, Cortisone, Deflazacort, Dexamethosone, Hydrocortisone, Methylprednisolone, Prednisolone, Triamcinolone, Ciclosporine, Sirolimus, Tacrolimus, Interferon Alpha, Interferon Beta,

[0020] In a particularly preferred embodiment the active agent is designed to treat sleep maintenance insomnia and as such the active agent is a sedative or hypnotic, such as zolpidem, zaleplon or zopiclone.

[0021] The term "active agent" is understood to include solvates (including hydrates) of the free compound or salt, crystalline and non-crystalline forms, as well as various polymorphs. For example, the active agent can include all optical isomers of the compounds and all pharmaceutically acceptable salts thereof either alone or in combination threo isomers can be indicated as "threo" and the combined erythro isomers as "erythro".

[0022] In accordance with the invention, formulations are provided which are to be taken by a subject and which do not initially administer the active agent when the subject first takes the formulation. However, at a later time point the agent is administered to the subject as a "pulse" of agent.

[0023] In relation to the treatment of sleep maintenance insomnia, the subject takes a formulation in accordance with the invention and which comprises a sleep inducing/maintaining agent. Initially, the agent is substantially not released from the formulation, but after a period of time, for example, when a subject suffering from sleep maintenance insomnia may be expected to wake up, the agent is released in a pulse, so as to treat the subject and reduce the likelihood of them waking up through the night. It is desired that the agent is released in a pulse like manner so that the drug does not remain in the subject's system for a long period of time, in order to ensure that the subject is able to wake up at a suitable time in the morning and not to feel drowsy, a common side-effect of sleep inducing/maintaining agents.

[0024] The L-HPC is LH-11. LH-11 and LH-21 are particular types of L-HPC and may be obtained from Shin-Etsu Chemical Co., Ltd., Tokyo, Japan. L-HPCs are insoluble in water and comprise a glucose backbone which is substituted to a minimal extent by hydroxypropyl groups

LH-11 is mostly fibrous and has a mean particle size of 55µm. LH-11 has a hydroxypropyl content of around 11% and a molecular weight of around 130,000. LH-21 is moderately fibrous and has a mean particle size of 45µm. LH-21 has a molecular weight of around 120,000 and a hydroxypropyl content of around 11%

[0025] The wax may be any suitable wax such beeswax, carnuba wax, microcrystalline wax, hydrogenated castor oil. A particularly preferred wax is a glyceryl ester, such as glycerol behenate.

[0026] In a preferred formulation of the present invention as defined herein above, the wax and L-HPC are present in a ratio of 40:60 to 60:40 w/w. More preferably the ratio is 45:55 to 55:45 w/w, or 50:50 w/w. The skilled addressee will appreciate that with appropriate variation of the ratio, the delay in drug release can be tailored for a particular application. For example, a 50:50 w/w ratio of glycerol behenate as a wax, with LH-11 as the L-HPC employed as a delayed release layer in accordance with the present invention, is observed to provided a delayed release of approximately 3 hours. However, the same ratio with LH-21 as the L-HPC provides a delay in release of only 2 hours. Also reducing the amount of wax in comparison to the L-HPC is observed to reduce the delay significantly and conversely increasing the amount of wax to L-HPC ratio results in a significant increase in the delay of release. Thus with appropriate control of the ratio of wax to L-HPC and the type of wax/L-HPC, it is possible to control the time delay in release of the active agent, from a press-coated tablet comprising a delayed release layer surrounding a core comprising the active agent.
The delayed release layer surrounding the core may also comprise an amount of an active agent or agents, which may be the same or different to the active agent in the core, and which is designed to be released during dissolution/disintegration of the delayed release layer.

[0027] The subject to be treated is an animal, e.g. a mammal, especially a human.

[0028] The amount of active agent to be administered will be sufficient to be therapeutic or prophylactic. By therapeutic or prophylactic is meant one capable of achieving the desired response, and will be adjudged, typically, by a medical practitioner. The amount required will depend upon one or more of at least the active compound(s) concerned, the patient, the condition it is desired to treat or prevent and the formulation. However, it is likely to be in the order of from 1 µg to 1 g of compound per kg of body weight of the patient being treated.

[0029] Different dosing regimes may likewise be administered, again typically at the discretion of the medical practitioner. The formulation of the present invention may allow for at least daily administration although regimes where the compound(s) is (or are) administered more infrequently, e.g. every other day, weekly or fortnightly, for example, are also embraced by the present invention.

[0030] By treatment is meant herein at least an amelioration of a condition suffered by a patient; the treatment need not be curative (i.e. resulting in obviation of the condition). Analogously references herein to prevention or prophylaxis herein do not indicate or require

complete prevention of a condition; its manifestation may instead be reduced or delayed via prophylaxis or prevention according to the present invention.

[0031] For use according to the present invention, the compounds or physiologically acceptable salt, solvate, ester or other physiologically acceptable functional derivative thereof described herein are presented in a press-coated tablet form comprising the compound or physiologically acceptable salt, ester or other physiologically functional derivative thereof, together with one or more pharmaceutically acceptable excipients therefore and optionally other therapeutic and/or prophylactic ingredients. Any excipients are acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0032] The tablets of the present invention may be prepared using reagents and techniques readily available in the art and/or exemplary methods as described herein.

[0033] The tablets include those suitable for oral, rectal or vaginal administration. The tablets may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy.

[0034] Compressed tablets may be prepared by compressing the core tablet in a suitable machine an active compound in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, lubricating agent, surface-active agent or dispersing agent. The core tablet is subsequently coated with the materials for forming the delayed release layer. Tablets may be optionally coated, for example, by way of a further gastro-resistant coating.

[0035] Tablets suitable for rectal administration are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of a tablet with the softened or melted carrier(s) followed by chilling and shaping in moulds.

[0036] The tablets of the present invention may be prepared using pharmaceutical processes namely by direct compression or by granulation processing and final tableting. The process may comprise the steps of initially forming a core comprising the active agent and subsequently surrounding core with the delayed release layer. The core may be formed by dispersing one or more active agents with one or more excipients, such as a cellulose ether, typically a L-HPC, such as LH-21.

[0037] The delayed release layer may be formed by melting the wax component and subsequently admixing the other components including the L-HPC. The mixture may then be allowed to cool and solidify before being ground and/or forced through a sieve, in order to achieve granules of the size range 500μm -1 mm. The core may then be coated with the delayed release layer material by direct compression. Typically the core is sandwiched between top and bottom layers of the delayed release material and hence completely

surrounds the core.

[0038] The tableting for the formulation of tablets may be conducted using an apparatus ordinarily employed for the formation or granulation of tablets. Examples may include single-punch tableting machine, rotary tableting machine and tableting tester.

[0039] Tableting is conducted usually under a pressure of 50 to 300 MPa, preferably 80 to 200 MPa. At a pressure less than 50 MPa, the resulting tablet may have insufficient hardness, which disturbs easily handling, while pressures exceeding 300 MPa may serve to cause a delay in disintegration.

[0040] The core and/or delayed release layer may include a filler, such as a water insoluble filler, water soluble filler, and mixtures thereof. The water insoluble filler, may be a calcium salt or talc. Exemplary water soluble fillers such as water soluble sugars and sugar alcohols, preferably lactose, glucose, fructose, mannose, galactose, the corresponding sugar alcohols and other sugar alcohols, such as mannitol, sorbitol, and xylitol.

[0041] The filler in the delayed release layer can be the same or different as the filler in the core composition, if any. For example, the core composition can include a water soluble filler while the press coat composition can include a water insoluble filler.

[0042] Other excipients can also be present in the core and/or delayed release layer, including lubricants (such as talc and magnesium stearate), glidants (such as fumed or colloidal silica), pH modifiers (such as acids, bases and buffer systems), and pharmaceutically useful processing aids. It will be appreciated that such other excipients may be the same or different in the core and delayed release layer, if any.

[0043] In a preferred embodiment of the invention, the core components (active agent and optional excipients) are blended together and compressed into suitable cores. The blending can take place in any order of addition. Preferably, the cores are blended by starting with the smallest volume component and then successively adding the larger volume components.

[0044] The tablet can be further coated with optional additional coatings. The additional coatings can be pH-dependent on pH-independent, aesthetic or functional; where the coating is a gastro-resistant coating (intented to prevent release in the stomach), the 'clock' or time for delayed release, as defined herein, will not start until gastric emptying occurs and dissolution of the gastro-resistant coating takes place (as can be determined, for example, by employing scintigraphy studies). The time taken for dissolution of the gastro-resistant coating together with the delay from the time-delay layer will ensure drug release in the lower reaches of the intestine, particularly the distal ileum and/or colon. Such additional coatings preferably include film forming materials. For subjects who may additionally find it difficult to go to sleep, the delayed release layer and/or additional coating may include a sleep inducing agent for immediate release.

Detailed Description

[0045] The present invention will now be further described by way of example and with reference to the figure which show:

Figure 1 shows the release profile of a drug from a tablet comprising glycerol behenate and LH-11 in a 50/50 w/w ratio in a delayed release layer;

Figure 2 shows the release profile of a drug from a tablet comprising glycerol behenate and LH-21 in a 50/50 w/w ratio in a delayed release layer;

Figures 3 and 4 show the release profile of a drug from a tablet comprising glycerol behenate and LH-11 (figure 3) and LH-21 (figure 4) in 30:70 w/w ratio, in a delayed release layer.;

Figure 5 shows Gamma Scintigraphy Images showing release of delayed release formulation of Zolpidem;

Figure 6 shows Pharmacokinetic analysis of drug levels in plasma, in 6 subjects; and

Figure 7 shows the release profile of a tablet comprising a delayed release layer of 50/50 w/w glycerol behenate/LH32.

Formulation for treating sleep maintenance insomnia

1. Clinical Need

[0046] This formulation profile was designed as a treatment for people that fall asleep initially, then reawaken and are unable to sleep 2-3 hours later.

2. Methods

2.1. Core Tablet Blend and Core Tablet Compression

[0047]

1. (i) 1g Zolpidem tartrate, 5.1g ac-di-sol, 2.0g lactose and 0.9g magnesium stearate. Powder mix of the above, except magnesium stearate, for 10 min in turbula mixer, then magnesium stearate added and all mixed for further 5 min.

2. (ii) 90mg core tab blend-compressed in a 6.9 mm die/punch set at 1 ton for 10 seconds.
3. (iii) Tablets are stored in amber glass bottle until use.

2.2. Granules (to surround core tablet)

[0048]

(i) Glycerol behenate (GB) and LH-11 weighed into tared weigh boats according to Table 1:

Table 1

Excipient	Weight (g)
GB	10
LH-11	10

(ii) GB placed in a glass beaker on a hot plate set at 100°C. Once the GB melted, LH-11 added gradually whilst stirring until a uniform mix is achieved.
(iii) The mix stirred continuously until cooled to room temperature. The granules are left for at least 30 min at room temperature before the next step.
(iv) The cooled granules forced through a 1 mm sieve (using a spatula and a brush) and collected on a 500 µm sieve so that the granules used are in the size range 500 µm - 1 mm.
(v) Granules stored in amber glass screw-top jar until use.

2.3. Formulation Compression

[0049]

1. (i) A 13 mm die and matching flat-faced punches used to compress the formulation. For 6 tablets, 12 x 250 mg granules (to surround core tablet) are weighed into tared weigh boats.
2. (ii) 250 mg granules placed onto the lower punch, the core tablet dropped on and centralised (centralising tool) before placing the other 250 mg granules on top.
3. (iii) The formulation is compressed at 5 ton for 2 minutes in a 13 mm die/punch set.

2.4. Dissolution

[0050] Dissolution performed in 900 ml sodium phosphate buffer (0.01 M, at pH7) at 37°C, with UV analysis at 242 nm.

3. Results (50:50, GB:LH-11)

[0051] As can be seen from Figure 1, a delay of approximately 3 hours is observed, followed by a rapid pulsed release of drug.

4. Supporting Data

4.1. LH-21 instead of LH-11 (50:50, GB:LH-21)

[0052] As can be seen in Figure 2, substituting LH-11 for LH-21, results in a decrease in the delay of release time. Such a decrease may not be desired for all envisaged applications.

4.2. 80:20, GB:LH-11

[0053] No release of zolpidem core tablet over 12 hours, data not shown.

4.3. 80:20, GB:LH-21

[0054] No release of zolpidem core tablet over 12 hours, data not shown.

4.4. 30:70, GB:LH-11

[0055] As can be seen in Figure 3, reducing the glycerol behenate to LH-11 ratio results in a significant decrease in the delay of release time.

4.5. 30:70, GB:LH-21

[0056] As can be seen in Figure 4, reducing the glycerol behenate to LH-21 ratio results in a significant decrease in the delay of release time.

[0057] Using LH-21 in the outer granules instead of LH-11 releases the core tablet approximately 30 min earlier in both examples shown above.

Extraction Method / Analysis of Plasma levels of Zolpidem

Materials

[0058] Human plasma, lithium heparin, origin USA : Sera laboratories international Ltd, Bx H911239 Zolpidem tartrate
DEE: Fisher laboratory reagent grade Bx 1097413

[0059] NaOH: prepared using Q3 water and NaOH: Sigma Aldrich, reagent grade beads, 97% Bx 01209BH

Method

[0060] vortex blank plasma
add 400ul blank plasma to glass screw cap tubes

Calibration

[0061] Blank preparation - to be prepped before standards
add 100ul mobile phase to 400ul blank plasma

[0062] vortex 10 secs
add 50ul 1M NaOH
vortex 10 secs
add 4mL DEE and vortex 3 mins (note: DEE decanted from bottle fresh every day)
pipette tips changed after every addition of mobile phase/DEE

Standard preparation

[0063] Starting with lowest concentration standard, vortex standard
Add 100ul standard to 400ul blank plasma

[0064] Vortex 10secs
Add 50ul 1M NaOH
Vortex 10secs
Add 4mL DEE and vortex 3 mins (note: DEE decanted from bottle fresh every day)

[0065] Pipette tips changed after every addition of standard/DEE
Centrifuge samples 3 mins at 2000rpm

[0066] Remove top layer into clean labelled glass screwtop tube using glass pipette
Evaporate to dryness under nitrogen at 40°C (also used RVC to evaporate, 40°C, 100mbar, 25mins)
Reconsititute in 100ul mobile phase. Allow to stand for 30 mins and then vortex 3 mins
Transfer to HPLC vial with insert

Sample preparation

[0067] Vortex samples to mix
Add 500ul sample to glass screwtop tube
Add 50ul 1M NaOH
Vortex 10secs
Add 4mL DEE and vortex 3 mins (note: DEE decanted from bottle fresh every day)

[0068] Pipette tips changed after every addition of standard/DEE
Centrifuge samples 3 mins at 2000rpm

[0069] Remove top layer into clean labelled glass screwtop tube using glass pipette
Evaporate to dryness under nitrogen at 40°C (also used RVC to evaporate, 40°C, 100mbar, 25mins)
Reconsititute in 100ul mobile phase. Allow to stand for 30 mins and then vortex 3 mins
Transfer to HPLC vial with insert

Mobile Phase Preparation

Materials

[0070] Potassium phosphate monobasic, SAFC lot 1370660
NaOH: Sigma Aldrich, reagent grade beads, 97% Bx 01209BH
Acetonitrile: Fisher HPLC gradeBx 1095614
20mM potassium phosphate buffer prepared with Q3 water, adjusted to pH 6 with NaOH
Buchner filtered through 0.2um 47mm nylon membrane

Chromatographic Conditions

[0071] Gynkotek HPLC system with Perkin Elmer LS 40 fluorescence detector
Column: phenomenex Lichrospher RP-18 100A 125 x 4.00mm 5 micron with guard column
Detection: excitation: 251 nm emission:289

[0072] Gradient: starting conditions 60% buffer 40% acetonitrile flowrate 1mL/min
Increase from 40 - 80% acetonitrile over 10 mins, hold at 80% for 4 mins
Return to starting conditions for 2 mins prior to next injection
Injection volume 20uL

Spiked Standard Range

1 - 150ng/mL plasma

[0073] Clinical Trial Protocol - Zolpidem 10 mg delayed-release (2 hour time-delay) Clinical studies were carried out in Healthy male volunteers aged between 18-65 years inclusive with a body mass index (BMI) between 18.0 and 29.9 kg/m^2 Gastrointestinal transit of the delayed-release tablets was characterised by inclusion of a radiolabel marker, technetium-99m (^{99m}Tc), complexed with diethylenetriaminepentaacetic acid (DTPA) which prevents absorption from the gastrointestinal tract. The radiolabel is incorporated into the core tablet. Each tablet was radiolabelled with 4 MBq 99mTc-DTPA and administered with 240 ml of water at bedtime.

[0074] Subjects received a standard dinner comprising roast chicken with salad, low fat yoghurt and one cup of decaffeinated tea, coffee or juice 4 hours prior to dosing.

[0075] Scintigraphic imaging was performed using a Siemens E-Cam gamma camera fitted with a low-energy high-resolution collimator. Subjects were imaged in a standing position except during periods of sleep where the subjects were imaged lying down.
The following imaging schedule was used:

Anterior static acquisitions of 25-second duration each were collected immediately after dosing then every 15 minutes until complete release of radiolabel marker.

A 5 mL pre-dose blood sample was taken from each subject 15 minutes before dosing. Following dosing blood samples were taken according to the following schedule:

[0076] Every 15 minutes until burst release observed by scintigraphy then every 15 minutes for 2 hours then every 30 minutes for 1 hour then hourly until end of study day (9 hours post-dose). See figure 5.
Blood samples were centrifuged at 2000 g for 10 minutes and the plasma fraction removed and stored at -20 °C for subsequent analysis. See Figure 6.

[0077] Figure 7 shows the release profile of a tablet formulation comprising a delayed release layer of 50/50 w/w glycerol behenate/LH32 demonstrating the ability to vary the period of delay before pulsed drug release.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **STEVENS HNE**Chronopharmaceutical Drug Delivery. J Pharm Pharmac., 1998, vol. 50, 5- [0002]
- **GHIMIRE M**European Journal of Pharmaceutics and Biopharmaceutics, 2007, 67- [0002]

PULSERENDE LÆGEMIDDELFRIGIVELSE

PATENTKRAV

1. Pressecoatet tabletformulering for en forsinket, efterfulgt af en pulserende frigivelse af et aktivt stof, hvilken tablet omfatter

(a) en kerne, der omfatter det eller de aktive stoffer sammen med en eller flere excipienser; og

(b) et forsinket frigivelseslag, der omfatter kernen og omfatter en voks og lav-substitueret hydroxypropylcellulose (L-HPC), der primært er fibrøs og har en gennemsnitlig partikelstørrelse på 55µm, et hydroxypropylindhold på ca. 11 % og en molekylvægt på ca. 130.000, i et forhold på 40:60 til 60:40 vægt/vægt; hvor det forsinkede frigørelseslag forsinker frigørelse af det aktive middel i kernen i mellem 1,5 - 8 timer efter en persons administration af tabletten, og hvorefter der sker en pulserende frigivelse af det aktive middel fra kernen, således at mindst 70 % af det aktive middel i kernen frigives inden for 5-80 minutter.

2. Pressecoatet tablet ifølge et hvilket som helst foregående krav, der omfatter én eller flere af følgende aktive stoffer:

gastrolægemidler

antacider - aluminiumhydroxid, magnesiumcarbonat, magnesiumtrisilicat, hydrotalcit, simethiconalginater,

antispamodika - atropinsulphat, dicycloverinhydrochlorid, hyoscinbutylbromin, propanthelinbromid, alverincitrat, mebeverinhydrochlorid,

mobilitetsstimulanter - metoclorpramid, domperidon

H2-receptorantagonister - cimetidin, famotidinenizatidin, ranitidin

antimuskariner - pirenzepin

chelater - trikaliumdicitratbismuthat, sucralfat,

prostaglandinanaloger- misoprostol

aminosalicylater - balsazidnatrium, mesalazin, olsalazin, sulphasalazin

kortikosteroider - beclometasondipropionat, budenosid, hydrokortison, pednisolon

der påvirker immunrespons - ciclosporin, mercaptopurin, methotrexat, adalimumab, infliximab

stimulerende laksantia - bisacodyl, dantron, docusat, natriumpicosulfat,

lægemidler, der påvirker galdesammensætning og -strømning - ursodeoxycholsyre

galdesyresekvestreringsmidler - colestyramin, oxyphencyclimin, camylofin, mebeverin, trimebutin, rociverin, dicycloverin, dihexyverin, difemerin, piperidolate benzilon, mepenzolat, pipenzolat, glycopyrronium, oxyphenonium, penthienat, methanthelin, propanthelin, otiloniumbromid, tridihexethyl, isopropamid, hexocyclium, poldin, bevonium, diphemanil, tiemoniumiodid, prifiniumbromid, timepidium bromid, fenpiverinium papaverin, drotaverin, moxaverine 5-HT3-antagonister (såsom alosetron, cilansetron), 5-HT4-agonister (såsom mosaprid, prucaloprid, tegaserod) fenpipran, diisopromin, chlorbenzoxamin, pinaverium, fenoverin, idanpramin, proxazol, alverin, trepibuton, isomethepten, caroverin, phloroglucinol, silicones, trimethyldiphenylpropylamine atropin, hyoscyaminscopolamin (såsom

butylscopolamin, methylscopolamine), methylatropin, fentonium, cimetropiumbromid primære dopaminantagonister, såsom metoclopramid/bromoprid, cleboprid, domperidon, og alizaprid, 5-HT4-agonister, såsom cinitaprid og cisaprid,

protonpumpehæmmere omeprazol, lansoprazol, pantoprazol, esomeprazol, rabeprazolnatrium,

opioider og opiodreceptorantagonister, såsom kodein, morfin, loperamid, diphenoxylat, methylnaltrexonbromid

analgetisk, acetaminophen, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamat, mefenamsyre, meloxicam, nabumeton, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, celecoxib, buprenorphin, butorphanol, kodein, hydrocodon, hydromorphon, levorphanol, meperidin, metadon, morfin, nalbuphin, oxycodon, oxymorphon, pentazocin, propoxyphen, tramadol, kodein

søvnlægemidler hypnotika - nitrazepam, flurazepam, loprazolam, lormetazepam, temazepam, zaleplon, zolpidem, zopiclon, chloralhydrat, triclofos, clomethiazol, quazepam, triazolam, estazolam, clonazepam, alprazolam, eszopiclon, rozerem, trazodon, amitriptylindoxepin, benzodiazepinlægemidler, melatonin, diphenhydramin og urtemedicin såsom lægebaldrian

kardiovaskulær medicin

hjerteglycosider - digoxin, digitoxin,

phosphodiesterasehæmmere - enoximon, milrinon

thiazider og beslægtede diuretika - bendroflumethiazid, chlortalidon, cyclopenthiazid, inapamid, metolazon, xipamid

diuretika - furosemid, bumetanid, torasemid,

kaliumsparende diuretika og aldosteronantagonister - amiloride hydrochlorid, triamteren, weplerenon, spironolacton,

osmotiske diuretika - mannitol

lægemidler mod arytmier - adenosin, amiodaronhydrochlorid, disopyramid, flecainidacetat, propafenonhydrochlorid, lidocain-hydrochlorid,

beta-adrenoreceptorblokerende lægemidler - propanalol, atenolol, acebutolol, bisprolol fumarat, carvedilol, celiprolol, esmolol, lebatolol, metoprololtartrat, nadolol, nebivolol, oxprenolol, pindolol, solatol, timolol,

hypertension - ambrisentan, bosentan, diazoxid, hydralazin, iloprost, minoxidil, sildenafil, sitaxentan, natriumnitroprussid, clonidin, methyldopa, moxonidin, guanethidinmonosulfat, doxazosin, indoramin, prazosin, terazosin, phenoxybenzamin, phentolaminmesilat,

lægemidler, der påvirker renin-angiotensinsystemet - captropril, cilazapril, enalaprilmaleat, fosinopril, imidapril, lisinopril, moexipril, perindoprilerbumin, quinapril, ramipril, trandolapril, candesartan-cilexetil, eprosartan, irbesartan, losartan, olmesartan-medoxomil, telmisartan, valsartan, aliskiren.

nitrater, calciumkanalblokkere og antianginale lægemidler - glyceryltrinitrat, isosorbiddinitrat, isosorbidmononitrat, amlodipin, diltiazem, felodipin, isradipin, lacidipin, lercanidipin, nicardipin, nifedipin, nimodipin, verapamil, ivabradin, nicorandil, ranolazin,

periferiske vasodilatorer og beslægtede lægemidler - cilostazol, inositol-nicotinat, moxisylyt, naftidrofuryloxalat, pentoxifyllin,

sympatometika - dopamin, dopexamin, efedrin, metaraminol, noradrenalinsyretartrat, norefidrinbitartrat, phenylefidrin,

antikoagulantia og protamin - heparin, bemiparin, dalteparin, enoxaparin, tinzaparin, danaparoid, bivalirudin, lepirudin, epoprostenol, fondaprinux, warfarin, acenocoumarol, phenindion, dabigatranetexilat, rivaroxaban, protaminsulfat,

blodpladehæmmende lægemidler - abciximab, asprin, clopidogrel, dipyridamol, eptifibatid, prasugrel, tirofiban,

fibrinolytiske og antifibrinolytiske lægemidler - alteplase, reteplase, streptokinase, tenecteplase, urokinase, etamsylat, tranexamsyre,

lipidregulerende lægemidler - atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin, colesevam, colestyramin, colestipol, ezetimib, bezafibrat, ciprofibrat, fenofibrat, gemfibrozyl, acipmox, nikotinsyre, omega-3 fedtsyreforbindelser, ethanolaminoleat, natriumtetradecylsufat,

CNS-lægemidler - benperidol, chlorpromazin, flupentixol, haloperidol, levomepromazin, pericyazin, perphenazin, pimozid, prochlorperazin, promazin, sulpirid, trifluoperazin, zuclopenthixol, amisulprid, aripiprazol, clozapin, olanzapin, paliperidon, quetiapin, riperidon, sertindol, zotepin, flupentixol, fluphenazin, olanzapinembonat, pipotiazinpalmitat, risperidon, zuclopenthixoldecanoat, carbamazepin, valproat, valproesyre, lithiumcarbonat, lithiumcitrat, amitriptylin, clomipramin, dosulepin, imipramin, lofepramin, nortriptylin, trimipramin, mianserin, trazodon, phenelzin, isocarboxazid, tranylcypromin, moclobemid, citalopram, escitalopram, fluoxetin, fluvoxamin, paroxetin, sertralin, agomelatin, duloxetin, flupentixol, mirtazapin, reboxetin, trytophan, venflaxin, atomoxetin, dexametamin, methylphenidat, modafinil, eslicarbazepin, ocarbazepen, ethosuximid, gabapentin, pregabalin, lacosamid, lamotrigin, levetiracetam, phenobarbital, primidon, phenytoin, rufinamid, tiagabin, topiramat, vigabatrin, zonisamid, ropinirol, rotigotin, co-beneldopa, levodopa, co-careldopa, rasagilin, selegilin, entacapon, tolcapon, amantidin, orphenadrin, procyclidin, trihexyphenidyl, haloperidol, piracetam, riluzol, tetrabenazin, acamprosat, disulfiram, bupropion, varenicilin, buprenorphin, lofexidin, donepezil, galantamin, memantin, rivastigimin,

antiinfektionsmidler - benzylpenicillin, phenoxymethylpenicillin, flucloxacillin, temocillin, amoxicillin, ampicillin, co-amoxiclav, co-fluampicil, piperacillin, ticarcillin, pivmecillinam, cephalosporiner, cefaclor, cefadroxil, cefalexin, cefixim, cefotaxim, cefradin, ceftazidim, cefuroxim, ertapenem, imipenem, meropenem, aztreonam, tetracyclin, demeclocyclin, doxocyclin, lymecyclin, minocyclin, oxytetracyclin, tigecyclin, gentamicin, amikacin, neomycin, tobramycin, erythromycin, azithromycin, clarithromycin, telithromycin, clindamycin, chloramphenicol, fusidinsyr, vancomycin, teicoplanin, daptomycin, linezolid, quinupristin, colistin, co-trimoxazol, sulpadiazin, trimethoprim capreomycin, cycloserin, ethambutol, isoniazid, pyrazinamid, rifabutin, rifampicin, streptomycin, dapson, clofazimin, metronidazol, tinidazol, ciproflaxacin, levoflaxacin, moxifloxacin, nalidixinsyre, norflaxin, orflaxacin, nitrofurantoin, methenaminhippurat, amphotericin, anidulafungin, caspofungin, fluconazol, flucytosin, griseofluvin, itraconzol, ketoconazol, micafungin, nystatin, posaconazol, terbinafin, voriconazol, abacavir, didanosin, emtricitabin, lamivudin, stavudin, tenofovirdisoproxil, zidovudin, atazanavir,

darunavir, fosamprenavir, indinavir, lopinair, nelfinavir, ritonavir, saquinavir, tipranavir, efavirenz, etravirin, nevarapin, enfuvirtid, maraviroc, raltegravir, aciclovir, famciclovir, inosinpranobex, valaciclovir, cidofovir, gangciclovir, foscarnet, valgangciclovir, adefovir dipivoxil, entecavir, telbivudin, amantadin, oseltamivir, zanamivir, palivizumab, ribavirin, artemether, chloroquin, mefloquineprimaquin, proguanil, pyrimethamin, quinin, doxycyclin, diloxanidfuroat, metronidaziol, tinidazol, mepacrinenatrium-stibogluconat, atovaquon, pentamidine isetionat, mebendazol, piperazin, andre: benztropiprocyclidinbiperiden, amantadin bromocriptin pergolid entacapon tolcapon selegelin pramipexol, budesonid, formoterol, quetiapinfumarat, olanzapin, pioglitazon, montelukast, zoledronsyr, valsartan, latanoprost, irbesartan, clopidogrel, atomoxetin, dexamfetamin, methylphenidat, modafinil, bleomycin, dactinomycin, daunorubicin, idarubicin, mitomycin, mitoxantron, azacitidin, capecitabin, cladribin, clofarabin, cytarabin, fludarabin, flourouracil, gemcitabin, mercaptopurin, methotrexat, nelarabin, pemetrexed, raltitrexed, thioguanin, apomorphin, betamethason, kortison, deflazacort, dexamethoson, hydrokortison, methylprednisolon, prednisolon, triamcinolon, ciclosporin, sirolimus, tacrolimus, interferon-alfa, interferon-beta.

3. Pressecoatet tablet ifølge krav 2 til anvendelse i en fremgangsmåde til behandling af én eller flere af følgende sygdomme eller tilstanden:

forstyrrelser i centralnervesystemet, f.eks. neuropatisk smerte, apopleksi, demens, Alzheimers sygdom, Parkinsons sygdom, neuronal degeneration, meningitis, rygmarvslæsion, cerebral vasospasme, amyotrofisk lateral sklerose

kardiovaskulær sygdom, hypertension, atherosklerose, angina, arteriel obstruktion, periferisk arteriesygdom, myokardiepatologi, arytmi, akut myokardieinfarkt, angina, kardiomyopati, kongestivt hjertesvigt, koronær arteriesygdom (CAD), karotid arteriesygdom, endocarditis, hyperkolesterolæmi, hyperlipidæmi, periferisk arteriesygdom (PAD)

urogenitale forstyrrelser; erektil dysfunktion, urinvejsorgansygdomme godartet prostatisk hypertrofi (BPH), tubulær acidose, diabetisk nefropati, glomerulonefritis, glomerulosklerose, urinvejsinfektion, fækal inkontinens

øjensygdom, glaukom, blephartitis, okulær hypertension, retinopati, conjunctivitis, scleritis, retinitis, keratitis, corneal ulcer, iritis, korioretinal inflammation, makulært ødem, xerophthalmi

lungesygdom, astma, pulmonalhypertension, akut respiratorisk distress-syndrom, COPD, emfysem, pneumoni, tuberkulose, bronkitis, akut bronkitis, bronchiectasis, bronchiolitis, bronkopulmonal dysplasi, byssinose, coccidioidomykose (cocci), cystisk fibrose, influenza, lungecancer, mesotheliom metaboliske sygdomme; hypercalciuri, hyperglykæmi, hyperinsulinæmisk hypoglykæmia, hyperinsulinisme, hyperlysinæmi, hypoglykæmi

eksokrin og endokrin; Addisons sygdom, hypoaldosteronisme, Cushings syndrom, diabetes, Goitre, hyperthyroidisme, hypothyroidisme, thyroiditis, pancreatitis

leverforstyrrelser, hepatitis, ikke-alkoholisk fedtleversygdom, cirrose, levercancer, primær skleroserende cholangitis, primær biliær levercirrose, Budd-Chiari syndrom,

autoimmune og Inflammatoriske sygdomme, multipel sklerose rheumatoid artritis, psoriasis, diabetes, sarkoidose, Addisons sygdom, alopeki areata, amyotrofisk lateral sklerose, ankyloserende

spondylitis, polyartikulær artritis, atopisk allergi, topisk dermatitis, autoimmun hepatitis, cøliaki, Chagas sygdom, glutensensitiv sygdom, Cogan syndrom, Crohns sygdom, Cushings syndrom, diabetes mellitus type 1, endometriose, eosinofil fasciitis, fibromyalgi/fibromyositis, gastritis, glomerulonefritis, Graves' sygdom, Guillain-Barré syndrome (GBS), Hashimotos encephalitis, Hashimotos thyroiditis, hæmolytisk anæmi, idiopatiske inflammatoriske demyelinerende sygdomme, idiopatisk lungefibrose, interstitial cystitis, juvenil idiopatisk artritis, juvenil rheumatoid artritis, Kawasakis sygdom, Lichen sclerosus, lupus erythematosus, Ménières sygdom, myasthenia gravis, myositis, narkolepsi, pernicøs anæmi, perivenous encephalomyelitis, polymyalgia rheumatica, primær biliær levercirrose, psoriatisk artritis, Reiters syndrom, rheumatoid feber, sarkoidose, skizofreni, Sjögrens syndrom, spondyloartropati, ulcerøs colitis

muskelknogleforstyrrelser: osteoartritis, osteoporose, osteonekrose, Arthritis, Pagets sygdom Bursitis, costochondritis, tendonitis

hudforstyrrelser; acne, alopeki, candidiasis, cellulitis, dermatitis, eksem, epidermolysis bullosa, erythrasma, herpes, erysipelas, folliculitis, impetigo, ringorm, scabies, tinea, trichomycosis

øre-næse-halsfortyrrelser; otitis, sinusitis, laryngitis, pharyngitis, Menieres sygdom, labyrinthitis,

andre: akut og kronisk smerte, virusinfektion, cancer, mastoiditis, myringitis, otitis media, rhinitis, sinusitis, sialadenitis, retropharyngeal absces, tonsillopharyngitis, gastrointestinale forstyrrelser

irritabel tarmsyndrom, nekrotiserende entercolitis, non-ulcer dyspepsia, kronisk intestinal pseudo-obstruktion, funktionel dyspepsi, colonisk pseudo-obstructioduodenogastrisk reflux, gastroesophageal refluxsygdom, ileus inflammation, gastroparese, halsbrand, konstipation - (f.eks. konstipation associeret med anvendelse af medikamenter, såsom opioider), kolorektal cancer, kolonpolypper, diverticulitis, kolorektal cancer, Barretts esophagus, blødning i fordøjelseskanalen, cøliaki, colonpolypper, konstipation, Crohns sygdom, cyklisk opkastningssyndrom, forsinket gastrisk tømning (gastroparese), diarré, diverticulosis, duodenale sår, fækal inkontinens, galdesten, gas i fordøjelseskanalen, gastritis, gastroesophageal refluxsygdom, halsbrand, hiatushernie, hæmokromatose, hæmorider, hiatushernie, Hirschsprungs sygdom, indigestion, inguinal hernia, lactoseintolerans, peptiske sår, polypper, porfori, primær biliær levercirrose, primær skleroserende cholangitis, proctitis, hurtig gastrisk tømning, korttarmsyndrom, mavesår, ulcerøs colitis, ulcer, Whipples sygdom.

4. Pressecoatet tablet ifølge krav 1, hvor det aktive middel designet til at behandle søvnløshed eventuelt er et sedativt eller hypnosemiddel, såsom zolpidem, zaleplon eller zopiclon.

5. Tablet ifølge et hvilket som helst foregående krav, hvor voksen er bivoks, carnubavoks, mikrokrystallinsk voks, en hydrogeneret castorolie eller en glycerylester.

6. Tablet ifølge krav 5, hvor glycerylesteren er glycerolbehenat.

7. Tablet ifølge et hvilket som helst foregående krav, hvor voksen og L-HPC er til stede i et forhold på 45:55 til 55:45 vægt/vægt.

8. Tablet ifølge et hvilket som helst foregående krav, der endvidere omfatter en supplerende coating, hvor coating er pH-afhængig, pH-uafhængig, æstetisk eller funktionel.

9. Pressecoatet tablet ifølge et hvilket som helst foregående krav, hvor det aktive middel er et sedativt eller hypnotisk middel.

DRAWINGS

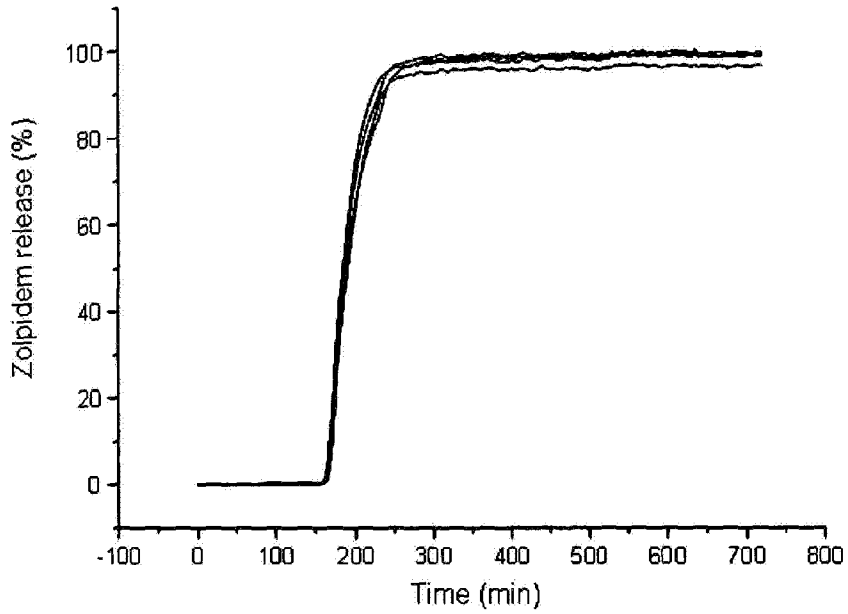

Figure 1

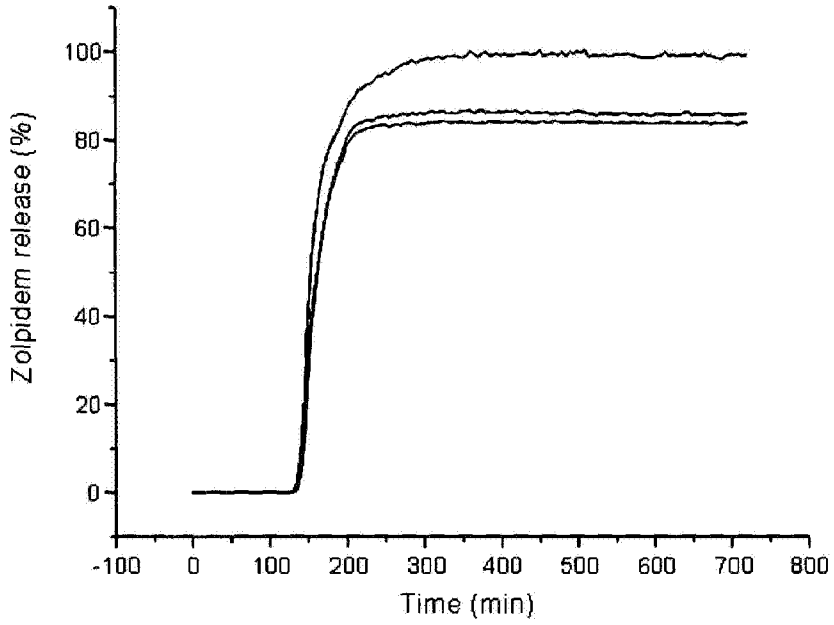
Zolpidem release (%)
100
80
60
40
20
0
-100
0
100
200
300
400
500
600
700
800
Time (min)

Figure 2

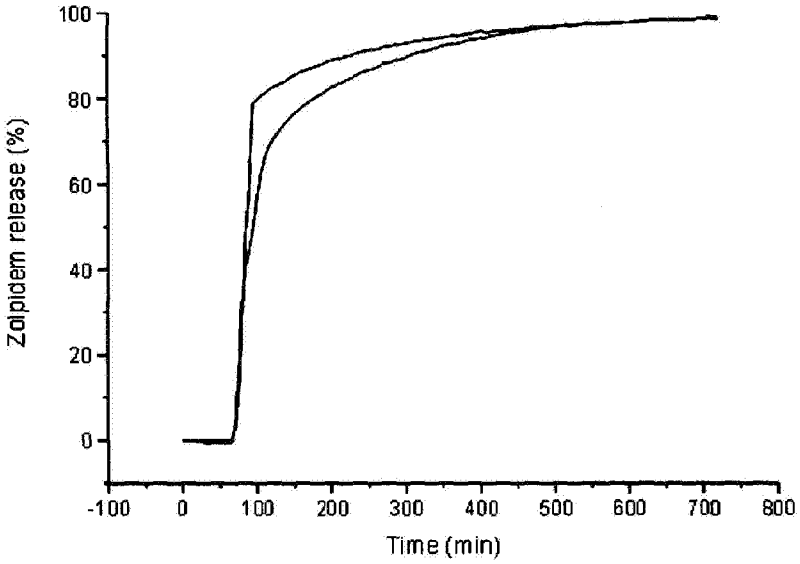
Zolpidem release (%)
100
80
60
40
20
0
-100
0
100
200
300
400
500
600
700
800
Time (min)

Figure 3

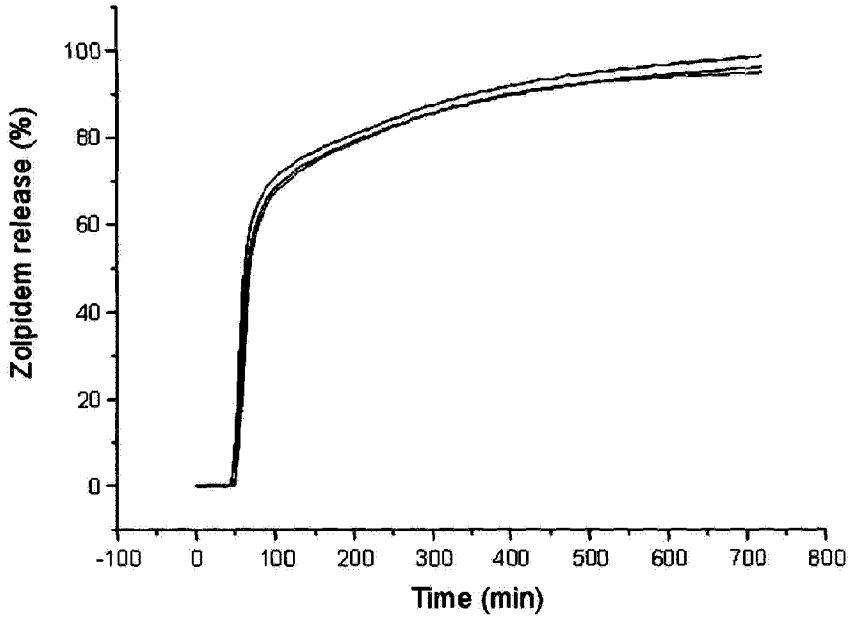
Zolpidem release (%)
100
80
60
40
20
0
-100
0
100
200
300
400
500
600
700
800
Time (min)

Figure 4

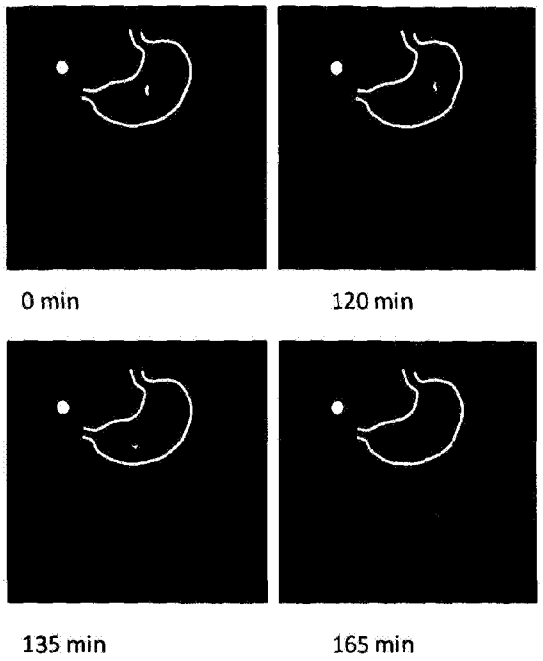

Figure 5

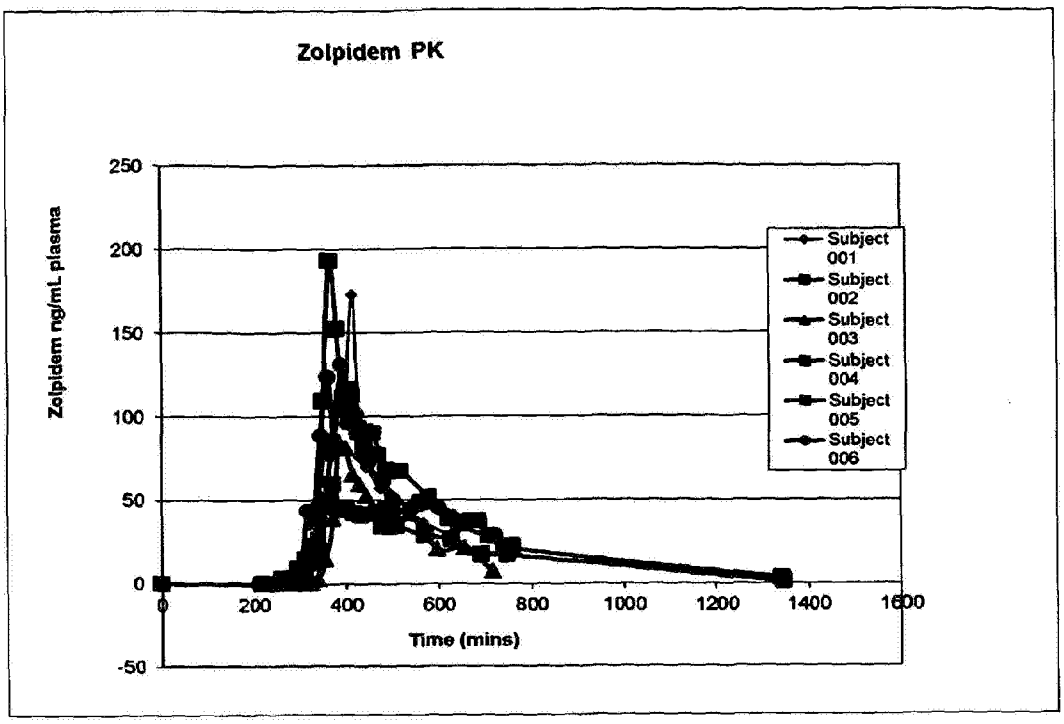
Zolpidem PK
Zolpidem ng/mL plasma
250
200
150
100
50
0
-50
0
200
400
600
800
1000
1200
1400
1600
Time (mins)
Subject 001
Subject 002
Subject 003
Subject 004
Subject 005
Subject 006

Figure 6

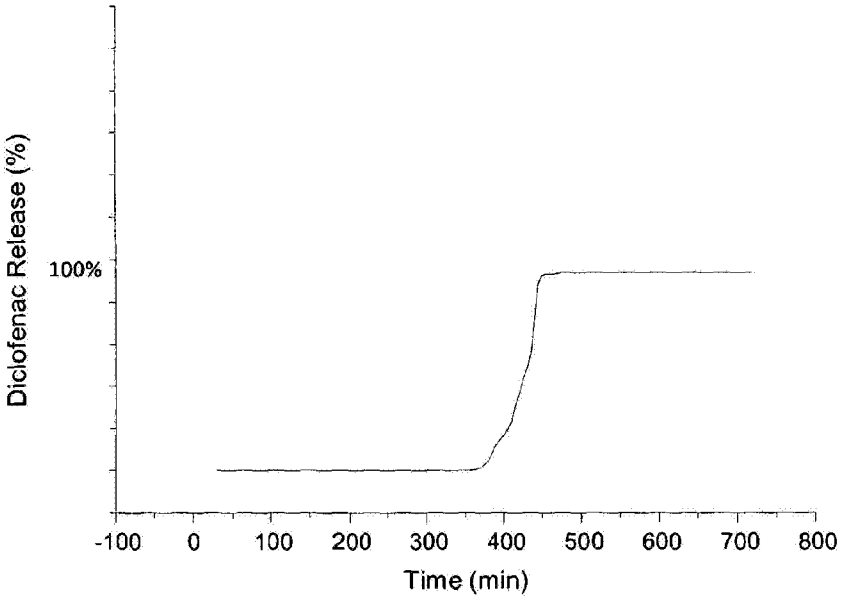
Diclofenac Release (%)
100%
-100
0
100
200
300
400
500
600
700
800
Time (min)

Figure 7