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(54) **Title**: PROGRAMMED DRUG DELIVERY

(57) **Abstract**: There is provided a programmed release pharmaceutical compositions of one or more active substances with a coating of co-processed glyceryl behenate and inorganic calcium salts, and compositions containing such coating. The invention also relates to the dosage forms of specific geometry, which advantageously delays the release of the active substance from the core for a period of about 2 hours to about 10 hours after oral administration.

PROGRAMMED DRUG DELIVERY

Field Of The Invention:

The present invention discloses programmed release pharmaceutical compositions of one or more active substances with a coating of co-processed glyceryl behenate and inorganic calcium salts, and compositions containing such coating. The invention also relates to the dosage forms of specific geometry, which advantageously delays the release of the active substance from the core for a period of about 2 hours to about 10 hours after oral administration.

Background Of The Invention:

Circadian rhythms are physical, mental and behavioral changes that follow a roughly 24-hour cycle, responding primarily to light and darkness in an organism's environment. Circadian rhythms are produced by natural factors within the body, but they are also affected by signals from the environment. Light is the main cue influencing circadian rhythms, turning on or turning off genes that control an organism's internal clocks. Circadian rhythms can change sleep-wake cycles, hormone release, body temperature and other important bodily functions. For example, an asthmatic attack generally happens in the early morning, the stomach pH decreases during the night and in some hypertension diseases the pressure value is higher during the daytime, while a decrease occurs during the night.

Various circadian phase dependent patterns have been well documented in conditions such as asthma, arthritis, epilepsy, migraine, allergic rhinitis, cardiovascular disease (myocardial infarction, angina, stroke), chronic inflammation and pain, such as rheumatoid arthritis (RA), polymyalgia rheumatica (PMR) and peptic ulcer disease, with particular times where symptoms are more prominent and/or exacerbated. Treating these conditions require different amounts of drug at particular times, which synchronize the circadian cycle and provide adequate relief. Immediate release dosage forms may be impractical if the symptoms of the disease

are pronounced during the night or early morning. Therapy with modified release dosage forms with zero order drug release theoretically leads to controlled and constant levels of drug in plasma throughout the day and at times may not be sufficient to synchronize the biological response i.e. they do not provide extra therapeutic levels at the time of pronounced symptoms. Further, the modified release dosage forms may produce adverse effects with little therapeutic benefit due to unwanted plasma drug concentration at other times of day.

To fulfill the specific therapeutic needs of such diseases, which depend on circadian rhythmicity, new drug delivery systems are required for the time-programmed administration of the active ingredients. Such dosage forms should release the drug both at the rate and time, which is in sync with the circardian rhythm. For example, the assumption in the evening of a dosage form able to start releasing the dose some hours after ingestion at a proper rate could be a suitable therapeutic regimen for all diseases, which show a night symptomatic recrudescence.

Various attempts have been made by several researchers for development of a delivery system modifying the release of the active ingredient providing desired therapeutic effect to overcome the symptoms that are linked to circadian fluctuations and achieve better patient compliance.

Recently various chronopharmaceutical technologies have emerged, such as, Oros® Technology, Ceform® Technology, Contin® Technology, Diffucaps® Technology, Chronotopic® Technology, Egalet® Technology, Codas® Technology, GeoClock® Technology, Port® Technology, Three Dimensional Printing® (3DP) Technology, TimeRx® Technology, Chronomodulated infusion pump and Controlled Release Microchip.

Several approaches to obtain programmed release of the active substance from a dosage form are known. Some approaches involve use of coating of multiparticulate active ingredients with polymethacrylate polymers, use of multiple layer tablets, press coating, use of various rate controlling polymers, etc.

Inorganic salt of calcium ion is available as Emcompress® (Edward mendell, USA), A Tab® (Rhodia, USA), Di Tab® (Rhodia, USA), Fujicalin® (Fuji Chemical Industry, Japan), Calstar (FMC Biopolymer) which contains dicalcium phosphate; Tricalcium phosphate is available as Tri Tab® (Rhodia, USA); Calcium sulphate is available as Delaflo® (JWS Delavau, USA); Calcium lactate pentahydrate is available as Puracal DC® (Purac, USA); Calcium lactate trihydrate is available as Puracal TP® (Purac, USA).

Dicalcium phosphate also known as calcium hydrogen orthophosphate dihydrate; calcium monohydrogen phosphate dihydrate; Di-Cafos; dicalcium orthophosphate; DI-TAB; E341; Emcompress; phosphoric acid calcium salt (1:1) dihydrate; and secondary calcium phosphate. Dicalcium phosphate is the most common inorganic salt used in direct compression as a filler-binder. The milled material is typically used in wet-granulated, roller-compacted or slugged formulations. The 'unmilled' or coarse-grade material is typically used in direct-compression formulations. Dibasic calcium phosphate dihydrate is nonhygroscopic and stable at room temperature. However, under certain conditions of temperature and humidity, it can lose water of crystallization below 100^0C. This has implications for certain types of packaging and aqueous film coating since the loss of water of crystallization appears to be initiated by high humidity and by implication high moisture vapor concentrations in the vicinity of the dibasic calcium phosphate dihydrate particles. However, dibasic calcium phosphate dihydrate is abrasive and a lubricant is required for tableting. Water of crystallization of dicalcium phosphate dihydrate could possible be released during processing and thus chemically interact with hydrolysable drug.

It is also well known that, dicalcium phosphate is insoluble and very abrasive, which generally leads to reduced tooling life due to wear on the equipment during tablet manufacture. High levels of lubricants are required to overcome the abrasiveness, but elevated levels of hydrophobic lubricants can impact the mechanical strength of the tablets and disintegration/dissolution performance. Further, due to the propensity of dicalcium phosphate towards brittleness, it tends to exhibit failure in a plane

normal to the compaction axis, i.e. experience tablet capping and lamination phenomena.

Properties of dicalcium phosphate has been modulated by the use of glyceryl behenate. Such modified dicalcium phosphate has been used as an excipient in immediate and non-immediate release dosage forms. However, use of such modified excipient as coating aid has not been explored let alone its advantages in exhibiting programmed drug delivery.

Glyceryl dibehenate is a mixture of glycerol esters. It is also known as Compritol 888 ATO; 2,3-dihydroxypropyl docosanoate; docosanoic acid, 2,3-dihydroxypropyl ester; E471; glycerol behenate; glyceroli dibehenas; and glyceryl monobehenate. It is a mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols.

Glyceryl behenate is used in cosmetics, foods, and oral pharmaceutical formulations. In pharmaceutical formulations, glyceryl behenate is mainly used as a lubricant in the preparation of oral tablets and capsules. It has also been investigated for use in the preparation of sustained-release tablets; as a matrix-forming agent for the controlled release of water-soluble drugs; and it can also be used as a hot-melt coating agent sprayed onto a powder or drug-loaded sugar beads and granules. It may also be incorporated via extrusion/spheronization into pellets, which can be further compressed into tablets.

One of the major problem associated with programmed release formulations is that they suffer from the disadvantages that sometimes neither the minimum quantity of active substance is released therefrom "in vitro" after fixed intervals (programmed-release profile with indication of the minimum amount to be released at fixed intervals), nor are they are immune to the influence and possible variations of the preparation during the aging or storage thereof (stability of the programmed-release rate of the preparation over time). Moreover, lag phase in most of the programmed release formulations is dependent on geometry of dosage form such as tablet

geometry or presence of weak points in the tablet. This leads to uneven rupture of the coating, thus leading to variation in drug release. Undesired batch-to-batch variation in release of the active ingredient is common with such type of dosage form.

Coating thickness is another detrimental factor affecting the lag time. Improper positioning and thickness of the coating over the core may lead to intra-subject and intersubject variance in bioavailability.

U.S. Patent No. 7,364,755 discloses a modified calcium phosphate excipient with a fatty acid wax in a weight ratio of 50:50 to 95:5.

PCT Patent Application No. 2005013953 discloses an extended release tablet wherein the matrix material is co-processed with calcium phosphate and fatty acid wax having a ratio within the range of 85: 15 to 65: 35, respectively.

U.S. Patent Application No. 20060057200 ('200) discloses a tablet composition wherein the ratio of the thickness of the press coating on the sides of the tablet to the upper side or lower side is preferably about 2.2-2.6mm (for side edges): about 1.2-1.6mm for the upper side and about 1.0-1.4 mm for lower side of the tablet. The '200 application discloses the use of glyceryl behenate, calcium phosphate and povidone in coating composition, by using wet granulation process, for delaying the release of active substance.

U.S. Patent Application No. 20070110807 ('807) discloses a press-coated tablet comprising a core containing an drug substance, and a coating, the core disposed within the coating such that the coating has a first thickness about an axis A-B and a thickness about an orthogonal axis X-Y, such that the coating about the axis X-Y is thicker than the coating about the axis A-B, to provide a lag time of between about 2 hours to about 6 hours.

U.S. Patent Application No. 20100196427 ('427) discloses a delayed-release dosage form of a glucocorticoid in which the release is delayed for a time period of 2-10

hours after intake. The '427 application disclose the use of glyceryl behenate, calcium phosphate and povidone in coating composition, by using wet granulation process, for delaying the release of active substance.

U.S. Patent Application No. 20100222312 ('312) and PCT Publication No. 2010084188 disclose a method for treatment of asthma by administering a delayed-release dosage form of a glucocorticoid to a subject in need thereof. The release of the active substance is delayed for a time period of 2-10h after intake. The '427 application disclose the use of glyceryl behenate, calcium phosphate and povidone in coating composition, by using wet granulation process, for delaying the release of active substance.

U.S. Patent No. 5,279,832 and European Patent No. 0495349 discloses a delayed release dosage form with a core, which contains the active substance and a coating. The coating has selected areas which are thinner than the average thickness of the coating and/or areas which are predetermined rupture sites.

U.S. Patent No. 5,792,476 discloses a pharmaceutical composition of a glucocorticoid with a regulated sustained release such that at least 90% by weight of the glucocorticoid is released during a period of about 40-80 min, starting about 1-3 hour after the entry of said glucocorticoid into the small intestine of a mammal.

U.S. Patent Nos. 6,372,254 and 6,730,321 discloses a press coated, pulsatile drug delivery system having an immediate-release compartment, which contains a compressed blend of an active agent and one or more polymers, substantially enveloped by an extended-release compartment, which contains a compressed blend of the active agent and hydrophilic and hydrophobic polymers.

U.S. Patent Application No. 20070243253 disclose a delayed release drug formulation comprising a particle with a core and a coating for the core, the core comprising a drug and the coating comprising a mixture of a first material which is susceptible to attack by colonic bacteria and a second material which has a pH

threshold at about pH 5 or above, wherein the first material comprises at least one polysaccharide.

Though, there are various techniques are available in the art for preparing a programmed release dosage form of various active substances employing different polymeric excipients, still a need exists for a dosage form which is independent of the geometry of the composition, free from lag phase variation and provides release of active substance at a fixed duration. Further, such programmed release dosage form should have minimal batch-to-batch variation.

Summary Of The Invention:

In one aspect, the present invention provides a programmed release pharmaceutical composition, comprising of a core comprising one or more active substances optionally along with one or more pharmaceutically acceptable excipients, a coating, surrounding the said core, comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said coating delays the release of the active substances from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the present invention provides a programmed release pharmaceutical composition, comprising of a core comprising one or more active substances optionally along with one or more pharmaceutically acceptable excipients, a coating, surrounding the said core, comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate prepared by melt granulation, wherein the said coating delays the release of the active substances from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the present invention provides a programmed release pharmaceutical composition, comprising of a core comprising one or more active substances optionally along with one or more pharmaceutically acceptable excipients, a coating, surrounding the said core, comprising co-processed mixture of

one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said core is disposed within the said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges the core.

In another aspect, the present invention provides a press-coated tablet, comprising of a core comprising one or more active substances and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges the core, wherein the dosage form delays the release of the active substance from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the present invention provides a press-coated tablet, comprising of a core comprising prednisone and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges the core, wherein the dosage form delays the release of the active substance from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the present invention provides a press-coated tablet, wherein the ratio of width of the tablet to the length of the tablet is less than the about 1.33:1.

In another aspect, the present invention provides a programmed release press-coated tablet, comprising of a core comprising one or more corticosteroid and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical

edges of the core, wherein the dosage form delays the release of the corticosteroid from the core for a period of about 2 hours to about 10 hours after oral administration.

A programmed release press-coated tablet, comprising of a core comprising prednisone and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges of the core, and the dosage form delays the release of the corticosteroid from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the present invention provides a method for delaying the release of one or more active substances from the core for a period between about 2 hours to about 10 hours, wherein the method comprise applying the coating composition to the core; wherein the coating composition comprises co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate.

In another aspect, the present invention provides a coating composition for delaying the release of one or more corticosteroid from the core for a period of about 2 hours to about 10 hours; wherein the coating composition comprises co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate optionally along with one or more pharmaceutically acceptable excipients.

In another aspect, the present invention provides a programmed release press-coated tablet, comprising of a core comprising of prednisone optionally with one or more corticosteroid and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating

thickness around the vertical edges of the core, wherein the dosage form delays the release of prednisone from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the present invention provides a method of treating circadian phase dependent pathologies such as asthma, arthritis, chronic inflammation and pain, such as rheumatoid arthritis and polymyalgia rheumatica wherein the method comprises administering a programmed release pharmaceutical composition, comprising of a core comprising one or more active substances optionally along with one or more pharmaceutically acceptable excipients, a coating, surrounding the said core, comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said coating delays the release of the active substances from the core for a period of about 2 hours to about 10 hours after oral administration to a patient in need of such treatment.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutically acceptable excipients may include diluents, disintegrants, binders, bulking agents, anti-adherents, anti-oxidants, buffering agents, colorants, flavoring agents, coating agents, plasticizers, stabilizers, preservatives, lubricants, glidants, chelating agents, and the like known to the art used either alone or in combination thereof.

Detailed Description Of The Invention:

The present inventors, while trying to develop a programmed release dosage form, surprisingly found that when dosage forms comprising core coated with a coating composition comprising one or more inorganic salts of calcium ions co-processed with glyceryl behenate are exposed to aqueous media, the coating ruptures into two equal halves after a fixed time interval, thus releasing the active substance contained in the core.

The coating composition provides a lag phase of from about 2 hours to about 10 hours. This lag phase in the release of the active substance from the core can be modulated by changing the ratio of glyceryl behenate to inorganic salts of calcium ions in the coating composition. To exemplify few, the present inventors found that when glyceryl behenate and dicalcium phosphate were co-processed in a ratio of 30:70, a lag phase of about 4 hour and 05 minutes was observed. Further, when glyceryl behenate and dicalcium phosphate were co-processed in a ratio of 50:50, a lag phase of about 9 hours and 11minutes was observed. Present inventors have thus surprisingly discovered that such a coating composition has reduced the batch-to-batch variations of the formulation during the aging or storage thereof, and provides a consistent lag time with minimal variation. Further, the programmed release dosage form did not required specialized tooling for preparation.

Further, the inventors found that by modifying the geometry of the press coated tablets containing a core coated with said coating, such that the thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges of the core, delays the release of the active substances from the core for a period of about 2 hours to about 10 hours. For instance, when glyceryl behenate and dicalcium phosphate were co-processed in a ratio of 30:70 and press coated on the core with geometry of 1.5mm thickness around the horizontal edge of the core and 1.75mm thickness around the vertical edge of the core, a lag phase of about 4h to 5h can be observed. Further, when glyceryl behenate and dicalcium phosphate were co-processed in a ratio of 50:50, and press coated on the core with 1.5mm thickness around both, the horizontal edge and the vertical edge of the core, a lag phase of about 9 hours to about 10 hours can be observed

Thus, the present inventors have now developed a programmed release pharmaceutical dosage form comprising various active ingredients, which helps to control the initial burst release of the active ingredient, achieves desirable dissolution profile and consistent release pattern after a lag phase of about 2 hours to about 10 hours.

The term “dosage form” as used herein refers to a pharmaceutical preparation in which dose or doses of one or more therapeutically active ingredients are included. It may be in form of, for example, a tablet, tablet-in-tablet, trilayer tablet, in-lay tablet, coated pellets, granules, multiple unit pellet system, pellets/granules filled in a capsule or combinations thereof.

The term “programmed release” as used herein refers to the release of drug after a certain lag phase, for example, 2 hours. The drug release may be monophasic or biphasic. The site of the release may be programmed too.

In the present invention, “coating thickness around the vertical edges of the core” of the tablet is used interchangeably with “length”. The term “length” of the tablet refers to the thickness of the tablet, or the sides which comes in contact with the upper and lower punch.

In the present invention, “coating thickness around the horizontal edges of the core” of the tablet is used interchangeably with “width”. The term “width” refers to diameter of the tablet, or the edges which are in contact to die while compression.

The term “Programmed release” as used herein refers to the release of drug after a certain lag phase. The drug release may be monophasic or biphasic. The site of the release may be programmed too.

“Modified release dosage forms” as used herein is defined (e.g. as by the United States Pharmacopoeia “USP”) as those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional immediate release dosage forms. The USP considers that the terms controlled release, prolonged release and sustained release are interchangeable. Accordingly, the terms “modified-release”, controlled-release”, “control-releasing”, “rate-controlled release”, “extended release”, “prolonged-release”, and “sustained-release” are used interchangeably herein, For the discussion herein, the definition of the term “modified-release” encompasses the scope of the definitions

for the terms “extended release”, “enhanced-absorption”, “controlled release”, “sustained release” and “delayed release”.

As defined in the U.S. Pharmacopeia (USP), delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are intended to delay the release of medication until the dosage form has passed through the acidic medium of the stomach. In vitro dissolution tests for these products should document that they are stable under acidic conditions and that they release the drug only in a neutral medium (e.g., pH 6.8).

“Lag time” is the time to disintegrate the tablet and to release the drug after administration of the programmed release dosage form.

The term “co-processing” or “co-processed mixture” as used herein refers to a combination of two or more excipients by an appropriate process, which involves but is not limited to wet granulation, melt granulation, etc.

The term “bioavailable” as used herein, includes, but is not limited to the rate and extent to which the drug(s) become bioavailable to the site of action after administration.

The term "Cmax " is the highest plasma concentration of the drug attained within the dosing interval.

The term "Tmax " is the time period, which elapses after administration of the dosage form at which the plasma concentration of the drug attains the highest plasma concentration of drug attained within the dosing interval.

The term "AUC_{0-t} " as used herein, means area under plasma concentration-time curve from drug administration to last observed concentration at time t.

The term "$AUC_{0-\alpha}$" as used herein, means area under the plasma concentration-time curve extrapolated to infinite time.

The term "mean", when preceding a pharmacokinetic value (e.g. mean Tmax) represents the mean value of the pharmacokinetic value taken from a population of patients or healthy volunteers.

In an aspect, the programmed release pharmaceutical composition comprising of a core comprising one or more active substances optionally along with one or more pharmaceutically acceptable excipients, a coating, surrounding the said core, comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said coating delays the release of the active substance from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the programmed release pharmaceutical composition comprising of a core comprising one or more active substances optionally along with one or more pharmaceutically acceptable excipients, a coating, surrounding the said core, comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges of the core and the said coating delays the release of the active substance from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the press-coated tablet comprising of a core comprising one or more active substances and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical

edges of the core, wherein the dosage form delays the release of the active substance from the core for a period of about 2 hours to about 10 hours after oral administration.

A wide variety of active agents may be employed in the present invention, which may be incorporated by reference to U.S. Patent Application No. 20070110807 into the specification of the present invention. Drugs for treating conditions the symptoms of which result from nocturnal circadian rhythms are particularly suitable. Accordingly, drugs for treating incontinence, sleep disorders, apnoea, asthma, epilepsy, bronchitis, parkinsonism, rheumatoid arthritis, allergic rhinitis and ischaemic heart diseases, cluster and migraine headache, congestive heart failure, and depression are particularly suitable for use in tablets according to the present invention. Further, drug substances that are metabolized by cytochrome P450 are also particularly suitable, they include: Amitriptyline, caffeine, clomipramine, clozapine, fluvoxamine, haloperidol, imipramine, mexilitine, oestradiol, olanzepine, paracetamol, propranolol, tacrine, theophylline, warfarin, Bupropion, Cyclophosphamide, Celecoxib, Diclofenac, Flubiprofen, Ibuprofen, glimepirideindome, thacin, naproxen, phenytoin, piroxicam, tenoxicam, citalopram, diazepam, lansoprazole, omeprazole, pantoprozole, propanolol, topiramate, Alpranolol, chlorpromazine, clomipramine, codeine, Desipramine, dextromethorphan, diphenhydramine, donepezil, flecainide, fluoxetine, labetalol, Methadone, metoprolol, mianserin, nortripyline, ondansetron, oxprenolol, oxycodone, paroxetine, perhehexilene, pethidine, promethazine, risperdone, thioridazine, ticlopidine, timolol, trimipramine, paracetamol, alprazolam, amiodarone, budesonide, buprenorphine, buspirone, Calcium Channel Blockers, carbamazepine, cisapride, clarithromycin, clonazepam, cocaine, cortisol, cyclosporine, dexamethasone, erythromycin, fentanyl, ketoconazole, losartan, miconazole, midazolam, quinidine, sertraline, statins, tacrolimus, tamoxifen, TCAs, triamzolam, zolpidem, or mixtures thereof.

Additional examples of drug classes and drugs that can be employed in tablets of the present invention include:

Antihistamines (e.g., azatadine maleate, brompheniramine maleate, carbinoxamine maleate, chlorpheniramine maleate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, doxylamine succinate, methdilazine hydrochloride, promethazine, trimeprazine tartrate, tripelennamine citrate, tripelennamine hydrochloride and triprolidine hydrochloride);

Antibiotics (e.g., penicillin V potassium, cloxacillin sodium, dicloxacillin sodium, nafcillin sodium, oxacillin sodium, carbenicillin indanyl sodium, oxytetracycline hydrochloride, tetracycline hydrochloride, clindamycin phosphate, clindamycin hydrochloride, clindamycin palmitate HCL, lincomycin HCL, novobiocin sodium, nitrofurantoin sodium, metronidazole hydrochloride); antituberculosis agents (e.g., isoniazid);

Cholinergic agents (e.g., ambenonium chloride, bethanecol chloride, neostigmine bromide, pyridostigmine bromide);

Antimuscarinics (e.g., anisotropine methylbromide, clidinium bromide, dicyclomine hydrochloride, glycopyrrolate, hexocyclium methylsulfate, homatropine methylbromide, hyoscyamine sulfate, methantheline bromide, hyoscine hydrobromide, oxyphenonium bromide, propantheline bromide, tridihexethyl chloride);

Sympathomimetics (e.g., bitolterol mesylate, ephedrine, ephedrine hydrochloride, ephedrine sulphate, orciprenaline sulphate, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, ritodrine hydrochloride, salbutamol sulphate, terbutaline sulphate);

Sympatholytic agents (e.g., phenoxybenzamine hydrochloride); miscellaneous autonomic drugs (e.g., nicotine);

Iron preparations (e.g., ferrous gluconate, ferrous sulphate);

Haemostatics (e.g., aminocaproic acid);

Cardiac drugs (e.g., acebutolol hydrochloride, disopyramide phosphate, flecainide acetate, procainamide hydrochloride, propranolol hydrochloride, quinidine gluconate, timolol maleate, tocainide hydrochloride, verapamil hydrochloride);

Antihypertensive agents (e.g., captopril, clonidine hydrochloride, hydralazine hydrochloride, mecamylamine hydrochloride, metoprolol tartrate); vasodilators (e.g., papaverine hydrochloride);

Non-steroidal anti-inflammatory agents (e.g., choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, meclofenamate sodium, naproxen sodium, tolmetin sodium);

Opiate agonists (e.g., codeine hydrochloride, codeine phosphate, codeine sulphate, dextromoramide tartrate, hydrocodone bitartrate, hydromorphone hydrochloride, pethidine hydrochloride, methadone hydrochloride, morphine sulphate, morphine acetate, morphine lactate, morphine meconate, morphine nitrate, morphine monobasic phosphate, morphine tartrate, morphine valerate, morphine hydrobromide, morphine hydrochloride, propoxyphene hydrochloride);

Anticonvulsants (e.g., phenobarbital sodium, phenytoin sodium, troxidone, ethosuximide, valproate sodium);

Tranquilizers (e.g., acetophenazine maleate, chlorpromazine hydrochloride, fluphenazine hydrochloride, prochlorperazine edisylate, promethazine hydrochloride, thioridazine hydrochloride, trifluoroperazine hydrochloride, lithium citrate, molindone hydrochloride, thiothixine hydrochloride);

Chemotherapeutic agents (e.g., doxorubicin, cisplatin, floxuridine, methotrexate, combinations thereof);

Lipid lowering agents (e.g., gemfibrozil, clofibrate, HMG-CoA reductase inhibitors, such as for example, atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin);

H_2-antagonists (e.g., cimetidine, famotidine, nizatidine, ranitidine HCl);

Anti-coagulant and anti-platelet agents (e.g., warfarin, cipyridamole, ticlopidine);

Bronchodilators (e.g., albuterol, isoproterenol, metaproterenol, terbutaline);

Stimulants (e.g., benzamphetamine hydrochloride, dextroamphetamine sulphate, dextroamphetamine phosphate, diethylpropion hydrochloride, fenfluramine hydrochloride, methamphetamine hydrochloride, methylphenidate hydrochloride, phendimetrazine tartrate, phenmetrazine hydrochloride, caffeine citrate);

Barbiturates (e.g., amylobarbital sodium, butabarbital sodium, secobarbital sodium);

Sedatives (e.g., hydroxyzine hydrochloride, methprylon); expectorants (e.g., potassium iodide);

Antiemetics (e.g., benzaquinamide hydrochloride, metoclopropamide hydrochloride, trimethobenzamide hydrochloride);

Gastrointestinal drugs (e.g., ranitidine hydrochloride); heavy metal antagonists (e.g., penicillamine, penicillamine hydrochloride);

Antithyroid agents (e.g., methimazole);

Genitourinary smooth muscle relaxants (e.g., flavoxate hydrochloride, oxybutynin hydrochloride);

Vitamins (e.g., thiamine hydrochloride, ascorbic acid);

Steroids, particularly glucocorticoids (e.g., prednisolone, methylprednisolone, prednisone, cortisone, hydrocortisone, methylprednisolone, betamethasone, dexamethasone, triamcinolone).

Unclassified agents (e.g., amantadine hydrochloride, colchicine, etidronate disodium, leucovorin calcium, methylene blue, potassium chloride, pralidoxime chloride).

The active agents suitable for use in the composition of the present invention are corticosteroids. Suitable corticosteroids may be selected from one or more prednisone, prednisolone, methylprednisolone, cortisone, hydrocortisone, budesonide, dexamethasone, fludrocortisone, fluocortolone, cloprednole, deflazacort and triamcinolone. The preferred corticosteroid is prednisone.

Thus, in further aspect, the programmed release press-coated tablet comprising of a core comprising one or more corticosteroids and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges of the core. In an embodiment, the dosage form delays the release of the corticosteroid from the core for a period of about 2 hours to about 10 hours after oral administration.

In an embodiment, the programmed release press-coated tablet comprises a core comprising prednisone and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges of the core, wherein the dosage form delays the

release of the prednisone from the core for a period of about 2 hours to about 10 hours after oral administration.

In another aspect, the present invention provides a method for delaying the release of one or more active substances from the core for a period of about 2 hours to about 10 hours, wherein the method comprise applying the coating composition to the core; wherein the coating composition comprises glyceryl behenate co-processed with one or more inorganic salts of calcium ion.

In a further aspect, the method for delaying the release of one or more corticosteroids from the core for a period of about 2 hours to about 10 hours, wherein the method comprise applying the coating composition to the core; wherein the coating composition comprises co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate.

In a further aspect, the present invention provides a coating composition for delaying the release of one or more active substances from the core for a period of about 2 hours to 10 hours; wherein the coating composition comprises co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate, optionally with one or more pharmaceutically acceptable excipients.

The core is composed of either an immediate release or controlled release pharmaceutical composition consisting of the active ingredient in admixture with suitable excipients. If necessary, the core can be protected by a water-soluble or water-insoluble film before coating with the coating composition of one or more inorganic salts of calcium ion co-processed with glyceryl behenate. The core may be prepared by various techniques known in the art such as direct compression, dry granulation, melt granulation, wet granulation.

Typically a core may contain 0.1 to 90% by weight of active substance.

The programmed release composition of the present invention is in the form of a tablet, a tablet-in-tablet, a trilayer tablet, an in-lay tablet, coated pellets, granules, multiple unit pellet system, and pellets/granules filled in a capsule.

The tablets may also be compressed in the form of two or more layer tablet or press-coated in the form of tab-in-tab or tab-in-tab-in-tab. The penetration of aqueous fluid takes place through pores formed due to solubilization of the pore forming agent. For the purpose of present invention, pore forming agent include one or more inorganic salts of calcium ion.

The shape of the dosage form may be square, rectangular, circular, oval, donut, cylindrical, pentagonal, hexagonal, heptagonal, octagonal, pillowed shaped or a centrally notched round tablet.

Inorganic salts of calcium ion include, but not limited to calcium phosphate, calcium phosphate dihydrate, calcium phosphate anhydrous, dibasic calcium phosphate, dibasic calcium phosphate monohydrate, dibasic calcium phosphate dihydrate, anhydrous dibasic calcium phosphate, monobasic calcium phosphate, tribasic calcium phosphate, calcium acetate, calcium carbonate, calcium chloride, calcium hydroxide, calcium pyrophosphate, calcium sulfate, calcium sulfate anhydrous, calcium sulfate dihydrate, or calcium sulfate hemihydrate.

In an embodiment, the inorganic salt of calcium ion is calcium phosphate dehydrate, or dibasic calcium phosphate dehydrate, or mixture thereof.

In an embodiment, the coating composition is prepared by co-processing glyceryl behenate and dicalcium phosphate with one or more pharmaceutically acceptable excipients. The coating may be polymeric film and/or compression coating.

In a further embodiment, the co-processed (mixture of) glyceryl behenate and inorganic salts of calcium ion are prepared by melt granulation process.

In a further embodiment, the ratio of glyceryl behenate and inorganic salts of calcium ion in the co-processed coating mixture ranges from about 10:90 to about 90:10.

In a further embodiment, the ratio of glyceryl behenate and inorganic salts of calcium ion of the co-processed mixture in the coating ranges from about 15:85 to about 55:45.

In a further embodiment, the programmed release composition is provided in the form of a press coated tablet.

In a further embodiment, the coating over the core of the programmed release composition may be applied as a film coating, spray coat, multiple layer compression coating or as press coating.

In a further embodiment, the ratio of width of the composition to the length of the composition is less than the ratio of about 1.33:1.

In a further embodiment, the coating composition further comprises one or more hydrophilic polymer, hydrophobic polymer or non-polymeric rate controlling excipients.

Suitable hydrophillic polymers include, but not limited to cellulose derivatives; polyhydric alcohols; saccharides, gums and derivatives thereof; vinyl derivatives, polymers, copolymers or mixtures thereof; maleic acid copolymers; polyalkylene oxides or copolymers thereof; acrylic acid polymers and acrylic acid derivatives; or any combinations thereof.

Cellulose derivatives include, but are not limited to ethyl cellulose, methylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl ethylcellulose, carboxymethylethyl cellulose, carboxy- ethylcellulose, carboxymethyl hydroxyethylcellulose, hydroxyethylmethyl carboxymethyl cellulose, hydroxyethyl methyl cellulose,

carboxymethyl cellulose (CMC), methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, carboxymethyl sulfoethyl cellulose, sodium carboxymethyl cellulose, or combinations thereof.

Polyhydric alcohols include, but are not limited to polyethylene glycol (PEG) or polypropylene glycol; or any combinations thereof.

Saccharides, gums and their derivatives include, but are not limited to dextrin, polydextrin, dextran, pectin and pectin derivatives, alginic acid, sodium alginate, polygalacturonic acid, xylan, arabinoxylan, arabinogalactan, starch, hydroxypropyl starch, amylose and amylopectin, CMC agar; guar gum, locust bean gum, xanthan gum, karaya gum, tragacanth, carrageenan, acacia gum, arabic gum or gellan gum or the like; or any combinations thereof.

Vinyl derivatives, polymers, copolymers or mixtures thereof include, but are not limited to polyvinyl acetate, polyvinyl alcohol, mixture of polyvinyl acetate (8 parts w/w) and polyvinylpyrrolidone (2 parts w/w) (Kollidon SR), copolymers of vinyl pyrrolidone, vinyl acetate copolymers, polyvinylpyrrolidone (PVP); or combinations thereof.

Polyalkylene oxides or copolymers thereof include, but are not limited to, polyethylene oxide, polypropylene oxide, poly (oxyethylene)-poly (oxypropylene) block copolymers (poloxamers), or combinations thereof.

Maleic acid copolymers include, but are not limited to vinylacetate maleic acid anhydride copolymer, styrene maleic acid anhydride copolymer, styrene maleic acid monoester copolymer, vinylmethylether maleic acid anhydride copolymer, ethylene maleic acid anhydride copolymer, vinylbutyiether maleic acid anhydride copolymer, acrylonitrile methyl acrylate maleic acid anhydride copolymer, butyl acrylate, styrene maleic acid anhydride copolymer or the like or any combinations thereof.

Suitable acrylic acid polymers include any suitable polyacrylic acid polymers or carboxyvinyl polymers such as those available under the brand name carbopol. Pharmaceutically acceptable acrylic polymer may be include one or more, but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), methyl methacrylate, polymethacrylate, poly(methyl methacrylate), poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate.

Suitable hydrophobic polymer include, but are not limited to waxes, which are esters of fatty acids with long chain monohydric alcohols natural waxes are often mixtures of such esters, and may also contain hydrocarbons Waxes employed in the present invention include, but are not limited to, natural waxes, such as animal waxes, vegetable waxes, and petroleum waxes, paraffin waxes, microcrystalline waxes, petrolatum waxes, mineral waxes), and synthetic waxes Specific examples include, but are not limited to spermaceti wax, carnauba wax, Japan wax, bayberry wax, flax wax, beeswax, yellow wax, Chinese wax, shellac wax, lanolin wax, sugarcane wax, candelilla wax, castor wax paraffin wax, microcrystalline wax, petrolatum wax, carbowax, and the like, or mixtures thereof.

Waxes are also monoglyceryl esters, diglyceryl esters, or; glyceryl esters (glycerides) and derivatives and mixtures thereof formed from a fatty acid having from about 10 to about 22 carbon atoms and glycerol, wherein one or more of the hydroxyl groups of glycerol are substituted by a fatty acid. Glycerides employed in the present invention include, but are not limited to, glyceryl monostearate, glyceryl distearate, glyceryl tristearate, glyceryl dipalmitate, glyceryl tripalmitate, glyceryl monopalmitate, glyceryl palmitostearate, glyceryl dilaurate, glyceryl trilaurate, glyceryl monolaurate, glyceryl didocosanoate, glyceryl tridocosanoate, glyceryl monodocosanoate, glyceryl monocaproate, glyceryl dicaproate, glyceryl tricaproate, glyceryl monomyristate, glyceryl dimyristate, glyceryl trimyhstate, glyceryl monodecenoate, glyceryl

didecenoate, glyceryl tridecenoate, glyceryl behenate (compritol), polyglyceryl diisostearate, lauroyl macrogolglycerides (Gelucire), oleoyl macrogolglycerides, stearoyl macrogolglycerides, mixtures of monoglycerides and diglycerides of oleic acid (Peceol), or combinations thereof.

Fatty acids include, but are not limited to hydrogenated palm kernel oil, hydrogenated peanut oil, hydrogenated palm oil, hydrogenated rapeseed oil, hydrogenated rice bran oil, hydrogenated soybean oil, hydrogenated sunflower oil, hydrogenated castor oil (Lubritab), hydrogenated cottonseed oil, and mixtures thereof. Other fatty acids include, but are not limited to, decenoic acid, docosanoic acid, stearic acid, palmitic acid, lauric acid, myristic acid, or the like, or mixtures thereof.

Non-polymeric rate controlling excipients include, but are not limited to fats, waxes, fatty acids, fatty acid esters, long chain monohydric alcohol or their ester or any combinations thereof.

For the purpose of present invention, the programmed release composition of present invention further comprise one or more pharmaceutically acceptable excipient selected from the group consisting of diluents, fillers, binders, disintegrant, lubricants, glidants and colorant.

Examples of suitable diluents include, but are not limited to one or more of lactose, lactose monohydrate, mannitol, sucrose, maltodextrin, dextrin, maltitol, sorbitol, xylitol, powdered cellulose, cellulose gum, microcrystalline cellulose, starch, calcium phosphate, or metal carbonate.

Examples of suitable binders include, but are not limited to one or more of starch, gums, pregelatinized starch, polyvinyl prrolidone (PVP), copovidone, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC) and carboxymethyl cellulose (CMC) and their salts.

Examples of suitable lubricants include, but are not limited to one or more of talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium stearyl fumarate, talc and sodium benzoate.

Compositions of the present invention may include a glidant such as, but not limited to, colloidal silica, silica gel, precipitated silica, or combinations thereof.

Examples of suitable disintegrants include, but are not limited to one or more of starch, croscarmellose sodium, crospovidone, and sodium starch glycolate.

The composition of the invention optionally include usual auxiliaries known in the art such as saliva stimulating agents like citric acid, lactic acid, malic acid, succinic acid, ascorbic acid, adipic acid, fumaric acid, tartaric acids; cooling sensation agents like maltitol, monomenthyl succinate, ultracool; stabilizers like gums, agar; taste masking agents like acrylic polymers, copolymers of acrylates, celluloses, resins; coloring agents like titanium dioxide, natural food colors, dyes suitable for food, drug and cosmetic applications and effervescing agents like citric acid, tartaric acid, sodium bicarbonate, sodium carbonate and the like.

The present invention further provides a method of treating circadian phase dependent pathologies such as asthma, arthritis, epilepsy, migraine, allergic rhinitis, cardiovascular disease, chronic inflammation, pain, rheumatoid arthritis, polymyalgia rheumatica and peptic ulcer, wherein the method comprises administering a pharmaceutical composition of the present invention to a patient in need of such treatment.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Examples

Example 1: Prednisone MR Tablets-1, 2 and 5 mg

Wet granulation process

Coating material composition

Core Shell Unit composition		
Sr. No.	**Ingredients/Grade**	**%w/w**
Intragranular Ingredients		
1.	Calcium hydrogen phosphate dihydrate (Calipharm D)	70-80
2.	Microcrystalline Cellulose (Avicel PH 101)	3.2-3.6
3.	Glycerol dibehenate (Compritol 888 ATO)	10-20
4.	Povidone K29/32	3-7
5.	Purified Water	q.s
6.	Colloidal Anhydrous Silica	0.5-1.0
7.	Magnesium Stearate	0.5-1.0

Procedure:

Intragranular ingredients were taken together and sifted. The sifted material was transferred to rapid mixer granulator. The sifted material in rapid mixer granulator was granulated using the prepared binder solution. The granules obtained were dried and then mixed with colloidal anhydrous silica and magnesium stearate.

Example 2: Core Tablet Unit Composition

Core Tablet Unit Composition		
Sr. No.	**Ingredient/Grade**	**%w/w**
Intragranular Ingredients		
1.	Prednisone	1-10
2.	Microcrystalline Cellulose (Avicel PH 101)	15-25
3.	Lactose Monohydrate (Pharmatose 200 M)	65-75
4.	Red Ferric Oxide E172	0.1-0.7
Binder Solution		
5.	Povidone (PVP K-30)	2-8
6.	Purified Water	q.s
Extragranular Ingredients		
7.	Croscarmellose Sodium (Ac-Di-Sol)	4-8
8.	Colloidal Silicon Dioxide (Aerosil 200)	0.3-1.0
9.	Magnesium Stearate	0.2-1.0

Procedure:

Intragranular ingredients were taken together and sifted except Red Ferric Oxide which was sifted seperately. All the ingredients were transferred into suitable rapid mixer granulator and dry mixed with impeller at a low speed. Wet granulation was carried out using the binder solution. The granules obtained were dried and collected in a pre-labeled container. Extragranular material were taken together, sifted and collected in a pre-labeled container. This mixture was then transferred into low shear blender and prelubrication was done.

Example 3:

Compression: (1mg Strength)

Tooling: 5.0mm round standard concave plain on both sides

Avg.Wt: 60.6 mg

Uniformity of Weight: 58.3-62.4 mg

Hardness: 40-43N

Thickness: 2.70-2.83 mm

Disintegration time: 1 min 12 sec

Friability: 0.07% w/w

Compression of Prednisone MR Tablets-1 mg

Tooling: 8.0 mm round Flat Faced Beveled Edges debossed with '45' on one side and plain on other side.

Avg.Wt.: 457-461 mg

Uniformity of Weight: 458.3-463.2 mg

Hardness: 55-65 N

Thickness: 5.92-5.98 mm

Example 4: Dissolution Conditions:

Sr. No.	Time points (h)	6.8 pH Phosphate Buffer	% RSD
1	2	0	0
2	3	54	29.63
3	4	84	19.05
4	5	86	15.12
5	6	90	8.89

Example 5: Prednisone MR Tablets-1, 2 and 5 mg

Melt granulation process

Coating material composition

Core Shell Unit composition		
Sr. No.	**Ingredient/Grade**	**%w/w**
Intragranular Ingredients		
1.	Calcium hydrogen phosphate dihydrate (Calipharm D)	55-75
2.	Glycerol dibehenate (Compritol 888 ATO)	15-35
Extragranular Ingredients		
3.	Yellow ferric oxide	0.05-0.2
4.	Povidone K29/32	2-8
5.	Colloidal Silicon Dioxide (Aerosil 200)	0.5-1.0
Lubricants		
6.	Magnesium Stearate	0.5-2

Procedure:

Accurately weighed quantity of Glyceryl dibehenate was melted in SS vessel at a temperature of 65-75^{0}C to form a true liquefied wax**.** Calcium hydrogen phosphate dihydrate was sifted and added to melted glyceryl dibehenate. The mixture was then granulated while hot with vigorous mixing. The obtained material was then cooled. This was then passed through mesh and collected in a pre-labeled container. Yellow ferric oxide was sifted and collected in a pre-labeled container. Granules of glyceryl behenate and calcium hydrogen phosphate dihydrate along with yellow ferric oxide, povidone, Magnesium Stearate and colloidal silicon dioxide were transferred into double cone blender and prelubricated. Blend was unloaded and compressed.

Example 6: Core Tablet Unit Composition

Core Tablet Unit Composition		
Sr. No.	**Ingredient/Grade**	**%w/w**
Intragranular Ingredients		
1.	Prednisone	1-10
2.	Microcrystalline Cellulose (Avicel PH 101)	15-25
3.	Lactose Monohydrate (Pharmatose 200 M)	65-75
4.	Red Ferric Oxide E172	0.1-0.7
5.	Maize Starch (Unipure FL)	5-15
Binder Solution		
6.	Purified Water	q.s.
Extragranular Ingredients		
7.	Magnesium Stearate	0.2-1.0

Procedure:

All Intragranular ingredients were taken together and sifted except Red Ferric Oxide which was sifted seperately. All the ingredients were transferred into suitable rapid mixer granulator and dry mixed with impeller at a low speed. Wet granulation was carried out using the binder solution. The granules obtained were dried and collected in a pre-labeled container. Extragranular material were taken together, sifted and collected in a pre-labeled container. This mixture was then transferred into low shear blender and prelubrication was done.

Example 7: Core Compression: (5 mg Strength)

Tooling: 5.0mm round standard concave plain on both sides

Avg.Wt: 60.6 mg

Uniformity of Weight: 59.6-61.4 mg

Hardness: 25-35

Thickness: 2.3-2.4 mm

Disintegration time: 20 sec

Friability: 0.07% w/w

Compression of Prednisone MR Tablets- 5 mg (Finished Product)

Tooling: 8.0 mm round FFBE embossed with W5 on one side and plain on other side.

Description: Round, yellow colored, press/compression coated FFBE debossed with W5 on one side and plain on other side.

Average Weight: 460.0 mg.

Layer-I: 200.0 mg, Layer-II 200.0 mg and Core tablet Weight: 60.0 mg

Thickness: 5.70-6.10 mm

Hardness: 45-80N

Friability: 0.021%w/w (At optimum Hardness)

Disintegration Time: 4 hrs 05 min in water

4 hrs 30 min in pH 6.8 Phosphate Buffer

Example 8: Dissolution Profile

No. of Units	**6**	**24**
Dissolution media	6.8 pH phosphate buffer	6.8 pH phosphate buffer
Apparatus	USP -II ,Paddle	USP -II ,Paddle
Speed	50 RPM	50 RPM
Volume	900 mL	900 mL

Lag Phase	3 h 35 min to 4 h 01 min (for optimum hardness- 50-60N) 3 h 58 min to 4 h 52 min (for high hardness-70-75 N)	3 h 47 min to 5 h 04 min (for optimum hardness-50-60N)

Example 9: Ondansetron MR Tablets- 4 and 8 mg

Melt granulation process

Coating material composition

Procedure:

Coating material composition was prepared as described in Example 5 using melt granulation process.

Example 10: Core Tablet Unit Composition

Core Tablet Unit Composition		
Sr. No.	**Ingredient/Grade**	**%w/w**
Intragranular Ingredients		
1.	Ondansetron hydrochloride dihydrate equivalent to Ondansetron hydrochloride	1-10
2.	Anhydrous Lactose (DCL 21)	65-75
3.	Microcrystalline cellulose (Avicel PH102)	6-10
4.	Prezelatinized Starch	10-14
5.	Colloidal silicon dioxide (Aerosil 200)	2-4
Binder Solution		
6.	Purified Water	q.s

7.	Magnesium Stearate	0.5-1

Procedure:

All Intragranular ingredients were taken together and sifted except Red Ferric Oxide which was sifted seperately. All the ingredients were transferred into suitable rapid mixer granulator and dry mixed with impeller at a low speed. Wet granulation was carried out using the binder solution. The granules obtained were dried and collected in a pre-labeled container. Extragranular material were taken together, sifted and collected in a pre-labeled container. This mixture was then transferred into low shear blender and prelubrication was done.

.

Example 11: Core Compression: (4 mg Strength)

Tooling: 5.0mm round standard concave plain on both sides

Avg.Wt: 60.3 mg

Uniformity of Weight: 59.5-61.3 mg

Hardness: 25-35

Thickness: 2.3-2.4 mm

Disintegration time: 20 sec

Friability: 0.06% w/w

Compression of Ondansetron Tablets- 4 mg (Finished Product)

Tooling: 8.0 mm round FFBE embossed with W5 on one side and plain on other side.

Description: Round, press/compression coated FFBE debossed with W5 on one side and plain on other side.

Average Weight: 460.0 mg.

Layer-I: 200.0 mg, Layer-II 200.0 mg and Core tablet Weight: 60.0 mg

Thickness: 5.70-6.10 mm

Hardness: 45-80N

Friability: 0.022%w/w (At optimum Hardness)

Disintegration Time: 4 hrs 10 min in water

4 hrs 40 min in pH 6.8 Phosphate Buffer

Example 12: Dissolution Profile

No. of Units	6	24
Dissolution media	6.8 pH phosphate buffer	6.8 pH phosphate buffer
Apparatus	USP -II ,Paddle	USP -II ,Paddle
Speed	50 RPM	50 RPM
Volume	900 mL	900 mL
Lag Phase	3 h 40 min to 4 h 10 min (for optimum hardness-50-60N) 3h 58 min to 4 h 52 min (for high hardness-70-75 N)	3 h 53 min to 4 h 50 min (for optimum hardness - 50-60N)

Example 13: Alprazolam MR Tablets- 0.5 and 1 mg

Melt granulation process

Coating material composition

Procedure:

Coating material composition was prepared as described in Example 5 using melt granulation process.

Example 14: Core Tablet Unit Composition

Core Tablet Unit Composition		
Sr. No.	**Ingredient/Grade**	**%w/w**
Intragranular Ingredients		
1.	Alprazolam	0.1-5
2.	Mannitol (Pearlitol SD 200)	70-80
3.	Microcrystalline cellulose (Avicel PH102)	10-20
4.	FD&C Yellow No. 6 Aluminum	0.2-0.7

	Lake	
5.	Colloidal silicon dioxide (Aerosil 200)	2-5
Extragranular Ingredients		
6.	Magnesium Stearate	0.1-1

Procedure:

All intragranular material were taken together and sifted except colorant which was sifted seperately. All the ingredients were transferred into suitable rapid mixer granulator and dry mixing was carried out with impeller slow speed. Extragranular material magnesium stearate were sifted and collected in a pre-labeled container separately. Sifted magnesium stearate was then transferred into low shear blender and lubrication was done.

Example 15: Core Direct Compression: (0.5 mg Strength)

Tooling: 5.0mm round standard concave plain on both sides

Avg.Wt: 60.5 mg

Uniformity of Weight: 59.8-61.1 mg

Hardness: 25-35

Thickness: 2.3-2.4 mm

Disintegration time: 20 sec

Friability: 0.06% w/w

Compression of Alprazolam Tablets- 0.5 mg (Finished Product)

Tooling: 8.0 mm round FFBE embossed with W5 on one side and plain on other side.

Description: Round, yellow colored, press/compression coated FFBE debossed with W5 on one side and plain on other side.

Average Weight: 460.0 mg.

Layer-I: 200.0 mg, Layer-II 200.0 mg and Core tablet Weight: 60.0 mg

Thickness: 5.70-6.10 mm

Hardness: 45-80N

Friability: 0.022%w/w (At optimum Hardness)

Disintegration Time: 4 hrs 15 min in water

4 hrs 40 min in pH 6.8 Phosphate Buffer

Example 16: Dissolution Profile

No. of Units	**6**	**24**
Dissolution media	6.8 pH phosphate buffer	6.8 pH phosphate buffer
Apparatus	USP -II ,Paddle	USP -II ,Paddle
Speed	50 RPM	50 RPM
Volume	900 mL	900 mL
Lag Phase	3 h 45 min to 4 h 15 min (for optimum hardness -50-60N) 3hrs 58 min to 4 hrs 52 min (for high hardness-70-75 N)	3 h 58 min to 4 h 43 min (for optimum-50-60N hardness)

Example 17: Albuterol MR Tablets- 2 and 4 mg

Melt granulation process

Coating material composition

Procedure:

Coating material composition was prepared as described in Example 5 using melt granulation process.

Example 18: Core Tablet Unit Composition

Core Tablet Unit Composition		
Sr. No.	**Ingredient/Grade**	**%w/w**

Intragranular Ingredients		
1.	Albuterol	1-10
2.	Lactose Monohydrate (Pharmatose 200 M)	60-80
3.	Pregelatinized starch (Starch 1500)	10-20
4.	Sodium lauryl sulfate	2-5
Binder Solution		
5.	Purified Water	q.s
Extragranular Ingredients		
6.	Pregelatinized starch (Starch 1500)	3-7
7.	Sodium lauryl sulfate	3-7
8.	Magnesium Stearate	0.5-1.5

Procedure:

All intragranular material were sifted and transferred into suitable rapid mixer granulator. Dry mixing was carried out with impeller on slow speed. Wet granulation was performed using the binder solution. Resultant granules were dried and collected in a pre-labeled container. Extragranular material magnesium stearate was sifted and collected in a pre-labeled container separately. Sifted magnesium stearate was then transferred into low shear blender and lubrication was done.

Example 19: Core Compression: (0.5 mg Strength)

Tooling: 5.0mm round standard concave plain on both sides

Avg.Wt: 60.5 mg

Uniformity of Weight: 59.8-61.1 mg

Hardness: 25-35

Thickness: 2.3-2.4 mm

Disintegration time: 20 sec

Friability: 0.06% w/w

Compression of Albuterol Tablets- 0.5 mg (Finished Product)

Tooling: 8.0 mm round FFBE embossed with W5 on one side and plain on other side.

Description: Round, press/compression coated FFBE debossed with W5 on one side and plain on other side.

Average Weight: 460.0 mg.

Layer-I: 200.0 mg, Layer-II 200.0 mg and Core tablet Weight: 60.0 mg

Thickness: 5.70-6.10 mm

Hardness: 45-80N

Friability: 0.022%w/w (At optimum Hardness)

Disintegration Time: 4 hrs 15 min in water

4 hrs 40 min in pH 6.8 Phosphate Buffer

Example 20: Dissolution Profile

No. of Units	**6**	**24**
Dissolution media	6.8 pH phosphate buffer	6.8 pH phosphate buffer
Apparatus	USP -II ,Paddle	USP -II ,Paddle
Speed	50 RPM	50 RPM
Volume	900 mL	900 mL
Lag Phase	3 h 38 min to 4 h 02 min (for optimum hardness-50-60N) 3h 58 min to 4 h 52 min (for high hardness-70-75 N)	3 h 45 min to 4 h 35 min (for optimum-50-60N hardness)

Example 21: Budesonide MR Tablets- 3 mg

Melt granulation process

Coating material composition

Procedure:

Coating material composition was prepared as described in Example 5 using melt granulation process.

Example 22: Core Tablet Unit Composition

Core Tablet Unit Composition		
Sr. No.	**Ingredient/Grade**	**%w/w**
Intragranular Ingredients		
1.	Budesonide	1-5
2.	Lactose monohydrate (Pharmatose 200 M)	60-70
3.	Crospovidone (PPXL 10)	5-15
Binder Solution		
4.	Povidone (PVP K-30)	1-5
5.	Purified Water	q.s
Extragranular Ingredients		
6.	Crospovidone (PPXL 10)	7-13
7.	Colloidal Silicon Dioxide	1-5
8.	Magnesium Stearate	1-3

Procedure:

All intragranular material were sifted and transferred into suitable rapid mixer granulator. Dry mixing was carried out with impeller on slow speed. Wet granulation was performed using the binder solution. Resultant granules were dried and collected in a pre-labeled container. Extragranular material magnesium stearate was sifted and collected in a pre-labeled container separately. Sifted magnesium stearate was then transferred into low shear blender and lubrication was done.

Example 23: Core Compression: (0.5 mg Strength)

Tooling: 5.0mm round standard concave plain on both sides

Avg. Wt: 60.1 mg

Uniformity of Weight: 59.5-60.8 mg

Hardness: 25-35

Thickness: 2.4-2.5 mm

Disintegration time: 20 sec

Friability: 0.05% w/w

Compression of Budesonide Tablets- 0.5 mg (Finished Product)

Tooling: 8.0 mm round FFBE embossed with W5 on one side and plain on other side.

Description: Round, press/compression coated FFBE debossed with W5 on one side and plain on other side.

Average Weight: 460.0 mg.

Layer-I: 200.0 mg, Layer-II 200.0 mg and Core tablet Weight: 60.0 mg

Thickness: 5.80-6.30 mm

Hardness: 45-80N

Friability: 0.025%w/w (At optimum Hardness)

Disintegration Time: 4 hrs 10 min in water

4 hrs 35 min in pH 6.8 Phosphate Buffer

Example 24: Dissolution Profile

No. of Units	**6**	**24**
Dissolution media	6.8 pH phosphate buffer	6.8 pH phosphate buffer
Apparatus	USP -II ,Paddle	USP -II ,Paddle
Speed	50 RPM	50 RPM
Volume	900 mL	900 mL
Lag Phase	3 h 46 min to 4 h 15 min (for optimum hardness-50-60N) 3h 58 min to 4 h 52 min (for high hardness-70-75 N)	3 h 55 min to 4 h 45 min (for optimum-50-60N hardness)

We Claim-

1. A programmed release pharmaceutical composition, comprising of
   a core comprising one or more active substances optionally along with one or more pharmaceutically acceptable excipients,
   a coating, surrounding the said core, comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate,
   wherein the said coating delays the release of the active substances from the core for a period of about 2 hours to about 10 hours after oral administration.

2. The programmed release pharmaceutical composition of claim 1, wherein the inorganic salts of calcium ion comprises one or more of calcium phosphate, calcium phosphate dihydrate, calcium phosphate anhydrous, dibasic calcium phosphate, dibasic calcium phosphate monohydrate, dibasic calcium phosphate dihydrate, anhydrous dibasic calcium phosphate, monobasic calcium phosphate, tribasic calcium phosphate, calcium acetate, calcium carbonate, calcium chloride, calcium hydroxide, calcium pyrophosphate, calcium sulfate, calcium sulfate anhydrous, calcium sulfate dehydrate, and calcium sulfate hemihydrate.

3. The programmed release pharmaceutical composition of claim 2, wherein the inorganic salt of calcium ion is calcium phosphate dihydrate or dibasic calcium phosphate dihydrate.

4. The programmed release pharmaceutical composition of claim 1, wherein the co-processed mixture is prepared by melt granulation of inorganic salts of calcium ion and glyceryl behenate.

5. The programmed release pharmaceutical composition of claim 1, wherein the ratio of glyceryl behenate and inorganic salts of calcium ion in the co-processed mixture is about 10:90 to about 90:10.

6. The programmed release pharmaceutical composition of claim 1, wherein the coating is applied as multiple layer compression coating or press coating.

7. The programmed release pharmaceutical composition of claim 1, wherein the core is disposed within the coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges the core.

8. The programmed release pharmaceutical composition of claim 7, wherein the ratio of width of the composition to the length of the composition is less than the ratio of about 1.33:1.

9. The programmed release pharmaceutical composition of claim 1, wherein the coating composition further comprises one or more hydrophilic, hydrophobic polymers, or their mixtures.

10. The programmed release pharmaceutical composition of claim 1, wherein the active substance comprises one or more of ondansetron, alprazolam, albuterol sulphate, and corticosteroids.

11. The programmed release pharmaceutical composition of claim 10, wherein the corticosteroid comprises one or more of budesonide, dexamethasone, prednisone, prednisolone, methylprednisolone, cortisone, hydrocortisone, budesonide, dexamethasone, fludrocortisone, fluocortolone, cloprednole, deflazacort, and triamcinolone.

12. The programmed release pharmaceutical composition of claim 1, wherein the composition is in the form of a tablet, a tablet-in-tablet, a trilayer tablet, an in-lay tablet, coated pellets, granules, multiple unit pellet system, and pellets/granules filled in a capsule.

13. A press-coated tablet, comprising of a core comprising one or more active substances and optionally along with one or more pharmaceutically acceptable excipients, and a coating surrounding the said core, wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges the core, wherein the dosage form delays the release of the active substance from the core for a period of about 2 hours to about 10 hours after oral administration.

14. The press-coated tablet of claim 13, wherein the ratio of width of the tablet to the length of the tablet is less than the ratio of about 1.33:1.

15. The press-coated tablet of claim 13, wherein the active substance comprises one or more of budesonide, dexamethasone, prednisone, prednisolone, methylprednisolone, cortisone, hydrocortisone, budesonide, dexamethasone, fludrocortisone, fluocortolone, cloprednole, deflazacort, and triamcinolone.

16. The press-coated tablet of claim 13, wherein the coating comprises co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate.

17. The programmed release pharmaceutical composition of claim 16, wherein the co-processed mixture is prepared by melt granulation of inorganic salts of calcium ion and glyceryl behenate.

18. The press-coated tablet of claim 16, wherein the ratio of glyceryl behenate and inorganic salts of calcium ion in the co-processed mixture is about 10:90 to about 90:10.

19. A programmed release press-coated tablet, comprising of
    a core comprising prednisone and optionally along with one or more pharmaceutically acceptable excipients, and
    a coating surrounding the said core comprising co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate,
    wherein the said core is disposed within said coating such that the coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges of the core, and the dosage form delays the release of the corticosteroid from the core for a period of about 2 hours to about 10 hours after oral administration.

20. The press-coated tablet of claim 19, wherein the ratio of width of the tablet to the length of the tablet is less than the ratio of about 1.33:1.

21. The press-coated tablet of claim 19, wherein the ratio of glyceryl behenate and inorganic salts of calcium ion in the co-processed mixture is about 10:90 to about 90:10.

22. The programmed release pharmaceutical composition of claim 19, wherein the co-processed mixture is prepared by melt granulation of inorganic salts of calcium ion and glyceryl behenate.

23. A method of treating circadian phase dependent pathologies comprising asthma, arthritis, epilepsy, migraine, allergic rhinitis, cardiovascular disease, chronic inflammation and pain, such as rheumatoid arthritis, polymyalgia rheumatica and peptic ulcer, wherein the method comprises administering a programmed release pharmaceutical composition of claim 1 or 2 to a patient in need thereof.

24. A method for delaying the release of one or more active substances from the core for a period between about 2 hours to about 10 hours, wherein the method comprise applying the coating composition to the core; wherein the coating composition comprises co-processed mixture of one or more inorganic salts of calcium ion and glyceryl behenate.

Dated 23rd day of August, 2012

For Wockhardt Limited

(Mandar Kodgule)
Authorized Signatory

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/054258

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K31/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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)
EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 10 2004 043863 A1 (NITEC PHARMA AG REINACH [CH]) 16 March 2006 (2006-03-16)	1-3, 5-12, 19-21, 23,24
Y	examples page 6, paragraph 0041 figure 2	1-12, 19-24

X	WO 2004/093843 A1 (JAGOTEC AG [CH]; VERGNAULT GUY [FR]; GRENIER PASCAL [FR]; DRAGAN CHRIS) 4 November 2004 (2004-11-04)	1-3, 5-12, 19-21, 23,24
Y	examples claims 1-20	1-12, 19-24

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October 2012	18/01/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schüle, Stefanie

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/054258

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/075080 A1 (SOMNUS THERAPEUTICS INC [US]; CUPIT GARY [US]; MCCORMICK ANNE [US]; OS) 1 July 2010 (2010-07-01)	1-3,5-9, 12,23,24
Y	examples claims 1-32	1-12, 19-24

Y	WO 2005/013953 A1 (SYNTHON BV [NL]; CUCALA ESCOI JOAN [ES]; MARGALLO LANA INNOCENCIA [ES]) 17 February 2005 (2005-02-17) cited in the application examples claims 1-20 example 1	1-12, 19-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/054258

Box No. II 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
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:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-12(completely); 19-24(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-12(completely); 19-24(partially)

A pharmaceutical composition comprising a core and a coating. The coating contains calcium ion and glyceryl behenate.

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2. claims: 13-18(completely); 19-24(partially)

A pharmaceutical composition comprising a core and a coating.The coating thickness around the horizontal edges of the core is less than or equal to the coating thickness around the vertical edges the core.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/054258

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 102004043863 A1	16-03-2006	BR PI0515345 A	22-07-2008
		CN 101035517 A	12-09-2007
		DE 102004043863 A1	16-03-2006
		EP 2386295 A2	16-11-2011
		JP 2010047607 A	04-03-2010
		KR 20110126757 A	23-11-2011
		RU 2011119347 A	20-11-2012
		SG 155908 A1	29-10-2009
		US 2006057200 A1	16-03-2006
		US 2012213910 A1	23-08-2012
		ZA 200701900 A	30-07-2008
WO 2004093843 A1	04-11-2004	AT 512659 T	15-07-2011
		AU 2004231362 A1	04-11-2004
		BR PI0409652 A	25-04-2006
		CA 2523158 A1	04-11-2004
		CN 1777412 A	24-05-2006
		CN 102525993 A	04-07-2012
		DK 1631251 T3	03-10-2011
		EP 1631251 A1	08-03-2006
		ES 2368066 T3	14-11-2011
		IL 171494 A	28-04-2011
		JP 4790597 B2	12-10-2011
		JP 2006524229 A	26-10-2006
		KR 20060015528 A	17-02-2006
		MX PA05011446 A	31-05-2006
		PT 1631251 E	19-09-2011
		SI 1631251 T1	28-10-2011
		US 2007110807 A1	17-05-2007
		US 2012177734 A1	12-07-2012
		US 2012177739 A1	12-07-2012
		WO 2004093843 A1	04-11-2004
		ZA 200509477 A	27-09-2006
WO 2010075080 A1	01-07-2010	CA 2746884 A1	01-07-2010
		EP 2375903 A1	19-10-2011
		US 2012039954 A1	16-02-2012
		WO 2010075080 A1	01-07-2010
WO 2005013953 A1	17-02-2005	US 2005048118 A1	03-03-2005
		WO 2005013953 A1	17-02-2005
		WO 2005013954 A1	17-02-2005