(12) STANDARD PATENT (11) Application No. **AU 2007291509 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Controlled release oral dosage formulations comprising a core and one or more barrier layers

(51) International Patent Classification(s)
A61K 9/32 (2006.01) ***A61K 9/26*** (2006.01)
A61K 9/16 (2006.01) ***A61K 9/36*** (2006.01)
A61K 9/24 (2006.01)

(21) Application No: **2007291509** (22) Date of Filing: **2007.08.29**

(87) WIPO No: **WO08/025535**

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/824,054	**2006.08.30**	**US**
60/824,043	**2006.08.30**	**US**

(43) Publication Date: **2008.03.06**
(44) Accepted Journal Date: **2013.05.02**

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(56) Related Art
DE 199 06 290 A1 (FALK PHARMA GMBH) 17 August 2000
EP 0 526 862 A1 (VECTORPHARMA INTERNATIONAL S.P.A) 10 February 1993

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 March 2008 (06.03.2008)

PCT

(10) International Publication Number
WO 2008/025535 A1

(51) International Patent Classification:
A61K 9/32 (2006.01) *A61K 9/24* (2006.01)
A61K 9/36 (2006.01) *A61K 9/26* (2006.01)
A61K 9/16 (2006.01)

(21) International Application Number:
PCT/EP2007/007549

(22) International Filing Date: 29 August 2007 (29.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/824,043 30 August 2006 (30.08.2006) US
60/824,054 30 August 2006 (30.08.2006) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

WO 2008/025535 A1

(54) **Title:** CONTROLLED RELEASE ORAL DOSAGE FORMULATIONS COMPRISING A CORE AND ONE OR MORE BARRIER LAYERS

(57) **Abstract:** Controlled release oral dosage formulations containing one or more active agent, and methods of use thereof, are provided for the once-a-day treatment. The formulation can be in the form of a trilayer tablet containing a core or central layer and one or more barrier layers. The core may contain one or more enteric materials or polymeric materials which modulates the release of the active agent.

CONTROLLED RELEASE ORAL DOSAGE FORMULATIONS COMPRISING A CORE AND ONE OR MORE BARRIER LAYERS

FIELD OF THE INVENTION

This invention is generally in the field of controlled or modified release formulations of pharmaceutically active agents.

BACKGROUND OF THE INVENTION

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

A controlled release formulation is a pharmaceutical composition capable of releasing a drug at a pre-determined rate and/or at a pre-determined time after administration to maintain a desirable pharmacological activity for some desirable period of time. Such preparations provide a supply of a drug to the body during a predetermined period of time or at a predetermined absorption site and thus maintain drug levels in a therapeutic range for longer periods of time than conventional, e.g. immediate release formulations.

Dosage forms comprising a core containing a drug dispersed in release-controlling materials are a popular means of producing controlled release formulations. Materials most commonly employed for this purpose are hydrophilic materials, e.g. hydrophilic polymers that swell and gel upon contact with a physiological medium. When a dosage form is exposed to a physiological medium, the periphery will begin to hydrate and form a gel matrix. As the medium continues to penetrate the dosage form the thickness of the gel matrix increases. Drug release occurs by diffusion through the matrix and/or by erosion of the matrix. A variety of desirable release profiles can be produced by carefully selecting the hydrophilic material and the dimensions and geometry of the dosage form compositions. However, over time, as the thickness of the gel matrix increases, the drug concentration in the dosage form decreases, the surface area of the dosage form decreases and as a result the rate of release decreases.

For many active agents, the rate or extent of absorption is not linear as the agent passes through the GI tract. Many active agents have so-called absorption windows. An absorption window is a term given to an area or region of the GI tract where a drug is absorbed more efficiently or at a higher rate compared with other regions of the GI tract. Some active agents are more prone to degradation or metabolism in certain regions of

the GI tract than others. As such, it would be beneficial if a controlled release dosage form could deliver the drug almost exclusively to a particular absorption window for a given active agent, or preferentially avoid or reduce the rate of release in areas of the GI tract where degradation or metabolism of an active agent is high. Further, the ability to deliver an active agent to the absorption window may increase efficacy of the drug substances and/or diminish or eliminate adverse side effects.

There exists a need to provide a controlled release dosage form that, upon administration, releases an active agent initially at a slow rate but which increases over time, in order to release a drug from the dosage form mainly to the lower region of the GI tract. In particular, there exists a need to provide a dosage form providing for slower drug release rates at pH levels below about 5.5 and increased rate of release at higher pH levels.

It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

It is therefore an object of the invention in a preferred embodiment to provide controlled release formulations which delay release of one or more active agents until the formulation reaches the absorption window, and methods of making and using thereof.

It is an object of the invention in a preferred embodiment to provide a controlled release dosage form that, upon administration, releases an active agent initially at a slow rate and which rate increases over time, in order to release a drug from the dosage form mainly to the lower region of the GI tract.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a multilayer controlled release solid oral dosage formulation comprising

(a) a core comprising one or more active agents and one or more enteric materials;

(b) two or more barrier layers, one above the core and one below the core comprising one or more swellable, erodible, or gellable polymers; and

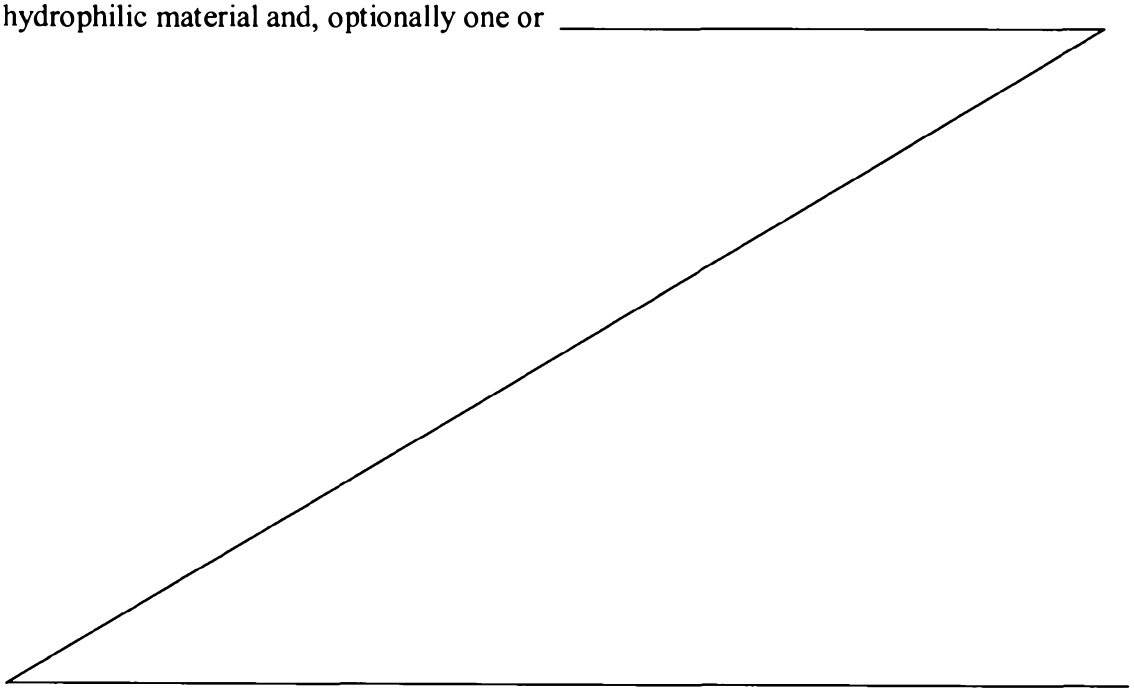
wherein, upon administration to a subject, the active agent is released with an ascending release rate in response to the changes in pH as the dosage formulation descends the GI tract.

According to a second aspect of the invention, there is provided a method of treating a cardiovascular disorder, the method comprising administering to a patient in need thereof the formulation of the first aspect.

According to a third aspect of the invention, there is provided use of a formulation of the first aspect in the manufacture of a medicament for treating a cardiovascular disease.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

Controlled release formulations for the delivery of an active agent, and methods of making and using thereof, are described herein. In one embodiment, the formulation contains a core containing an active agent and an enteric material, optionally a hydrophilic material and, optionally one or



more barrier layers. The formulation can be administered in any solid oral dosage form such as a tablet or caplet. In one embodiment, the controlled release formulation is a tablet containing a core containing a dihydropyridine calcium channel blocker, such as nisoldipine, and an enteric material, and at least one barrier layer above or below the central layer which contains one or more erodible, swellable and/or gellable polymeric materials. The concentration of the enteric material in the core is from about 0.1% to about 20% by weight, preferably about 1 to 15%, more preferably about 5 to 10% by weight of the composition. The concentration of the one or more polymers in the barrier layer(s) is from about 5% to about 90% by weight of the barrier layer, preferably from about 50% to about 90% by weight of the barrier. In a preferred embodiment, the tablet is a trilayer tablet which contains a core, and two barrier layers, one above the core and one below. The barrier layers may be the same or different in composition and thickness. The core and/or barrier layers may contain one or more pharmaceutically acceptable additives, excipients, or carriers.

The core may contain one or more polymeric materials that modulate (i.e. slow and/or accelerate) the release of the active agent. The concentration of the polymeric material is from about 1% to about 95% by weight. The central layer and/or the barrier layers may also contain one or adjuvants, which, in combination with the polymeric materials, further modulate release of the active agent. The concentration of the adjuvant(s) is from about 1% to about 25% by weight of the compositions, preferably from about 5% to about 15% by weight of the composition.

The formulation may be coated with one or more modified release coatings, which further modulate the release of the active agent from the core. Suitable coatings include immediate release coatings, taste mask coatings, enteric coatings, sustained or extended release coatings, and delayed release coatings. The dosage forms may also be coated for aesthetic reasons such as to impart a color to the dosage form or to apply a surface finish to the dosage form.

The dosage form, upon administration to a subject, releases the active agent with an ascending release rate in response to the changes in pH as the dosage formulation descends the GI tract.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

As used herein, the term "enteric material" refers to a material that is typically employed in enteric coatings. Enteric materials are practically insoluble at acidic pH levels found in the stomach, but are increasingly soluble at higher pH levels found in the intestinal tract.

"Taste masking coating", as used herein, refers to a pH dependent coating that is insoluble in the mouth but dissolves in the acidic pH of the stomach.

"Extended release coating", as used herein, refers to a pH independent substance that will act as a barrier to control the diffusion of the drug from its core complex into the gastrointestinal fluids.

"Delayed release coating", as used herein, refers to a pH dependent coating that is insoluble in the acidic pH of the stomach and the pH within the mid to the upper small intestine, but dissolves within the lower small intestine or upper large intestine.

"C_{max}", as used herein, refers to the peak concentration in blood plasma. Unless otherwise stated, C_{max} refers to the peak concentration of the calcium channel blocker in blood plasma.

"T_{max}", as used herein, refers to the time to peak concentration in blood plasma. Unless otherwise stated, T_{max} refers to the time to peak concentration of the calcium channel blocker in blood plasma.

"λ_z", as used herein, refers to the elimination rate constant.

"$T_{1/2}$", as used herein, refers to the terminal half-life.

"AUC_{last}", as used herein, refers to the area under the concentration-time curve from time-zero to the time of the last quantifiable concentration.

"AUC_{inf}", as used herein, refers to the area under the plasma concentration time curve from time-zero extrapolated to infinity.

"Bioavailability", as used herein, refers to the rate and of uptake the

active ingredient or active agent absorbed from a drug product.

"Bioequivalence", as used herein, refers to the equivalent release of the same drug substance from two or more drug products or formulations. This leads to an equivalent rate and extent of absorption from these formulations.

As used herein, an "analog" of a chemical compound is a compound that, by way of example, resembles another in structure but is not necessarily an isomer (e.g., 5-fluorouracil is an analog of thymine).

As used herein, a "derivative" of a compound refers to a chemical compound that may be produced from another compound of similar structure in one or more steps. Derivatives generally involve the addition and/or modification of one or more functional groups on the parent compound.

As used herein, "controlled release elements" refers to materials that modulate release of the active agent from the formulation. The controlled release elements may be located in the core and/or the barrier layer(s). The controlled release elements may be organic or inorganic, naturally occurring or synthetic, materials including, but not limited to, polymeric materials, triglycerides, derivatives of triglycerides, fatty acids and salts of fatty acids, talc, small organic molecules and salts thereof, talc, boric acid, and colloidal silica.

As used herein, "coat-core nisoldipine 40 mg tablet" for purposes of comparison of pharmacokinetics and dosage refers to the version of the drug marketed as SULAR®, containing 8 mg of nisoldipine in the core and 32 mg of nisoldipine in the coat.

II. Compositions

A. Core

i. Active Agents

The core or central layer contains one or more active agents selected from the group including, but not limited to, hypnotics, sedatives, tranquilizers, anti-convulsants, muscle relaxants, analgesics, anti-inflammatory, anesthetics, anti-spasmodics, anti-ulcer-agents, anti-parasitics, anti-microbials, anti-fungal, cardiovascular agents, diuretics, cytostatics, anti-neoplastic agents, anti-viral agents, anti-glaucoma agents, anti-

depressants, sympathomimetics, hypoglycaemics, diagnostic agents, anti-cough, physic energizers, anti-parkinson agents, local anesthetics, muscle contractants, anti-malarials, hormonal agents, contraceptives, anorexic, anti-arthritic, anti-diabetic, anti-hypertensive, anti-pyretic, anti-cholinergic, bronchodilator, central nervous system, inotropic, vasodilator, vasoconstrictor, decongestant, hematinic, electrolyte supplement, germicidal, parasympathetolytic, parasymphatethomimetic, antiemetic, psychostimulant, vitamin, beta-blockers, H-2 blocker, beta-2 agonist, counterirritants, coagulating modifying agents, stimulants, anti-hormones, drug-antagonists, lipid-regulating agents, uricosurics, cardiac glycosides, ergot and derivatives thereof, expectorants, muscle relaxants, anti-histamines, purgatives, contrast materials, radiopharmaceuticals, imaging agents, anti-allergic agents, and combinations thereof.

Suitable active agents include, but are not limited to, codeine, ethylmorphine, dextromethorphan, noscapine, pentoxiverine, acetylcysteine, bromhexine, epinephrine, isoprenaline, orciprenaline, ephedrine, fenoterol, rimiterol, ipratropium, cholinetheophyllinate, proxiphylline, bechlomethasone, budesonide, deslanoside, digoxine, digitoxin, disopyramide, proscillaridin, chinidine, procainamide, mexiletin, flecainide, alprenolol, proproanolol, nadolol, pindolol, oxprenolol, labetalol, timolol, atenolol, pentaeritrityltetranitrate, isosorbiddinitrate, isosorbidmononitrate, niphedipin, phenylamine, verapamil, cyclandelar, nicotinylalcholhol, inositolnicotinate, alprostatdil, etilephrine, prenalterol, dobutamine, dopamine, dihydroergotamine, guanetidine, betanidine, methyldopa, reserpine, guanfacine, trimethaphan, hydralazine, dihydralazine, prazosine, diazoxid, captopril, nifedipine, nisoldipine, enalapril, nitroprusside, bendroflumethiaziede, hydrochlorthiazide, metychlothiazide, polythiazide, chlorthalidon, cinetazon, clopamide, mefruside, metholazone, bumetanide, ethacrynacide, spironolactone, amiloride, chlofibrate, nicotinic acid, nicheritrol, brompheniramine, cinnarizine, dexchlorpheniramine, clemastine, antazoline, cyproheptadine, promethazine, cimetidine, ranitidine, sucralfat, papaverine, moxaverine. atropin, butylscopolamin, emepron, glucopyrron,

hyoscyamine, mepensolar, methylscopolamine, oxiphencyclimine, probanteline, terodilin, sennaglycosides, sagradaextract, dantron, bisachodyl, sodiumpicosulfat, etulos, diphenolxylate, loperamide, salazosulfapyridine, pyrvin, mebendazol, dimeticon, ferrofumarate, ferrosuccinate, ferritetrasemisodium, cyanochobalamine, folic acid heparin, heparin co-factor, diculmarole, warfarin, streptokinase, urokinase, factor VIII, factor IX, vitamin K, thiotepa, busulfan, chlorambucil, cyclophosphamid, melfalan, carmustin, mercaptopurin, thioguanin, azathioprin, cytarabin, vinblastin, vinchristin, vindesin, procarbazine, dacarbazine, lomustin, estramustin, teniposide, etoposide, cisplatin, amsachrin, aminogluthetimid, phosphestrol, medroxiprogresterone, hydroxiprogresterone, megesterol, noretisteron, tamoxiphen, ciclosporin, sulfisomidine, bensylpenicillin, phenoxymethylpenicillin, dicloxacillin, cloxacillin, flucloxacillin, ampicillin, amoxicillin, pivampicillin, bacampicillin, piperacillin, mezlocillin, mecillinam, pivmecillinam, cephalotin, cephalexin, cephradin, cephadroxil, cephaclor, cefuroxim, cefotaxim, ceftazidim, cefoxitin, aztreonam, imipenem, cilastatin, tetracycline, lymecycline, demeclocycline, metacycline, oxitetracycline, doxycycline, chloramphenicol, spiramycin, fusidic acid, lincomycin, clindamycin, spectinomycin, rifampicin, amphotericin B, griseofulvin, nystatin, vancomycin, metronidazole, tinidazole, trimethoprim, norfloxacin, salazosulfapyridin, aminosalyl, isoniazid, etambutol, nitrofurantoin, nalidixic acid, metenamine, chloroquin, hydroxichloroquin, tinidazol, ketokonazol, acyclovir, interferon idoxuridin, retinol, tiamin, dexpantenol, pyridoxin, folic acid, ascorbic acid, tokoferol, phytominadion, phenfluramin, corticotropin, tetracosactid, tyrotropin, somatotropin, somatrem, vasopressin, lypressin, desmopressin, oxytocin, chloriongonadotropin, cortison, hydrocortison, fludrocortison, prednison, prednisolon, fluoximesteron, mesterolon, nandrolon, stanozolol, oximetolon, cyproteron, levotyroxin, liotyronin, propylthiouracil, carbimazol, tiamazol, dihydrotachysterol, alfacalcidol, calcitirol, insulin, tolbutamid, chlorpropamid, tolazamid, glipizid, glibenclamid, phenobarbital, methyprylon, pyrityldion, meprobamat, chlordiazepoxid, diazepam,

nitrazepam, oxazepam, dikaliumchlorazepat, lorazepam, flunitrazepam, alprazolam, midazolam, hydroxizin, chlomethiazol, propionmazine, alimemazine, chlorpromazine, levomepromazine, acetophenazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, dixyrazine, thioridazine, periciazin, chloprothixene, zuclopentizol, flupentizol, thithixen, haloperidol, trimipramin, opipramol, chlomipramin, desipramin, lofepramin, amitriptylin, nortriptylin, protriptylin, maptrotilin, coffein, cinnarizine, cyclizine, dimenhydinate, meclozine, prometazine, thiethylperazine, metoclopramide, scopolamine, phenobarbital, phenytoine, ethosuximide, primidone, carbamazepine, chlonazepam, orphenadrine, atropine, bensatropine, biperiden, metixene, procylidine, levodopa, bromocriptin, amantadine, ambenon, pyridostigmine, synstigmine, disulfiram, morphine, codeine, pentazocine, buprenorphine, pethidine, phenoperidine fentanyl, methadone, piritramide, dextropropoxyphene, ketobemidone, acetylsalicylic acid, phenazone, phenylbutazone, azapropazone, piroxicam, ergotamine, dihydroergotamine, cyproheptadine, pizitifen, flumedroxon, allopurinol, probenecid, sodiummaurothiomalate, auronofin, penicillamine, estradiol, estradiolvalerianate, estriol, ethinylestradiol, dihydrogesteron, lynestrenol, medroxiprogresterone, noretisterone, cyclophenile, clomiphene, levonorgestrel, mestranol, ornidazol, tinidazol, ekonazol, chlotrimazol, natamycine, miconazole, sulbentin, methylergotamine, dinoprost, dinoproston, gemeprost, bromocriptine, phenylpropanolamine, sodiumchromoglicate, azetazolamide, dichlophenamide, betacarotene, naloxone, calciumfolinate, in particular clonidine, theophylline, dipyradamol, hydrochlorthiazide, scopolamine, indomethacine, furosemide, potassium chloride, morphine, ibuprofen, salbutamol, terbutalin, and combinations thereof.

The active agent(s) can be chiral or achiral. Chiral molecules can exist as a single enantiomer, a mixture of enantiomers or diastereomers or a racemic mixture. As used herein, the term "stereoisomers" refers to compounds made up of the same atoms having the same bond order but having different three-dimensional arrangements of atoms which are not

interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomers" refers to two stereoisomers which are non-superimposable mirror images of one another. As used herein, the term "optical isomer" is equivalent to the term "enantiomer". As used herein the term "diastereomer" refers to two stereoisomers which are not mirror images and are not superimposable. The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers. The term "chiral center" refers to a carbon atom to which four different groups are attached. Choice of the appropriate chiral column, eluent, and conditions necessary to effect separation of the pair of enantiomers is well known to one of ordinary skill in the art using standard techniques (see e.g. Jacques, J. et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc. 1981).

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds listed above, wherein the parent compound is modified by making the acid or base addition salt thereof. Example of pharmaceutically acceptable salts include but are not limited to mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, tolunesulfonic, naphthalenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic salts.

The pharmaceutically acceptable salts of the compounds can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be

prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like diethyl ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, p. 704; and "Handbook of Pharmaceutical Salts: Properties, Selection, and Use," P. Heinrich Stahl and Camille G. Wermuth, Eds., Wiley-VCH, Weinheim, 2002.

As generally used herein "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

The amount of active agent(s) employed in a dosage form will depend on the active agent(s) to be employed and the nature and severity of the condition to be treated. The concentration of the active agent is generally from about 0.1% to about 90% by weight of the tablet, preferably from about 0.5% to about 20% by weight of the tablet, more preferably from about 1% to about 10% by weight of the tablet. Alternatively, the concentration of the active agent is generally from about 0.1% to about 90% by weight of the core, preferably from about 0.5% to about 20% of the core, more preferably from about 1% to about 10% of the core.

In the preferred embodiment, the active agent is a dihydropyridine calcium channel blocker, such as nisoldipine or a derivative, analogue, or polymorph thereof. Nisoldipine is a yellow crystalline substance, which is practically insoluble in water, but soluble in ethanol. Derivatives of nisoldipine, such as *m*-nisoldipine, are described in Wang *et al.*, *J. Chrom. B*, 835, 71-76 (2006)).

B. Controlled Release Elements

1. Enteric Material

The core or central layer contains an enteric material to delay the release of the one or more active agents until the formulation reaches the absorption window. Suitable enteric materials include, but are not limited to, cellulose polymers, such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name Eudragit ® (Rohm Pharma), such as poly(ethylacrylate-methylmethacrylate-triethylammonioethyl-metharylate chloride) (Eudragit® RS and Eudragit® RL) and poly(ethylacrylate-methylmethacrylate) (Eudragit® NE); alginates, alkali-soluble acrylic resins, hydroxypropyl methylcellulose phthalate, methacrylate-methacrylic acid co-polymers, polyvinyl acetate phthalate, styrol maleic acid copolymers, and the like, and combinations thereof. In one embodiment, the enteric material is cellulose acetate phthalate. The concentration of the enteric material is from about 0.1% to about 20% by weight, preferably about 1 to 15%, more preferably about 5 to 10% by weight of the composition.

2. Hydrophilic Materials

The core may also contain one or more hydrophilic materials that modulate (i.e. slow and/or accelerate) the release of the active agent(s). The hydrophilic material may be any of the materials known in the art used in dosage forms as matrix-forming release-controlling agents. Examples of such materials include, but are not limited to, methyl cellulose, carboxymethyl-cellulose sodium, crosslinked carboxymethylcellulose sodium, crosslinked hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethyl starch, polymethacrylate, polyvinylpyrrolidone, polyvinyl alcohols, polyethylene glycols, potassium methacrylate-divinyl benzene copolymer, carboxymethylcellulose, alginates, albumin, gelatine, crosslinked polyvinylpyrrolidone, soluble starch and derivatives thereof, polyesters, polyanhydrides, polymethylvinylether/anhydride copolymers, glucan,

scleroglucan, mannan, betacyclodextrins and cyclodextrin derivatives containing linear and/or branched polymeric chains and mixtures thereof. The various types of the materials mentioned above are commercially and cab be characterized by differences in chemico-physical characteristics such as solubility and gel formation. For example, the erodibility, gelation, and ability to swell of hydroxypropylmethyl cellulose can vary based on the molecular weight of the polymer and the degree of substitution. Therefore, one skilled in the art would be able to select from among polymers with the same molecular structure but differing in the molecular weight and/or viscosity, based on the desired release profile of the active agent. In one embodiment, the core contains Methocel® K4M, a hydroxypropyl methycellulose having a methoxy content of 19-24%, a hydroxypropoxyl content of 7-12%, and an apparent viscosity, as measured on a 2% aqueous solution by rotation, of 2308-3755 mPa (Colorcon, West Point, PA). In another embodiment, the core contains Methocel® K100LV, a hydroxypropyl methycellulose having a methoxy content of 19-24%, a hydroxypropoxyl content of 7-12%, and an apparent viscosity, as measured on 2% aqueous solution by rotation, of 78-117 mPa (Colorcon, West Point, PA).

The concentration of the hydrophilic material is from about 1% to about 90% by weight of the composition, preferably from about 10% to about 50% by weight, more preferably from about 10 to 45% by weight of the composition.

Upon contact with a physiological medium, the core containing the active agent, the enteric material and the hydrophilic material form a gel matrix. The gel matrix must have sufficient strength such that it maintains its structural integrity throughout the period of drug release. At low pH levels in the stomach, the enteric material remains insoluble. However, as the dosage form descends further down the GI tract, the enteric material is increasingly solubilised, thereby increasingly creating pores and channels in the matrix through which drug can diffuse at increasing rates. The enteric materials are not swellable and/or gellable in aqueous media, and thus, do

not contribute mechanical strength of the gel matrix. It is important that the desirable effect the enteric material has on the release rate is not offset by the unintended effect of prematurely destroying the structural integrity of the gel matrix. In order to ensure that a desired release rate can be obtained reproducibly, it is preferred that the enteric material is used in low amounts relative to the amount of hydrophilic material employed. Most preferably the ratio of hydrophilic material to the enteric material is about 1.5:1 to about 10:1, more particularly about 1.9:1 to about 5:1.

C. Barrier Layer(s)

The barrier layer(s) serve to prevent, for a predetermined amount of time, the release of the active agent contained in the central layer or core. The tablet can contain one or more barrier layers. When two barrier layers are present, the barriers layers may have the same composition or different compositions and/or the same thickness or different thicknesses.

In one embodiment, the barrier layer(s) contain(s) one or more swellable, erodible and/or gellable polymers. In a preferred embodiment, the swellable, erodible, and/or gellable polymer is hydroxypropylmethylcellulose. The weight average molecular weight of the hydroxypropylmethylcellulose is from about 1000 to about 4,000,000, more preferably from about 2000 to about 2,000,000. In one embodiment, the barrier layer(s) contain Methocel® E5, a hydroxypropyl methycellulose having a methoxy content of 28-30%, a hydroxypropoxyl content of 7-12%, and an apparent viscosity, as measured by rotation, of 4.2-6.1 mPa (Colorcon, West Point, PA). In another embodiment, the barrier layer(s) contain Methocel® E50, a hydroxypropyl methycellulose having a methoxy content of 28-30%, a hydroxypropoxyl content of 7-12%, and an apparent viscosity, as measured by rotation, of 39-59 mPa (Colorcon, West Point, PA). In a preferred embodiment, one barrier layer contains Methocel® E5 and the second barrier layer contains Methocel® E50.

Other suitable polymers include, but are not limited to, carboxyvinyl polymers; polyvinylalcohols; glucans, scleroglucans; mannans; xantans; alginic acid and its derivatives; polyanhydrides; polyaminoacids;

methylvinylethers/maleic anhydride copolymers; carboxymethylcellulose and its derivatives; ethylcellulose; methylcellulose; and other cellulosic polymers.

The polymers are present in an amount from about 5% to about 90% by weight of the barrier layer, preferably from about 25% to about 75% by weight of the barrier layer.

D. Other Release-Modifying Agents

The core layer and/or the barrier layers may also contain one or more adjuvants, which in combination with the polymeric materials allows for further modulation of the release of the active agent based on the desired release profile of the active agent. Suitable adjuvants include, but are not limited to, glyceryl monostearate, triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, cetyl alcohol, polyvinylpyrrolidone, glycerol, ethylcellulose, methylcellulose, sodium carboxymethylcellulose, other natural or synthetic substances well known to those skilled in the art, and combinations thereof. Other suitable adjuvants include, but are not limited to, magnesium stearate, stearic acid, talc, sodium benzoate, boric acid, polyoxyethylenglycols and colloidal silica. The concentration of the adjuvant(s) is from about 1% to about 25% by weight of the compositions, preferably from about 5% to about 15% by weight of the composition.

E. Additives, Excipients and Carriers

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active agent(s). As generally used herein "carrier" includes, but is not limited to, plasticizers, diluents, binders, lubricants, surfactants, pH modifying agents, anti-adherents, disintegrators, fillers, pigments, colorants, stabilizing agents, flavoring agents, glidants, and combinations thereof.

Suitable plasticizers include, but are not limited to, hydrogenated castor oil, cetyl alcohol, cetostearyl alcohol, fatty acids, glycerides and triglycerides and derivatives thereof, and polyoxyethylenglycols and derivatives thereof.

Diluents, also referred to as "fillers," are typically necessary to increase the bulk of a solid dosage form so that a practical size is provided for compression of tablets or formation of beads and granules. Suitable diluents include, but are not limited to, dicalcium phosphate dihydrate, calcium sulfate, lactose, sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar. The amount of active substance released in the first administration phase may be programmed regulating the exposed surface and the components constituting the layer (a) matrix, all obviously depending on to the same active principle solubility.

Binders are used to impart cohesive qualities to a solid dosage formulation, and thus ensure that a tablet or bead or granule remains intact after the formation of the dosage forms. Suitable binder materials include, but are not limited to, starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia, tragacanth, sodium alginate, cellulose, including hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, and veegum, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone.

Lubricants are used to facilitate tablet manufacture. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, glycerol behenate, polyethylene glycol, talc, and mineral oil.

Disintegrants are used to facilitate dosage form disintegration or "breakup" after administration, and generally include, but are not limited to,

starch, sodium starch glycolate, sodium carboxymethyl starch, sodium carboxymethylcellulose, hydroxypropyl cellulose, pregelatinized starch, clays, cellulose, alginine, gums or cross linked polymers, such as cross-linked PVP (Polyplasdone XL from GAF Chemical Corp).

Stabilizers are used to inhibit or retard drug decomposition reactions which include, by way of example, oxidative reactions.

Surfactants may be anionic, cationic, amphoteric or nonionic surface active agents. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions. Examples of anionic surfactants include sodium, potassium, ammonium of long chain alkyl sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylthioxyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. Cationic surfactants include, but are not limited to, quaternary ammonium compounds such as benzalkonium chloride, benzethonium chloride, cetrimonium bromide, stearyl dimethylbenzyl ammonium chloride, polyoxyethylene and coconut amine. Examples of nonionic surfactants include ethylene glycol monostearate, propylene glycol myristate, glyceryl monostearate, glyceryl stearate, polyglyceryl-4-oleate, sorbitan acylate, sucrose acylate, PEG-150 laurate, PEG-400 monolaurate, polyoxyethylene monolaurate, polysorbates, polyoxyethylene octylphenylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether, Poloxamer® 401, stearoyl monoisopropanolamide, and polyoxyethylene hydrogenated tallow amide. Examples of amphoteric surfactants include sodium N-dodecyl-.beta.-alanine, sodium N-lauryl-.beta.-iminodipropionate, myristoamphoacetate, lauryl betaine and lauryl sulfobetaine.

If desired, the tablets may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, dyes, pH buffering agents, or preservatives.

F. Modified Release Coatings

Compositions described herein, in the form of a solid dosage form, may be coated with one or more immediate and/or modified release coatings, which further modulate the release of the active agent(s) from the core or central layer. Suitable coatings include, but are not limited to, coatings which are soluble in, or permeable to, the acidic medium of the stomach (i.e. taste mask coatings and immediate release coatings); coatings which are insoluble in the acidic medium of the stomach but are soluble in the neutral environment of the small intestine (i.e. enteric coatings); coatings which are insoluble in the stomach and the environment of the mid to the upper small intestine, but dissolve in the lower small intestine or upper large intestine (i.e. delayed release coatings); and combinations thereof. The dosage forms may also be coated for aesthetic reasons such as to impart a color to the dosage form or to apply a surface finish to the dosage form.

1. Immediate Release Coatings

Immediate release coatings are formed of a polymer that dissolves within the oral cavity upon contact with saliva or which are insoluble in the neutral pH of the oral cavity and which dissolve at the low pH of the stomach.

Coatings which dissolve in the mouth may have properties such as mucoadhesion, to prolong contact of the particles with the buccal, sublingual or other oral cavity surfaces to enhance uptake of the active agent(s). Many mucoadhesive polymers are known and typically are characterized by a high density of carboxylic groups. See for example, U.S. Patent No. 6,235,313 and U.S. Patent No. 5,955,096 to Mathiowitz *et al.*

Coatings which dissolve in the stomach are typically used to provide properties such as taste-masking. The cationic polymer Eudragit® E 100 (Rohm Pharma) carries amino groups. Its films are, therefore, insoluble in the neutral medium of saliva, but dissolve by salt formation in the acid environment of the stomach. Such film coatings with a thickness of approximately 10 micrometers can prevent medication with a bitter or unpleasant taste from dissolving in the mouth upon ingestion or during swallowing. The protective film dissolves quickly under the acidic

conditions in the stomach allowing for the active agent(s) to be released. The coating composition may include conventional additives, such as plasticizers, pigments, colorants, stabilizing agents, glidants, etc.

2. Sustained or Extended Release Coatings

Sustained or extended release of the active agent(s) is possible with the use of a diffusion barrier coating on the drug-resin complex particles. Suitable coating materials include, but are not limited to, cellulose polymers, such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name Eudragit ® (Rohm Pharma), alginates, alkali-soluble acrylic resins, hydroxypropyl methylcellulose phthalate, methacrylate-methacrylic acid co-polymers, polyvinyl acetate phthalate, styrol maleic acid copolymers, copolymers available under the trade name Eudragit® (Rohm Pharma), such as poly(ethylacrylate-methylmethacrylate-triethylammonioethyl-metharylate chloride) (Eudragit® RS and Eudragit® RL) and poly(ethylacrylate-methylmethacrylate) (Eudragit® NE), and combinations thereof. Aqueous dispersions of such polymers are available under the trade names Eudragit® RS 30 D, Eudragit® RL 30 D and Eudragit® NE 30 D.

These copolymers may be used alone, in admixture with each other, and in admixture with plasticizers (for example, triethyl citrate), pigments, and other substances to alter the characteristics of the coating. In general, the major components of the coating should be insoluble in, and permeable to, water. However, it may be desirable to incorporate a water-soluble substance, such as methyl cellulose, to alter the permeability of the coating.

The coating materials may be applied as a suspension in an aqueous fluid. The coating composition may include conventional additives, such as plasticizers, pigments, colorants, stabilizing agents, glidants, etc. A plasticizer is normally present to reduce the fragility of the coating, and will generally represent about 10 wt. % to 50 wt. % relative to the dry weight of the polymer. Examples of typical plasticizers are, but not limited to,

polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and acetylated monoglycerides. A stabilizing agent may be used to stabilize particles in the dispersion. Typical stabilizing agents are nonionic emulsifiers such as sorbitan esters, polysorbates and polyvinylpyrrolidone. Glidants are recommended to reduce sticking effects during film formation and drying, and will generally represent approximately 25 wt. % to 100 wt. % of the polymer weight in the coating solution. One effective glidant is talc. Other glidants such as magnesium stearate and glycerol monostearates may also be used. Pigments such as titanium dioxide may also be used. Small quantities of an anti-foaming agent, such as a silicone (e.g., simethicone), may also be added to the coating composition.

3. Enteric Coatings

Enteric coated dosage forms can be prepared as described in references such as "Pharmaceutical dosage form tablets", eds. Liberman et. al. (New York, Marcel Dekker, Inc., 1989), "Remington – The science and practice of pharmacy", 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, and "Pharmaceutical dosage forms and drug delivery systems", 6th Edition, Ansel et.al., (Media, PA: Williams and Wilkins, 1995). Examples of suitable coating materials include but are not limited to cellulose polymers, such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name Eudragit ® (Rohm Pharma). Additionally, the coating material may contain conventional carriers such as plasticizers, pigments, colorants, glidants, stabilization agents, and surfactants.

III. Method of Manufacturing

The compositions described herein can be prepared using techniques well known in the art. Multilayer tablets may be prepared by compression molding. In compression molding, the core and the one or more barrier layers are prepared separately and then compressed using a multilayer

tableting press. Alternatively, the core could be prepared separately with the barrier layers added as a blend, and the composition compressed to form a tablet.

The geometric shape of the dosage forms described herein may vary depending on the type of release profile that is desired. In its simplest form, the dosage form might consist of a monolithic core. Alternatively, the core may consist of one of more layers containing one or more pharmaceutically active substances in each layer. Dosage forms of this type have been described in U.S. Patent Nos. 5,626,874, 5,422,123 and 6,027,748 to Conte *et al.*

Alternatively, one or more layers may contain no active agent(s). Each layer may contain the same or different release-controlling materials and excipients. In another embodiment, the dosage form may be a multiparticulate system. Each particle may contain the same or different pharmaceutically active substance and the same or different release-controlling materials and other adjuvants. In a preferred dosage form, the core is multilayered, e.g. having two or three layers, one or more of which contains active agent(s) and the other layers contain no active agent(s). In a particularly preferred embodiment the dosage form comprises a core consisting of three layers wherein an inner layer contains active agent(s) and the two outer layers do not contain active agent(s).

The formulations can be coated with a film coat that at least partially overcoats the core using techniques well known in the art. The coatings can be applied as a solid or as an aqueous suspension or organic solution. Suitable techniques for applying the coating include, but are not limited to, spray coating, pan coating, fluid bed coating, and compression coating.

IV. Methods of Administration

The dosage forms described herein can be administered to treat a variety of diseases or disorders. Although preferred patients are human, typically any mammal including domestic animals such as dogs and cats, may also be treated. The dosage forms are generally administered orally in the form of a tablet or caplet. The dosage forms can be administered in a

single dose, an escalating dose, or administered at an elevated dosage which is then decreased to a lower dosage after a particular circulating blood concentration of the active agent(s) has been achieved. One of skill in the art would be able to choose administration protocols and determine appropriate dosing regimes based on bioavailability and half-life of the pharmaceutically active substance to be administered. Appropriate dosages of the substance can be determined by one of skill in the art using routine experimentation and standard techniques utilizing dosages currently approved. Intra-patient variability is known in the art depending on the severity of symptoms and dosages are commonly adjusted to exact a particular therapeutic effect in a particular patient.

For many of the disclosed active agent(s) appropriate dosage ranges have been established to maximize circulating concentrations of the substance and minimize side-effects. Generally, the active agent can be administered in amounts between about 0.001 to 100 mg/kg of body weight, preferably 0.01 to 10 mg/kg, more preferably 0.1 to 10 mg/kg. In the specific case of calcium channel blockers, they can be administered at a dosage of between about 0.001 to 100 mg/kg of body weight of the patient, preferably 0.01 mg to 10 mg/kg, more preferably 0.1 to 1.0 mg/kg. Preferred daily doses of a calcium channel blocker are approximately 1-100 mg, preferably 2.5 mg to 50 mg to treat cardiovascular disorders such as hypertension, angina and cardiac arrhythmia.

By employing a mixture of enteric material(s) and hydrophilic material(s) to form a release-controlling matrix one can obtain release profiles characterized by the initial slow release of a drug substance, which over time as the dosage form descends in the GI tract, leads to increasing release rates in response to changes in pH. Such releases profiles may be highly desirable when it is necessary to release the majority of the dose of an active substance in the lower GI tract. By lower GI tract is meant the ileum and large intestine. The term "ileum" refers to the third part of the small intestine that continues to the duodenum and the jejunum. The term "large intestine" refers to a site consisting of the cecum, colon and rectum. The term

"cecum" refers to a blind sack starting from the large intestine and in one end of which the ileum opens.

The dosage forms described herein can be formulated to provide a variety of pharmacokinetic release profiles designed to target the release of active agent(s) at a higher release rate at a particular absorption site in the lower GI tract. As such, the use of these dosage forms may diminish or eliminate unwanted side effects of many active agents. They may also render active agents efficacious, yet reduced in dose, compared with known formulations of those active substances.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

A. Pharmacokinetic Parameters

In one embodiment, the compositions described herein provide an increased bioavailability (as measured by area under the drug plasma concentration-time curve (AUC)) as compared to the same dose of a calcium channel blocker, such as nisoldipine, in a reference formulation containing a slow release core and an immediate release coating (coat-core). In a preferred embodiment, the compositions provide an increase in bioavailability of nisoldipine as compared to the same dose of drug in SULAR®. In another embodiment, the compositions contain a reduced dose of nisoldipine, but exhibit a similar pharmacokinetic profile as SULAR®.

For example, a trilayer tablet containing 40 mg nisoldipine (Formulation A) exhibited a roughly 16% increase in the AUC_{last} compared to SULAR® 40 mg. This suggests that the dose of nisoldipine in the trilayer tablet can be reduced by approximately 15-17%, or 16% (i.e. to 34 mg) and still provide an effective amount of the drug. Accordingly, the 10 mg, 20 mg, 30 mg, and 40 mg dosage strengths of SULAR® can be replaced with reduced, bioequivalent dosage strengths (for example, 8.5 mg, 17 mg, 25.5 mg, and 34 mg). This may result in lower manufacturing costs due to the lower doses required to obtain the desired therapeutic effect.

In another embodiment, the compositions described herein contain one or more controlled release elements in an amount effective to provide a controlled release of the calcium channel blocker, the composition providing a T_{max} of the calcium channel blocker from about 9 to about 20 hours and an AUC_{last} of the calcium channel blocker from about 48 to about 63 hr*ng/ml under fasting conditions based on a 40 mg dose.

In yet another embodiment, the compositions described herein contain one or more controlled release elements in an amount effective to provide a controlled release of the calcium channel blocker, the composition providing a T_{max} of the calcium channel blocker from about 9 to about 20 hours and a Cmax of the calcium channel blocker from about 2.75 to about 4 ng/mL under fasting conditions based on a 40 mg dose.

The present invention will be further understood by reference to the following non-limiting examples.

Examples

Example 1. Trilayer Tablets Containing 40 mg of Nisoldipine

Three different formulations, each of which contained 40 mg of Nisoldipine, were prepared. The formulations are identified as Formulation A, Formulation B, and Formulation C and are described in Tables 1-3. Formulation C was coated with an enteric coating (5% weight gain) containing a combination of Eudragit® S100 (methacrylic acid copolymer type B) and Eudragit® L100 (methacrylic acid copolymer type A). Formulations A and B were coated with an OPADRY® II seal coat available from Colorcon, West Point, PA.

Table 1. Composition of Formulation A

Ingredient	First Barrier Layer (mg/tab)	Core (mg/tab)	Second Barrier Layer (mg/tab)	Total (mg)	Weight % (of the tablet)
Nisoldipine		40.00		40.00	7.1
Lactose Monohydrate, NF	76.5	32.35	57.375	166.23	29.5
Ferric Oxide, NF (yellow)	0.20		0.15	0.35	0.1
Hypromellose, USP, type 2208 (Methocel® K4M)		53.65		53.65	9.5
Sodium lauryl sulfate, NF		50.00		50.00	8.9
Methacrylic Acid Copolymer, Type B, NF (S)		21.40		21.40	3.8
Hypromellose Phthalate, NF	26.5		19.875	46.38	8.2
Glyceryl Behenate, NF	36.8		27.6	64.40	11.4
Povidone,USP (29/32)	7.00	10.70	5.25	22.95	4.1
Hypromellose, USP, type 2910 (Methocel® E5)			37.5	37.50	6.7
Hypromellose, USP, type 2910 (Methocel® E50LV)	50.0			50.0	8.9
Magnesium Stearate, NF (vegetable)	2.00	3.80	1.5	7.30	1.3
Colloidal Silicon Dioxide, NF	1.00	1.10	0.75	2.85	0.5
Totals	200	213	150	563	100%

Table 2. Composition of Formulation B

Ingredient	First Barrier Layer (mg/tab)	Core (mg/tab)	Second Barrier Layer (mg/tab)	Total (mg)	Weight % (of the tablet)
Nisoldipine		40.00		40.00	7.10
Lactose Monohydrate, NF	76.50	32.35	57.375	166.23	29.52
Ferric Oxide, NF (yellow)	0.20		0.15	0.35	0.06
Hypromellose, USP, type 2208 (Methocel® K4M)		53.65		53.65	9.53
Hypromellose, USP, type 2910 (Methocel® E4M)	76.50		57.375	133.88	23.78
Sodium lauryl sulfate, NF		50.00		50.00	8.88
Methacrylic Acid Copolymer, Type B, NF (S)		21.40		21.40	3.80
Glyceryl Behenate, NF	36.80		27.60	64.40	11.44
Povidone,USP (29/32)	7.00	10.70	5.25	22.95	4.08
Magnesium Stearate, NF (vegetable)	2.00	3.80	1.50	7.30	1.30
Colloidal Silicon Dioxide, NF	1.00	1.10	0.75	2.85	0.51
Totals	200.00	213.00	150.00	563.00	100%

Table 3. Composition of Formulation C

Ingredient	First Barrier layer (mg/tab)	Core (mg/tab)	Second Barrier layer (mg/tab)	Film Coat (mg/tab)	Total (mg)	Weight % (of the tablet)
Nisoldipine		40.00			40.00	6.14
Lactose Monohydrate, NF	76.5	32.35	57.375		166.23	25.53
Ferric Oxide, NF (yellow)	0.20		0.15		0.35	0.05
Hypromellose, USP, type 2208 (Methocel® K4M)		53.65			53.65	8.24
Sodium lauryl sulfate, NF		50.00			50.00	7.68
Methacrylic Acid Copolymer, Type B, NF (S)		21.40		25.45	46.85	7.20
Hypromellose Phthalate, NF	26.5		19.875		46.38	7.12
Glyceryl Behenate, NF	36.8		27.6		64.40	9.89
Povidone,USP (29/32)	7.00	10.70	5.25		22.95	3.53
Hypromellose, USP, type 2910 (Methocel® E5)			37.5		37.50	5.76
Hypromellose, USP, type 2910 (Methocel® E50LV)	50.0				50.00	7.68
Magnesium Stearate, NF (vegetable)	2.00	3.80	1.5		7.30	1.12
Colloidal Silicon Dioxide, NF	1.00	1.10	0.75		2.85	0.44
Methacrylic Acid Copolymer, Type A, NF				25.49	25.49	3.92
Triethyl Citrate, USP				35.86	35.86	5.51
Potassium Hydroxide, NF				1.21	1.21	0.19
Totals	200.00	213.00	150.00	88.00	651.00	100%

The formulations described above were prepared as follows:

Core or Central Layer

1. Nisoldipine and sodium lauryl sulfate were mixed in a high shear mixer for two minutes. Lactose monohydrate, povidone, methacrylic acid copolymer (type B), and hypromellose type 2208 (Methocel K4M) were added to the mixer and mixed for ten minutes.

2. The binding solution was prepared by dissolving povidone in purified water and adding sodium lauryl sulfate. The mixture was mixed in a suitable tank and left to rest until defoaming was complete.

3. The binding solution was added to the high shear mixer containing the mixture of step 1 and mixed briefly for two minutes. The resulting granulation was kneaded and transferred to a fluid bed dryer and dried until an LOD below 2.5% was obtained. After drying, the granulation was milled with an oscillatory mill.

4. After milling, one half of the granulation was placed into a diffusion blender. Colloidal silicon dioxide was added to the blender followed by the remainder of the granulation. The mixture was mixed for twenty minutes.

5. Magnesium stearate was premixed manually with 5% of the mixture from step 4. The premix was added to the granulation in a diffusion blender and mixed for ten minutes.

Barrier Layers

1. Lactose monohydrate, glyceryl behenate, ferric oxide (yellow), povidone, hypromellose type 2910 (Methocel E4M), and optionally hypromellose phthalate, were added to a high shear mixer and mixed for six minutes.

2. Purified water was added to the mixture in step 1 and kneaded for about two minutes.

3. The granulation was transferred to a fluid bed dryer and dried until an LOD below 2.5% was obtained. After drying, the granulation was milled on an oscillatory mill.

4. After milling, one half of the granulation was placed into a diffusion blender. Colloidal silicon dioxide was added to the blender followed by the remainder of the granulation. The mixture was mixed for twenty minutes.

5. Magnesium stearate was premixed manually with 5% of the mixture from step 4. The premix was added to the granulation in a diffusion blender and mixed for ten minutes.

Tableting

The central layer and the barrier layers were loaded into a HATA multi-layer tablet press and pressed to form the trilayer tablets.

Film Coat (Formulations A and B)

The film coatings are applied at a target of 5% weight gain on a 563 mg tablet. Opadry® II film coating compositions were obtained from Colorcon, West Point, Pennsylvania. Four different coating compositions were used: 49B97383 Beige, 49B97382 Beige, 49B92439 Yellow, and 49B97379 Beige. All of the film coat compositions contain polydextrose FCC, HPMC 2910/hypromellose 3cP, HPMC 2910/hypromellose 6cP, titanium dioxide, HPMC 2910/hypromellose 15cP, macrogol/PEG, iron oxide yellow, and carnauba wax. The coating compositions vary in the presence or absence of iron oxide black, iron oxide red, and FD&C yellow #5/Tartrazine Aluminum Lake. The tablets were coated as directed by the manufacturer.

Enteric Coating (Formulation C)

1. Potassium hydroxide was dissolved in purified water with agitation to form a 1N solution.

2. Methacrylic acid copolymer type B (Eudragit S100) was added slowly to a vortex of purified water and mixed until dissolved.

3. The 1N potassium hydroxide solution of step 1 was added to the solution of step 2 and the mixture was stirred gently.

4. Triethyl citrate was added to the solution of step 3 and stirred until the mixture was homogeneous.

5. Steps 1-4 were repeated using methacrylic acid copolymer type A (Eudragit L100) to form a homogeneous mixture.

6. The solution of step 4 was added to a mixing vessel and stirred slowly. The solution of step 5 was added to the vessel and the mixture was stirred for the required period of time.

7. The tablets of Formulation C were coated with the coating layer using a Glatt pan coater.

Example 2. Relative Bioavailability Study of Nisoldipine 40 mg Extended Release Tablets Under Fasting Conditions

The pharmacokinetic parameters of formulations A-C described in Example 1 were compared to those of a reference formulation (Formulation D). The reference formulation was SULAR® Nisoldipine Extended Release (40 mg). SULAR® is a coat-core formulation consisting of a core containing Nisoldipine, coated with an immediate release coating which also contains Nisoldipine. The components of SULAR®, and their concentrations, are given in Table 4.

The objective of this single-dose, open-label, randomized study was to compare, under fasting conditions, the rate of absorption and oral bioavailability of a test formulation of nisoldipine 40 mg extended-release tablets described in Example 1 to an equivalent oral dose of the commercially available reference product, Sular® 40 mg extended-release tablets, when administered to healthy subjects.

Table 4. Composition of SULAR® (Formulation D)

Ingredient	Coat (mg/tab)	Core (mg/tab)	Film Coat (mg/tab)	Total (mg/tab)	Weight % (of the tablet)
Nisoldipine	32.0	8.0		40.0	12.27
Crospovidone, NF		5.0		5.0	1.53
Lactose Monohydrate, NF	87.5	4.0		91.5	28.07
Magnesium Stearate, NF	1.0	0.2		1.2	0.37
Corn Starch, NF		10.0		10.0	3.07
Microcrystalline Cellulose, NF		17.2		17.2	5.28
Povidone, USP		1.8		1.8	0.55
Sodium lauryl sulfate, NF		0.8		0.8	0.25
Hydroxypropyl-cellulose, medium viscosity, NF	84.5			84.5	25.92
Hydroxypropyl-cellulose, low viscosity, NF	63.0			63.0	19.33
Hypromellose, USP			6.6	6.6	2.02
Ferric Oxide, NF (red)			0.11	0.11	0.03
Ferric Oxide, NF (yellow)			0.99	0.99	0.30
Macrogol, NF			2.2	2.2	0.67
Titanium Dioxide, USP			1.1	1.1	0.34
Totals	268.0	47.0	11.0	326.00	100.00

Thirty-two healthy adults participated in the comparison of the three formulations of nisoldipine 40 mg tablets described in Example 1 versus SULAR®. 31 subjects completed the study. Subjects received the assigned treatment during the first period and received the alternate treatment during the subsequent periods according to the randomization scheme. Dosing days were separated by a washout period of at least 7 days. An equal number of subjects were randomly assigned to each possible sequence of treatments. Drug administration consisted of an oral dose of the formulations described in Example 1 and SULAR® under fasting conditions.

Blood samples were drawn prior to dosing (pre-dose) at 1, 1.5, 2, 3, 4, 6, 7.5, 9, 10.5, 12, 14, 16, 18, 20, 21, 23, 24, 26, 28, 30, 36, and 48 hours post-dose.

Plasma samples were analyzed by CEDRA Corporation using a validated LC-MS-MS procedure with a lower limit of quantification of 0.0150 ng/mL for nisoldipine. Data were stored in the Watson LIMS System (Thermo Electron Corporation Version 6.4.0.02).

Data from all subjects who completed the study were to be included in the pharmacokinetic and statistical analyses. The concentration-time data were transferred from Watson directly to WinNonlin (Enterprise Version 4.0, Pharsight, Cary, NC) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were BLQ (< 0.0150 ng/mL) were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Full precision concentration data were used for all pharmacokinetic and statistical analyses.

The following pharmacokinetic parameters were calculated for each subject and period: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last

quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}), and are shown in Table 5. Formulation A was chosen for further testing.

A comparison of the pharmacokinetic parameters for Formulation A and the reference formulation (Formulation D) are shown in Table 6. Table 7 shows the statistical analysis of the non-transformed pharmacokinetic parameters of nisoldipine after Formulation A and the reference product (Formulation D).

Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the difference between the means of the test product and the reference product was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80%-125%.

Table 5. Pharmacokinetic Parameters of Nisoldipine After Oral Administration

Parameter	Treatment A: Test Formulation A				Treatment B: Test Formulation B				Treatment C: Test Formulation C				Treatment D: Reference Product			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	31	9.42	5.57	59.16	31	16.44	9.49	57.71	31	20.57	9.47	46.05	32	8.12	7.34	90.47
T_{lag} (hr)	31	0.03	0.18	556.78	31	3.31	4.03	122.00	31	0.00	0.00	NC	32	0.13	0.71	565.69
C_{max} (ng/mL)	31	4.03	2.51	62.22	31	2.83	1.13	39.96	31	2.75	1.47	53.54	32	3.49	1.52	43.42
AUC_{last} (hr*ng/mL)	31	62.61	24.53	39.18	31	48.92	24.65	50.39	31	51.86	30.68	59.16	32	53.46	23.26	43.51
AUC_{inf} (hr*ng/mL)	29	72.84	30.97	42.52	26	61.28	34.27	55.93	25	56.11	36.51	65.07	30	68.21	43.33	63.52
AUC_{Extrap} (%)	29	12.17	11.27	92.55	26	12.64	13.45	106.43	25	11.94	14.26	119.38	30	14.00	15.84	113.11
λ_z (hr^{-1})	29	0.0600	0.0247	41.06	26	0.0691	0.0337	48.78	25	0.0739	0.0299	40.53	30	0.0580	0.0238	41.02
$T_{1/2}$ (hr)	29	14.23	8.83	62.01	26	12.92	8.89	68.83	25	12.78	11.20	87.63	30	17.57	18.77	106.82
T_{last} (hr)	31	48.07	0.26	0.54	31	48.04	0.06	0.12	31	47.09	3.84	8.16	32	48.03	0.08	0.17
C_{last} (ng/mL)	31	0.470	0.370	78.77	31	0.491	0.441	89.67	31	0.532	0.533	100.15	32	0.441	0.408	92.39
MRT (hr)	29	25.40	12.19	47.98	26	28.45	13.68	48.08	25	27.89	16.00	57.37	30	28.61	24.66	86.18

Table 6. Pharmacokinetic Parameters of Nisoldipine After Oral Administration

Parameter	Treatment A: Test Formulation #1				Treatment D: Reference Product			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	31	9.42	5.57	59.16	32	8.12	7.34	90.47
T_{lag} (hr)	31	0.03	0.18	556.78	32	0.13	0.71	565.69
C_{max} (ng/mL)	31	4.03	2.51	62.22	32	3.49	1.52	43.42
AUC_{last} (hr*ng/mL)	31	62.61	24.53	39.18	32	53.46	23.26	43.51
AUC_{inf} (hr*ng/mL)	29	72.84	30.97	42.52	30	68.21	43.33	63.52
AUC_{Extrap} (%)	29	12.17	11.27	92.55	30	14.00	15.84	113.11
λ_z (hr^{-1})	29	0.0600	0.0247	41.06	30	0.0580	0.0238	41.02
$T_{1/2}$ (hr)	29	14.23	8.83	62.01	30	17.57	18.77	106.82
T_{last} (hr)	31	48.07	0.26	0.54	32	48.03	0.08	0.17
C_{last} (ng/mL)	31	0.470	0.370	78.77	32	0.441	0.408	92.39
MRT (hr)	29	25.40	12.19	47.98	30	28.61	24.66	86.18

Table 7. Statistical Analysis of the Non-Transformed Pharmacokinetic Parameters of Nisoldipine After Formulation A and the Reference Product

Dependent	Least Squares Mean		Ratio (%)	90% Confidence Interval		Power
Variable	Test	Reference	(Test/Reference)	Lower	Upper	
C_{max}	4.0176	3.4943	114.98	96.07	133.89	0.5385
AUC_{last}	62.1910	53.4555	116.34	102.23	130.46	0.7550
AUC_{inf}	67.0708	63.9262	104.92	80.56	129.28	0.3847
T_{max}	9.3247	8.1156	114.90	77.51	152.29	0.2270
T_{lag}	0.0252	0.1250	20.19	-659.85	700.23	0.1004
λ_z	0.0651	0.0644	100.99	83.73	118.25	0.6044
$T_{1/2}$	11.9103	14.3679	82.90	55.16	110.63	0.3241
MRT	22.5857	24.0788	93.80	70.83	116.77	0.4161

Table 8: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Nisoldipine after Test Formulation #1 and Reference Product

Dependent Variable	LS Mean[a]		Geometric Mean[b]		Ratio (%)[c]	90% CI[d]		Power	ANOVA
	Test	Ref	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	1.2424	1.1624	3.4639	3.1975	108.33	90.47	129.72	0.6537	44.97
$\ln(AUC_{last})$	4.0571	3.8763	57.8035	48.2441	119.81	100.89	142.29	0.6894	42.68
$\ln(AUC_{inf})$	4.1247	3.9602	61.8507	52.4682	117.88	90.92	152.85	0.4087	54.05

[a] Least Squares Mean for the Test Formulation #1 (Test) and Reference Product (Ref)

[b] Geometric Mean based on LS Mean of log-transformed parameter values

[c] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[d] 90% Confidence Interval

Note: Statistical analysis based n = 31 for C_{max}, AUC_{last} and n = 21 for AUC_{inf}

Example 3. Relative Bioavailability study of Nisoldipine 40 mg Extended Release Tablets Under Fed Conditions

The objective of this study was to compare the food effect of the Formulation A described in Example versus the food effect of the Sular® market formulation. To determine the food effects for Formulation A and Sular, the pharmacokinetic data for these two formulations from Example 2 under fasting conditions were used as a reference. The same 32 subjects from Example 2 were enrolled in the food effect study.

Twenty-six (26) subjects completed the study. In the first period, subjects received the assigned treatment and received the alternate treatment during the subsequent period according to the randomization scheme. Dosing days were separated by a washout period of at least 7 days. An equal number of subjects were randomly assigned to each possible sequence of treatments. Blood samples were taken and analyzed as described in Example 2. Table 9 shows pharmacokinetic data for Formulation A (Treatment E) and

the reference formulation (Sular, 40 mg extended-release) under fed conditions. Table 10 shows analysis of the non-transformed pharmacokinetic parameters of nisoldipine after test formulation A (Treatment E) and reference product (Treatment F) under fed conditions. Table 11 shows statistical analysis of the log-transformed systemic parameters of nisoldipine after test formulation A (Treatment E) and the reference product (Treatment F) under fed conditions.

Table 9. Statistical Analysis of the Non-Transformed Pharmacokinetic Parameters of Nisoldipine after Test Formulation #1 (Treatment E) and Reference Product (Treatment F) under Fed Conditions

Dependent	Least Squares Mean		Ratio (%)	90% Confidence Interval		Power
Variable	Test	Reference	(Test/Reference)	Lower	Upper	
C_{max}	9.0795	10.1485	89.47	63.66	115.27	0.3547
AUC_{last}	46.7358	49.9013	93.66	77.56	109.75	0.6596
AUC_{inf}	48.9166	52.8817	92.50	77.06	107.95	0.6910
T_{max}	6.1372	6.2904	97.56	81.34	113.79	0.6534
T_{lag}	0.0769	0.1154	66.67	-65.04	198.37	0.1101
λ_z	0.0547	0.0539	101.32	91.40	111.25	0.9523
$T_{1/2}$	13.2983	14.6139	91.00	75.23	106.76	0.6754
MRT	13.6435	16.3926	83.23	67.60	98.85	0.6822

Table 10. Statistical Analysis of the Non-Transformed Pharmacokinetic Parameters of Nisoldipine after Test Formulation A (Treatment E) and Reference Product (Treatment F) under Fed Conditions

Dependent	Least Squares Mean		Ratio (%)	90% Confidence Interval		Power
Variable	Treatment E	Treatment F	(E/F)	Lower	Upper	
C_{max}	9.0795	10.1485	89.47	63.66	115.27	0.3547
AUC_{last}	46.7358	49.9013	93.66	77.56	109.75	0.6596
AUC_{inf}	48.9166	52.8817	92.50	77.06	107.95	0.6910
T_{max}	6.1372	6.2904	97.56	81.34	113.79	0.6534
T_{lag}	0.0769	0.1154	66.67	-65.04	198.37	0.1101
λ_z	0.0547	0.0539	101.32	91.40	111.25	0.9523
$T_{1/2}$	13.2983	14.6139	91.00	75.23	106.76	0.6754
MRT	13.6435	16.3926	83.23	67.60	98.85	0.6822

Table 11: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Nisoldipine after Test Formulation #1 (Treatment E) and the Reference Product (Treatment F) under Fed Conditions

Dependent Variable	LS Mean[a]		Geometric Mean[b]		Ratio (%)[c]	90% CI[d]		Power	ANOVA
	Treatment E	Treatment F	Treatment E	Treatment F	(E/F)	Lower	Upper		CV%
$\ln(C_{max})$	2.1192	2.0365	8.3246	7.6641	108.62	87.54	134.78	0.5239	47.94
$\ln(AUC_{last})$	3.7901	3.7689	44.2614	43.3308	102.15	90.67	115.08	0.9256	25.53
$\ln(AUC_{inf})$	3.8330	3.8390	46.2024	46.4782	99.41	88.59	111.55	0.9389	24.65

Example 4. Trilayer Tablets Containing a Nisoldipine Core and Two Barrier Layers

Table 5 shows that the AUC_{last} for formulation A is approximately 17% higher than the AUC_{last} for the reference formulation having the same dosage of nisoldipine. This suggests that the dose of nisoldipine in formulation A can be reduced by approximately 16% and still exhibit a pharmacokinetic profile similar to the reference formulation.

Formulations containing 8.5, 17, 25.5, and 34 mg of Nisoldipine in the core were prepared based on the procedures described in Example 1. These dosages represent approximately 16% less than 10 mg, 20 mg, 30 mg, and 40 mg, respectively. The components of each formulation, and their concentrations, are shown in Tables 10-13.

Table 12. Nisoldipine Multilayer Tablet Formulations

	8.5 mg		17 mg		25.5 mg		34 mg	
04B4 barrier	Prototype B		Prototype A					
Ingredients	mg/tab	%	mg/tab	%	mg/tab	%	mg/tab	%
Methocel E5	17.50	25.00	25.00	25.00	37.50	25.00	37.50	25.00
HPMC Phthalate HP50	9.28	13.25	13.25	13.25	19.88	13.25	19.88	13.25
Lactose pulvis H2O	26.85	38.35	38.35	38.35	57.53	38.35	57.53	38.35
Compritol 888 ATO	12.88	18.40	18.40	18.40	27.60	18.40	27.60	18.40
Plasdone K29-32	2.45	3.50	3.50	3.50	5.25	3.50	5.25	3.50
Mg stearate	0.70	1.00	1.00	1.00	1.50	1.00	1.50	1.00
Aerosil 200	0.35	0.50	0.50	0.50	0.75	0.50	0.75	0.50
Total	70.00	100.00	100.00	100.00	150.00	100.00	150.00	100.00
Core (Active Layer)								
Ingredients	mg/tab	%	mg/tab	%	mg/tab	%	mg/tab	%
Nisoldipine	8.50	12.07	17.00	12.07	25.50	11.97	34.00	15.96
Lactose H2O	14.44	20.51	52.44	37.24	76.02	35.69	48.00	22.54
Methocel K4M	27.18	38.61	30.80	21.88	42.60	20.00	51.50	24.18
Eudragit S100	5.35	7.60	10.70	7.60	21.40	10.05	21.40	10.05
Plasdone	2.68	3.80	5.35	3.80	10.70	5.02	10.70	5.02
Sodium Lauryl Sulfate	10.63	15.09	21.25	15.09	31.88	14.97	42.50	19.95
Magnesium stearate	1.26	1.78	2.51	1.78	3.80	1.78	3.80	1.78
Aerosil 200	0.38	0.53	0.75	0.53	1.10	0.52	1.10	0.52
Total	70.40	100.00	140.80	100.00	213.00	100.00	213.00	100.00
01B4 barrier								
Ingredients	mg/tab	%	mg/tab	%	mg/tab	%	mg/tab	%
Methocel E50	22.50	25.00	25.00	25.00	50.00	25.00	50.00	25.00
HPMC Phthalate HP50	11.93	13.25	13.25	13.25	26.50	13.25	26.50	13.25
Lactose pulvis H2O	34.52	38.35	38.35	38.35	76.70	38.35	76.70	38.35
Compritol 888 ATO	16.56	18.40	18.40	18.40	36.80	18.40	36.80	18.40
Plasdone K29-32	3.15	3.50	3.50	3.50	7.00	3.50	7.00	3.50
Mg stearate	0.90	1.00	1.00	1.00	2.00	1.00	2.00	1.00
Aerosil 200	0.45	0.50	0.50	0.50	1.00	0.50	1.00	0.50
Total	90.00	100.00	100.00	100.00	200.00	100.00	200.00	100.00

Total tablet weight, uncoated	230.40		340.80		563.00		563.00	
	mg/ tablet	% wt gain	mg/ tablet	% wt gain	mg/ tablet	% wt gain	mg/ tablet	% wt gain
Opadry II Beige, 49B97383	11.52	5.00	--	--	--	--	--	--
Opadry II Yellow, 49B92439	--	--	7.04	5.00	--	--	--	--
Opadry II Beige, 49B97382	--	--	--	--	28.15	5.00	--	--
Opadry II Beige, 49B97379	--	--	--	--	--	--	28.15	5.00
Total tablet weight, coated	241.92	--	347.84	--	591.15	--	591.15	--
	mg/ tablet		mg/ tablet		mg/ tablet		mg/ tablet	
Opacode Black (S-1-27794)	0.20		0.20		0.33		0.33	
Total tablet weight, coated, imprinted	242.12		348.04		591.48		591.48	

Example 5. Bioequivalence of Lower Dose Sular® Geomatrix (34 mg nisoldipine) with Sular® (40 mg nisoldipine)

The bioequivalence of 34 mg nisoldipine Sular® Geomatrix® (i.e., Geomatrix) with 40 mg nisoldipine Sular® was confirmed with a single-dose, open-label, randomized, four-period, two-treatment, two-sequence replicate design crossover study. The study compared the rate of absorption and oral bioavailability of a test formulation, Geomatrix® 16-E, 34 mg tablets (Treatment E) versus that of the reference product, Sular® 40 mg tablets (Treatment F) following an overnight fast of at least 10 hours.

Study Design

This was a pivotal, single-dose, open-label, randomized, four-period, two-treatment, two-sequence replicate-design crossover study in which fifty-two (52) healthy adult subjects were scheduled to receive four separate single-dose administrations of nisoldipine extended-release tablets in four study periods following an overnight fast of at least 10 hours. Attempts were made to enroll an equal number of male and female subjects. Subjects who

successfully completed the screening process checked into the research center the night before dosing. Subjects who continued to meet inclusion/exclusion criteria the morning of dose were assigned a subject number, based on the order in which they successfully completed the screening process and procedures as outlined in the study protocol. Dosing days were separated by a washout period of at least 7 days.

Subjects received each of the treatments listed below twice in a 2-sequence randomized fashion during the four treatment periods. Test product "Treatment E" is Geomatrix® 16-E nisoldipine extended-release tablet administered in one 34 mg tablet. Reference product "Treatment F" is Sular® extended-release tablet administered in one 40 mg tablet.

Clinical Procedures Summary

During each study period, 6 mL blood samples were obtained prior to each dosing and following each dose at selected times through 36 hours post-dose. Two 6 mL blood samples were obtained at 48, 60, and 72 hours post-dose. A total of 96 PK blood samples were to be collected from each subject, 24 samples in each of four separate study periods.

In addition, blood was drawn and urine was collected for clinical laboratory testing (blood chemistries, hematology and urinalysis) at screening, baseline (Period 1 check-in), and at end-of-study discharge (72-hour procedures at Period 4). In addition, blood was drawn at check-in the evening before dosing in each of Periods 2, 3, and 4 for hematocrit and hemoglobin evaluations, which were reviewed by the Investigator prior to dosing in each of the three periods. Forty-nine (49) of the 52 subjects enrolled completed at least two periods of the study.

Procedures for Collecting Samples for Pharmacokinetic Analysis

Blood samples (1 x 6 mL, 2 x 6 mL) were collected in vacutainer tubes containing K_2-EDTA as a preservative at pre-dose (0) and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, 9.0, 10.5, 12.0, 14.0, 18.0, 24.0, 26.0, 28.0, 30.0, 36.0, 48.0, 60.0, and 72.0 hours after dosing during each study period.

Bioanalytical Summary

Plasma samples were analyzed for nisoldipine by CEDRA Corporation using validated LC-MS-MS procedures. The methods were validated for ranges of 0.0150 to 10.0 ng/mL and 1.00 to 100 pg/mL, based on the analysis of 0.250 mL and 1.00 mL of plasma, respectively.

Pharmacokinetic Analysis

Data from 49 subjects who successfully completed at least two study periods (one test, one reference) without protocol violation were included in the pharmacokinetic and statistical analyses. Three subjects did not complete the study; samples from these subjects were not analyzed. Two subjects experienced emesis during the study; these subjects were determined to be not evaluable for the period(s) in which emesis occurred during this comparative study of extended-release nisoldipine formulations. Although concentration-time data were acquired and retained in the data listing, data for one subject in Period 2 (Treatment E) and one subject in Period 4 (Treatment E) were excluded from the pharmacokinetic analysis set.

Concentration-time data were transferred from Watson LIMS directly to WinNonlin Enterprise Edition (Version 4.0, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing." Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses.

The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable

concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}).

Analysis of a linear mixed effect and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

Results

Plasma concentration-time data and pharmacokinetic parameters were summarized by treatment. Since subjects were scheduled to receive each treatment on two occasions, descriptive statistics by treatment are based on 93 to 95 observations. Quantifiable pre-dose concentrations were observed for some subjects. However, since the pre-dose concentrations were well below 5% of C_{max} for these subjects after a given treatment, the pre-dose concentrations were included in all pharmacokinetic analyses without adjustment.

The pharmacokinetic data and statistical analyses are shown below in Table 13 and Table 14. Due to the presence of secondary peaks and variability in the terminal phase of some individual profiles, lambda-z (λ_z) was estimated via linear regression of log concentration versus time data in WinNonlin. The data points that were included in the calculation were based on the regression with the largest adjusted R^2 value. This default estimation of λ_z was used throughout this study for all pharmacokinetic analyses.

Conclusions

The 90% confidence interval for comparing the maximum exposure, based on $\ln(C_{max})$, is within the accepted 80% to 125% limits. The 90% confidence intervals for comparing total systemic exposure, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, are within the accepted 80% to 125% limits. Therefore, the test formulation of Geomatrix® 16-E, 34 mg tablets is

bioequivalent to the reference product, Sular® 40 mg tablets, under fasting conditions.

Table 13: Pharmacokinetic Parameters of Nisoldipine after Administration of Test Formulation 16-E (Geomatrix, Treatment E) and the Reference Product (Sular, Treatment F)

Parameter	Treatment E: Test Formulation 16-E (Geomatrix)				Treatment F: Reference Product (Sular)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	93	9.22	5.13	55.61	95	8.49	7.79	91.84
C_{max} (ng/mL)	93	3.79	3.56	93.97	95	3.58	3.05	85.08
AUC_{last} (hr*ng/mL)	93	62.35	69.30	111.15	95	60.10	31.52	52.45
AUC_{inf} (hr*ng/mL)	93	65.24	74.67	114.46	95	65.45	36.41	55.63
AUC_{Extrap} (%)	93	3.84	3.41	88.68	95	6.43	8.77	136.33
λ_z (hr^{-1})	93	0.0554	0.0163	29.38	95	0.0527	0.0205	38.91
$T_{1/2}$ (hr)	93	13.68	4.25	31.05	95	17.08	13.74	80.49
T_{last} (hr)	93	72.00	0.00	0.00	95	72.00	0.01	0.01
C_{last} (ng/mL)	93	0.126	0.239	190.21	95	0.148	0.166	111.91

Note: Full precision data used in pharmacokinetic analysis

Table 14: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Nisoldipine Comparing Test Formulation 16-E (Geomatrix, Treatment E) to the Reference Product (Sular, Treatment F)

Dependent	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power
Variable	Test	Ref	(Test/Ref)	Lower	Upper	
$\ln(C_{max})$	3.0723	2.9941	102.61	93.61	112.47	0.9899
$\ln(AUC_{last})$	50.7356	54.6492	92.84	87.77	98.20	1.0000
$\ln(AUC_{inf})$	52.7416	58.7395	89.79	84.37	95.56	1.0000

[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

Figure 2 shows the mean nisoldipine concentration time profiles after administration of test formulation 16-E (Sular Geomatrix-Formulation E, 34 mg nisoldipine) and the referenced product (Sular, Formulation F, 40 mg nisoldipine).

Example 6. Bioequivalence of Lower Dose Sular Geomatrix (8.5 mg nisoldipine) with Sular (10 mg nisoldipine)

The bioequivalence of 8.5 mg nisoldipine Sular® Geomatrix® with 10 mg nisoldipine Sular® was confirmed with a single-dose, open label, randomized, four period, two-treatment, two-sequence replicate design crossover study. The study compared the rate of absorption and oral bioavailability of a test formulation, Geomatrix® 16-E, 8.5 mg nisoldipine tablets (Treatment G) versus that of the reference product, Sular® 10 mg nisoldipine tablets (Treatment H) following an overnight fast of at least 10 hours.

This was a pivotal, single-dose, open-label, randomized, four-period, two-treatment, two-sequence replicate-design crossover study in which fifty-two (52) healthy adult subjects were scheduled to receive four separate single-dose administrations of nisoldipine extended-release tablets in four study periods following an overnight fast of at least 10 hours. Attempts were made to enroll an equal number of male and female subjects. Subjects who continued to meet inclusion/exclusion criteria the morning of dose were assigned a subject number, based on the order in which they successfully completed the screening process and procedures as outlined in the study protocol. Dosing days were separated by a washout period of at least 7 days.

Subjects received each of the treatments listed below twice in a 2-sequence randomized fashion during the four treatment periods. Test product "Treatment G" is Geomatrix® nisoldipine extended-release tablet administered in one 8.5 mg tablet. Reference product "Treatment H" is Sular® extended-release tablet administered in one 10 mg tablet.

Clinical Procedures Summary

During each study period, one 6 mL blood sample was obtained within 60 minutes prior to each dose administration and following each dose at selected times through 36 hours post-dose. Two 6 mL blood samples were obtained at 48, 60, and 72 hours post-dose. A total of 96 PK blood samples were to be collected from each subject, 24 samples in each of four separate

study periods. Forty-Nine (49) of the 52 subjects enrolled completed at least two periods of the study.

Procedures for Collecting Samples for Pharmacokinetic Analysis

Blood samples (1 x 6 mL, 2 x 6 mL) were collected in vacutainer tubes containing K_2-EDTA as a preservative at pre-dose (0) and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, 9.0, 10.5, 12.0, 14.0, 18.0, 24.0, 26.0, 28.0, 30.0, 36.0, 48.0, 60.0, and 72.0 hours after dosing during each study period.

Bioanalytical Summary

Plasma samples were analyzed for nisoldipine by CEDRA Corporation using validated LC-MS-MS procedures. The methods were validated for ranges of 0.0150 to 10.0 ng/mL and 1.00 to 100 pg/mL, based on the analysis of 0.250 mL and 1.00 mL of plasma, respectively.

Pharmacokinetic Analysis

Data from 49 subjects who successfully completed at least the first two or at least the last two periods of the study (one test, one reference) without protocol violation were included in the pharmacokinetic and statistical analyses. Subject 501 experienced emesis in one study period. Although concentration-time data were acquired and retained in the data listing, this subject was determined to be not evaluable for all study periods and was excluded from the pharmacokinetic data set for the period(s) in which emesis occurred.

Concentration-time data were transferred from Watson LIMS directly to WinNonlin Enterprise Edition (Version 4.0, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing." Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses.

The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}).

Linear mixed-effects model procedures and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

Results

Plasma concentration-time data and pharmacokinetic parameters were summarized by treatment. Since subjects were scheduled to receive each treatment on two occasions, descriptive statistics by treatment are based on 96 or 94 observations. Mean concentration-time data are shown in Figure 3. Results of the pharmacokinetic and statistical analyses are shown below in Table 15 and Table 16.

Conclusions

The 90% confidence interval for comparing the maximum exposure, based on $\ln(C_{max})$, is within the accepted 80% to 125% limits. The 90% confidence intervals for comparing total systemic exposure, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, are within the accepted 80% to 125% limits. Therefore, the test formulation, Geomatrix 8.5 mg tablets, is bioequivalent to the reference product, Sular extended-release 10 mg tablets, under fasting conditions.

Table 15: Pharmacokinetic Parameters of Nisoldipine after Administration of Test Formulation 16-E (Geomatrix, Treatment A) and the Reference Product (Sular, Treatment B)

Parameter	Treatment G: Test Formulation 2B (Geomatrix)				Treatment H: Reference Product (Sular)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	96	8.59	4.07	47.39	94	7.35	4.12	56.04
C_{max} (ng/mL)	96	0.858	0.844	98.42	94	0.971	0.854	87.92
AUC_{last} (hr*ng/mL)	96	13.29	9.135	68.74	94	14.54	9.864	67.81
AUC_{inf} (hr*ng/mL)	96	13.80	9.435	68.37	94	15.28	10.43	68.25
AUC_{Extrap} (%)	96	3.77	3.31	87.74	94	4.46	5.69	127.74
λ_z (hr^{-1})	96	0.0530	0.0162	30.60	94	0.0494	0.0171	34.68
$T_{1/2}$ (hr)	96	14.46	4.89	33.85	94	16.53	8.54	51.67
T_{last} (hr)	96	72.00	0.00	0.00	94	72.00	0.01	0.01
C_{last} (ng/mL)	96	0.0223	0.0209	93.78	94	0.0247	0.0246	99.66

Table 16: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Nisoldipine Comparing Test Formulation 16-E (Geomatrix, Treatment A) to the Reference Product (Sular, Treatment B)

Dependent	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power
Variable	Test	Ref	(Test/Ref)	Lower	Upper	
$\ln(C_{max})$	0.7013	0.7942	88.30	81.68	95.46	0.9985
$\ln(AUC_{last})$	11.5097	12.5263	91.88	86.66	97.42	1.0000
$\ln(AUC_{inf})$	11.9760	13.1365	91.17	85.93	96.72	1.0000

It is understood that the disclosed methods are not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs.

CLAIMS

1. A multilayer controlled release solid oral dosage formulation comprising

(a) a core comprising one or more active agents and one or more enteric materials;

(b) two or more barrier layers, one above the core and one below the core comprising one or more swellable, erodible, or gellable polymers; and

wherein, upon administration to a subject, the active agent is released with an ascending release rate in response to the changes in pH as the dosage formulation descends the GI tract.

2. The formulation of claim 1, wherein the one or more active agents is selected from the group consisting of hypnotics, sedatives, tranquilizers, anti-convulsants, musclerelaxants, analgesics, anti-inflammatory, anesthetics, anti-spasmodics, anti-ulcer-agents, anti-parasitics, anti-microbials, anti-fungal, cardiovascular agents, diuretics, cytostatics, anti-neoplastic agents, anti-viral agents, anti-glaucoma agents, anti-depressants, sympathomimetics, hypoglycaemics, diagnostic agents, anti-cough, physic energizers, anti-parkinson agents, local anesthetics, muscle contractants, anti-malarials, hormonal agents, contraceptives, anorexic, anti-arthritic, anti-diabetic, anti-hypertensive, anti-pyretic, anti-cholingergic, bronchodilator, central nervous system, inotropic, vasodilator, vasoconstrictor, decongestant, hematinic, electrolyte supplement, germicidal, parasympathetolytic, parasymphatethomimetic, antiemetic, psychostimulant, vitamin, beta-blockers, H-2 blocker, beta-2 agonist, counterirritants, coagulating modifying agents, stimulants, anti-hormones, drug-antagonists, lipid-regulating agents, uricosurics, cardiac glycosides, ergot and derivatives thereof, expectorants, muscle relaxants, anti-histamines, purgatives, contrast materials, radiopharmaceuticals, imaging agents, anti-allergic agents, and combinations thereof.

3. The formulation of claim 1 or claim 2, wherein the concentration of the one or more active agents is from about 0.1% to about 90% by weight of the composition or from about 0.5% to about 20% by weight of the composition, or from about 1% to about 10% by weight of the composition.

4. The formulation of any one of the preceding claims, wherein the one or more enteric materials is selected from the group consisting of cellulose acetate phthalate,

alginates, alkali-soluble acrylic resins, hydroxypropyl methylcellulose phthalate, methacrylate-methacrylic acid co-polymers, polyvinyl acetate phthalate, styrol maleic acid copolymers, and combinations thereof.

5. The formulation of any one of the preceding claims, wherein the concentration of the one or more enteric materials is from about 0.1% to about 20% by weight of the compositions or from about 1 to about 15% by weight of the composition, or from about 5 to about 10% by weight of the composition.

6. The formulation of any one of the preceding claims, wherein the core or central layer further comprises one or more non-enteric polymeric materials that modulate the release of the one or more active agents.

7. The formulation of claim 6, wherein the one or more non-enteric polymeric materials are selected from the group consisting of crosslinked polyvinylpyrrolidone, hydroxypropylmethylcellulose, hydroxypropylcellulose, crosslinked sodium carboxymethylcellulose, carboxymethyl starch, acrylic and methacrylic acid polymers and copolymers, polyesters, polyanhydrides, polymethylvinylether/anhydride copolymers, potassium methacrylate-divinylbenzene copolymer, polyvinylalcohols, glucan, scleroglucan, mannan, starch and derivatives thereof, betacyclodextrins, cyclodextrin derivatives containing linear and/or branched polymeric chains, and combinations thereof.

8. The formulation of claim 7, wherein the one or more polymeric materials that modulate the release of the one or more active agents are present in a concentration from about 1% to about 90% by weight of the core, or from about 10% to about 45% by weight of the core.

9. The formulation of any one of the preceding claims wherein the one or more active agents is a calcium channel blocker.

10. The formulation of any one of the preceding claims, wherein the one or more swellable, erodible, or gellable polymers are selected from the group consisting of hydroxypropylmethylcellulose, carboxyvinyl polymers; polyvinylalcohols; glucans,

scleroglucans; mannans; xantans; alginates and derivatives thereof; polyanhydrides; polyaminoacids; methylvinylether/maleic anhydride copolymers; carboxymethylcellulose and derivatives thereof; ethylcellulose, methylcellulose, and other cellulosic derivatives; and combinations thereof.

11. The formulation of any one of the preceding claims, wherein the concentration of the one or more swellable, erodible, and/or gellable polymers is from about 5% and to about 90% by weight of the barrier layer(s) or from about 25% and to about 75% by weight of the barrier layer(s).

12. The formulation of claim 11, wherein the polymer is hydroxypropylmethylcellulose.

13. The formulation of any one of the preceding claims, wherein the core and/or the barrier layer further comprise one or more excipients selected from the group consisting of plasticizers, diluents, binders, lubricants, surfactants, pH modifying agents, anti-adherents, disintegrators, fillers, pigments, colorants, stabilizing agents, flavoring agents, glidants, and combinations thereof.

14. The formulation of any one of the preceding claims, wherein the formulation is in the form of a tablet or caplet.

15. The formulation of any one of the preceding claims, wherein the central layer and/or the barrier layer further comprises one or more adjuvants that further modulate the release of the active agent selected from the group consisting of glyceryl monostearate, triglyceride derivatives, semi-synthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, cetyl alcohol, polyvinylpyrrolidone, glycerol, ethylcellulose, methylcellulose, sodium carboxymethylcellulose, magnesium stearate, stearic acid, talc, sodium benzoate, boric acid, polyoxyethylenglycols, colloidal silica, and combinations thereof.

16. The formulation of any one of the preceding claims, further comprising one or more coating materials which modulate release of the active agent.

17. The formulation of claim 16, wherein the one or more coating materials are selected from the group consisting of immediate release coatings, taste masking coatings, sustained released coatings, enteric coatings, delayed release coatings, and combinations thereof.

18. A method of treating a cardiovascular disorder, the method comprising administering to a patient in need thereof the formulation of any of claims 1 to 17.

19. Use of a formulation of any one of claims 1 to 17 in the manufacture of a medicament for treating a cardiovascular disease.

20. A multilayer controlled release solid oral dosage formulation; its use thereof or a method of treating a cardiovascular disease substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.