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(54) Title: CARDIOVASCULAR THERAPEUTIC COMBINATIONS

(57) Abstract: The invention describes new pharmaceutical compositions, their method of manufacture and use of these compositions to be administered as combination therapy for the treatment of cardiovascular and related disorders and cardiovascular disorders associated with hyperhomocysteinemia, in particular a combination of vitamins and folic acid with cholesterol lowering drugs or lipid regulators and antihypertensive agents viz. β -adrenergic blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and the like.



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CARDIOVASCULAR THERAPEUTIC COMBINATIONS

PARENT CASE TEXT

This application is a continuation of PCT application No. PCT/IB03/02949 filed 24th July 2003: the entire contents of the aforementioned application being incorporated herein by reference.

FIELD OF INVENTION

The present invention relates to new pharmaceutical compositions, their method of manufacture and use of these compositions to be administered as combination therapy for the treatment of cardiovascular disorders associated with hyperhomocysteinemia, in particular a combination of vitamins and folic acid with cholesterol lowering drugs or lipid regulators and antihypertensive agents viz. β -adrenergic blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and the like. The combination therapy can also be useful in lowering the risk of cardiovascular disorders alongwith controlling hyperhomocysteinemia.

BACKGROUND OF INVENTION

Heart failure is one of the most common causes of death and disability in industrialized nations and is among the syndrome most commonly encountered in clinical practice. The diagnosis of heart failure carries a risk of mortality comparable to that of the major malignancies. In the past twenty years, advances in understanding the pathophysiology of heart failure and new developments in pharmacotherapy have added substantially to the physician's ability to alleviate the symptoms of this disease and slow the natural progression of underlying myocardial progress.

A primary goal in the treatment of heart failure is the alleviation of symptoms, which, is a direct result of the underlying hemodynamic disorder.

Hypertension is the most common cardiovascular disease. Elevated arterial pressure causes pathological changes in the vasculature and hypertrophy of the left ventricle of heart. As a consequence, hypertension is the principal cause of the stroke, leads to disease of the coronary arteries with myocardial infarction and sudden cardiac death, and is a major contributor to cardiac failure, renal insufficiency. The risk of cardiovascular disease, disability and death in hypertensive patients is also increased markedly by elevated low density lipoprotein; the coexistence of hypertension with these risk factors increases cardiovascular morbidity.

The chief goal of antihypertensive therapy include preventing major cardiovascular disorders such as myocardial infarction, arrhythmia, angina and the like. Although controlling blood pressure and reducing other known cardiovascular risk factors are pivotal in achieving these goals, additional strategies and/or combination therapy are needed to provide optimal protection against cardiovascular disease.

Combination therapy involves multiple doses of multiple medications. The most obvious benefit of drug combinations is the enhanced efficacy which fosters its widespread use. Theoretically, some drug combinations might produce synergistic effects that are greater than that predicted by summing the efficacies of the component drugs. Also, some combinations produce offsetting interactions that weaken side effects of therapy with single drug. Another benefit of the combination therapy concerns avoidance of adverse effects. In general, the rationale of the combination therapy has advantages such as (1) increased efficacy i.e. additive and synergistic effects, (2) reduced adverse events i.e. low dose strategy, drugs with offsetting actions, (3) enhanced convenience and compliance, (4) prolong duration of action and the like.

Homocystinuria is a rare autosomal recessive genetic disorder that usually results from defective activity of cystathionine beta-synthase. Homocystinuria is associated with a syndrome of mental retardation, skeletal and visual problems and arterial as well as venous thrombosis. There are two primary enzymes that, when a defect is present, can result in either homocystinuria or hyperhomocysteinemia as discussed below.

Homocysteine is a sulfur containing amino acid; it is a naturally occurring molecule in the body and is required in several reactions that occur within the cells that comprise the human body. It gets rapidly oxidized in plasma to the disulfides homocysteine and cysteine-homocysteine. This then metabolizes into three components namely, methionine, cystathionine, cysteine, which can be further used by the body. If the pathways to either cysteine or methionine are blocked, then homocysteine levels may rise.

Three enzymes are associated with elevated levels of homocysteine. These enzymes are methylenetetrahydrofolate reductase (MTHFR), cystathionine beta-synthase (CBS) and methionine synthase (MS).

Methionine synthase (MS) requires vitamin B12 (methylcobalamin) in order to carry out its reaction. If a patient does not have an adequate supply of vitamin B12, then homocysteine is not converted to methionine and the net result is an increase in homocysteine. Methylenetetrahydrofolate reductase (MTHFR) is required to form 5-methyl tetrahydrofolate. This is required in order to convert homocysteine to methionine. If this cannot be formed, then homocysteine levels will increase. The final enzyme associated with elevated homocysteine levels is CBS; this is required in order to convert homocysteine to cysteine. If this enzyme is not present, then homocysteine levels will increase.

Vitamin B12, the imperative cofactor in the transmethylation pathway needs to be converted to its active form, methylcobalamin for action. Deficiency of this vitamin even in the presence of normal enzyme levels of methionine synthase has been found to lead to hyperhomocysteinemia, as it acts as a co-factor for the enzyme methionine synthase. Upto 73% of the serum B12 is in the active methylcobalamin form. Methylcobalamin reaches a maximum concentration of 972 pg/ml in 3.5 hours and has a half-life of 12.5 hours.

Folic acid is a vitamin that occurs as folate in diet in various oxidation states, which is then converted in the body into active 'coenzyme' tetrahydrofolate (THF). This bioactivated reduced state acts as a source of one carbon group (methyl) required for the synthesis of

methionine from homocysteine. Deficiency of folic acid increases plasma homocysteine level by blocking the methyl source for methionine synthesis.

Pyridoxine in its active form, pyridoxal 5' -phosphate is a co-factor for enzyme cystathione beta-synthase for two successive reactions in the trans-sulfuration pathway of homocysteine to cystathione and cysteine. Vitamin B₆ deficiency (dietary) or increased requirements (in renal failure) may predispose to hyperhomocysteinemia even with normal enzyme levels.

Thus, the metabolic pathway of homocysteine involves vitamins, coenzymes and substrates including vitamin B₆, folic acid and vitamin B₁₂. Methionine in turn gets converted to homocysteine via demethylation. The tetrahydrofolate substrate required for the methionine/homocysteine metabolism is obtained from folic acid. Thus folic acid, vitamin B₆, B₂ and B₁₂ are all important constituents of this cycle. Administration of folic acid and vitamins thus lowers and regulates the homocysteine levels in the plasma without apparent toxicity.

Yet, deficiency of one or more vitamins is seen in nearly two-thirds of the patients with hyperhomocysteinemia. The three vitamins (vitamin B₁₂, folic acid and vitamin B₆) play an imperative role in the two major pathways; transmethylation and trans-sulfuration involved in the synthesis of methionine and cysteine from homocysteine, as discussed. Meta-analysis of various trials has shown folic acid alone to reduce plasma homocysteine levels by 25%. Folic acid with vitamin B₁₂ (methylcobalamin) in the same studies further reduced plasma homocysteine levels by another 7%. Use of folic acid alone has a disadvantage that it may mask underlying vitamin B₁₂ deficiency leading to macrocytic anaemia/ subacute combined degeneration of the spinal cord. High levels of folic acid may also cause central and peripheral nervous system damage. Methylcobalamin is preferred over vitamin B₁₂ since it is the biologically active form of the vitamin and has higher absorption. Vitamin B₁₂ requires conversion to methylcobalamin on absorption. Also there is increased utilization and tissue retention of methylcobalamin thereby reducing the plasma homocysteine to a greater extent. Although no studies of only vitamin B₆ supplementation have shown to significantly reduce plasma homocysteine levels, a study with diet fortified with vitamins B₆, B₁₂ and folic acid

reduced plasma homocysteine levels by 65% as compared to 3.5% with folic acid alone. Vitamin B₆ is known to decrease vascular events, which is independent of its effect on plasma homocysteine. Patients with pyridoxine deficiency are found to be at increased risks for ischaemic strokes. Vitamin B₆ may especially be deficient in patients with renal failure on dialysis that is also otherwise at an increased risk of developing hyperhomocysteinemia.

Elevated levels of homocysteine lead to atherosclerosis by causing irritation of blood vessels. It also causes oxidation of Low-density lipoprotein (LDL), an increase in the clotting of blood vessel, smooth muscle proliferation, platelet aggregation, promotion of chemotaxis and enhanced cytotoxicity. Consequentially, hyperhomocysteinemia leads to arterial vascular and venous thrombovascular disease.

It is observed that, most of the cardiovascular patients (suffering from hypertension, angina pectoris, etc) also exhibit high level of homocysteine in blood. Many of them also show increased levels of cholesterol and triglycerides in their blood.

Biochemical and pathological studies in cystinuric children showed that elevated blood cysteine might cause atherosclerosis. Studies have suggested that elevated homocysteine is a risk factor for atherosclerotic vascular disease and for arterial and venous thromboembolism. Moreover, moderate and intermediate hyperhomocysteinemia is present in patients with coronary, cerebral or peripheral arterial occlusive diseases. Also, a recent study demonstrated that the risk of coronary artery disease highly correlated with basal levels of homocysteine.

Clinical and pathologic studies show that elevated plasma levels of total cholesterol, LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease. Similarly, decreased levels of High-density lipoprotein (HDL-C) and its transport complex, apo A are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total cholesterol and Low-density lipoprotein (LDL-C), and inversely with the level of High-density lipoprotein (HDL-C). Therefore, the

pharmacotherapy for cardiovascular disorders should also include the treatment of homocystinuria.

The symptomatic treatment for cardiac failure is directed at improving haemodynamic function through the use of drugs that increase cardiac output and reduce ventricular filling pressures. Therefore the selected therapy for rapid improvement may include α -adrenergic blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, and the like. These drugs are administered either individually or in combination. Combination drug therapies are very common to achieve the dual advantages of dosage reduction and reduced adverse effects.

Calcium channel blocking agents are an important group of drugs for the treatment of hypertension. These drugs lower blood pressure by relaxing arteriolar smooth muscle and decreasing peripheral vascular resistance.

Amlodipine is a dihydropyridine calcium channel antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor-binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo.

In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial

oxygen demand, at any given level of exercise. Amlodipine blocks constriction and restore blood flow in coronary arteries and arterioles. This inhibition of coronary spasm is responsible for its effectiveness in vasospastic (Prinzmetal's or variant) angina. The effectiveness of 5-10 mg/day of amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing.

Statins exert their major effect i.e. reduction of low-density lipoprotein (LDL) through mevalonic acid like moiety that competitively inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA reductase) enzyme selectively.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL, IDL, LDL, and VLDL fractions.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. It also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. It reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

β -Adrenergic receptor antagonists are effective as antihypertensive agents. Antagonism of β -adrenergic receptors affects the regulation of the circulation through a number of mechanisms, including a reduction in myocardial contractility and cardiac output. An important consequence of blocking β -adrenergic receptors is reduction in secretion of rennin with a resulting fall in the

levels of angiotensin II. The reduction in angiotensin II, with its multiple effects on circulatory control contributes importantly to antihypertensive action of this class of drugs.

Atenolol is a β_1 selective (cardioselective) β -adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits β_2 -adrenoreceptors, chiefly located in the bronchial and vascular musculature.

In controlled clinical trials, atenolol given as a single daily dose was an effective antihypertensive agent providing 24-hour reduction of blood pressure. Several possible mechanisms have been proposed to explain the antihypertensive action of atenolol, which include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris.

Clinical and pathologic studies show that elevated plasma levels of total cholesterol, LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease. In heart diseases, atherosclerosis and hypertension are seen in most of the cases. Atorvastatin is a selective, competitive inhibitor of HMG-CoA, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-CoA to mevalonate, a precursor of steroids including cholesterol. Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. It also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. It reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in

patients with isolated hypertriglyceridemia. Amlodipine is a calcium channel antagonist. It inhibits the transmembrane influx of Ca ions into vascular smooth muscles and cardiac muscle. With chronic once daily oral administration, antihypertensive effectiveness of amlodipine is maintained for at least 24 hours. In patients with exertional angina, amlodipine reduces the total peripheral resistance and thus myocardial oxygen demand. It blocks coronary vasoconstriction and restores blood flow. This inhibition of coronary spasm is responsible for its effectiveness in vasospastic (Prinzmetal's or variant) angina. Atenolol is a β_1 -adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic activities. In controlled clinical trials, atenolol given as a single daily dose was an effective antihypertensive agent providing 24-hour reduction of blood pressure. Atenolol reduces the oxygen requirements of the heart making it useful for many patients in the long-term management of angina pectoris. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range, even when co-administered with beta-blockers.

Atherosclerosis is a condition characterized by irregularly distributed lipid deposits in the intima of arteries, including coronary, carotid and peripheral arteries. Atherosclerotic coronary heart disease (hereinafter termed "CHD") accounts for major deaths attributable to a cardiovascular event. Despite attempts to modify secondary risk factors such as, inter alia, smoking, obesity and lack of exercise, and treatment of dyslipidemia with dietary modification and drug therapy, CHD remains the most common cause of death in the Western countries. High levels of blood cholesterol and blood lipids are conditions involved in the onset of atherosclerosis. It is well known that inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) are effective in lowering the level of blood plasma cholesterol, especially low density lipoprotein cholesterol (LDL-C). It has now been established that lowering LDL-C levels affords protection from coronary heart disease.

Angina pectoris is a severe constricting pain in the chest, often radiating from the precordium to the left shoulder and down the left arm. Often angina pectoris is due to ischemia of the heart and is usually caused by coronary disease. The symptomatic management of angina pectoris

involves the use of a number of drugs, frequently as a combination of two or more of the following classes: β -blockers, nitrates and calcium channel blockers. Most, if not all, of these patients require therapy with a lipid lowering agents or lipid regulating agents as well.

Hypertension frequently coexists with hyperlipidemia and both are considered to be major risk factors for developing cardiac disease ultimately resulting in adverse cardiac events. This clustering of risk factors is potentially due to a common mechanism. Further, patient compliance with the management of hypertension is generally better than patient compliance with hyperlipidemia. It would therefore be advantageous for patients to have a single therapy which treats both of these conditions.

Hence, the combination of amlodipine, atorvastatin and atenolol therefore would achieve good control of lipid as well as blood pressure in a case of atherosclerosis with hypertension; coronary artery disease associated with atherosclerosis.

As the formulation is a fixed dose tablet to be administered once daily, it offers dosage convenience and good patient compliance. Hence, combination therapy can be used in various conditions such as Hypertension with Dyslipidemia and increased plasma homocysteine level (Hyperhomocysteinemia),. Hypertension with Dyslipidemia and Diabetic Neuropathy,. Angina Pectoris with Dyslipidemia and increased plasma homocysteine level (Hyperhomocysteinemia) and Angina Pectoris with Dyslipidemia and Diabetic Neuropathy and various other related disorders.

The parent PCT application no. PCT/IB03/02949 filed 24th July 2004 also describes combination therapy. The invention relates to combination therapy comprising one immediate or sustained release drug with another immediate releasing drug with the third immediate or sustained release drug having lower absorption and good aqueous solubility. The invention further describes the use of the said combination therapy in the treatment of variety of diseases such as non-insulin dependent diabetes mellitus, diseases of the cardiovascular system wherein the triple combination therapy is beneficial either therapeutically or prophylactically. Thus, the

invention relates to a delivery system comprising of combination of a minimum of three therapeutic agents of which at least one agent is released in sustained or controlled manner and is used for any beneficial ailments in humans.

Literature reports combination therapy for the treatment of multiple pathological processes involved in arterial and related heart diseases.

US patent 6,455,574 (Pfizer Inc.) describes a method of treating hypertension and hyperlipidemia comprising pharmaceutical combinations of amlodipine and its salts thereof with atorvastatin and its salts thereof to be administered in the form of kit preparation. The kit describes the container means for containing dosage forms comprising amlodipine and its salts thereof and atorvastatin and its salts thereof.

Patent No. WO9918957 (Dr. Reddy's Labs. Inc.) describes a stable solid pharmaceutical composition for oral administration comprising a combination of calcium channel blockers such as amlodipine with β -adrenergic blockers such as atenolol alongwith suitable pharmaceutical excipients for the treatment of cardiovascular diseases like angina pectoris, myocardial infarction, hypertension as described.

US patent 6,673,831 (Merck & Co.) describes a method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of an HMG-CoA reductase inhibitor in combination with folic acid or a pharmaceutically acceptable salt or ester thereof to a person at risk of developing atherosclerotic disease.

US patent 6,677,356 (Medicure International Inc.) describes a method of treating hypertension comprising concurrently administering a combination of a compound selected from the group consisting of pyridoxal-5'-phosphate, pyridoxal, pyridoxamine, a 3'-acylated pyridoxal analogue, and a therapeutic cardiovascular compound selected from the group consisting of an angiotensin converting enzyme (ACE) inhibitor, a calcium channel blocker, a β -adrenergic receptor antagonist, a vasodilator, a diuretic, an α -adrenergic receptor antagonist, a 3'-acylated

pyridoxal analogue, an angiotensin II receptor antagonist, an antithrombolytic agent, an antioxidant, and a mixture thereof.

Patent no. WO0211723 (Mr. M.R. Preston) describes a pharmaceutical composition comprising amlodipine and an atorvastatin compound selected from the group consisting of atorvastatin and hydroxylated atorvastatin metabolite wherein said pharmaceutical composition synergistically lowers blood pressure and systemic lipid concentrations.

US Patent 6,669,955 (Longwood pharmaceutical research Inc.) describes an orally administrable pharmaceutical formulation comprising combination of cholesterol-lowering agent, an inhibitor of rennin-angiotensin system, aspirin and optionally at least one of vitamin B6, B12 and folate and the active agents are contained in a unit dose preparation appropriate for once daily dosing. The formulation is provided as simple and convenient therapy to reduce the risk of cardiovascular events in individuals who are at elevated cardiovascular risk. The formulation is also therapeutic for individuals during or immediately following an occurrence of myocardial infarction.

Bergey et al., in European patent EU 457514 disclose the use of a cholesterol-lowering drug together with an ACE inhibitor to prevent, stabilize, or cause regression of atherosclerosis. The patent describes treatment for atherosclerosis only among all cardiovascular disorders.

US Patent 6,235,311 (Ullah et al.) describes pharmaceutical compositions that contain a statin plus aspirin, and optionally containing vitamins B6, B12 or folic acid and methods of their use for lowering serum cholesterol, preventing, inhibiting, or treating atherosclerosis or reducing the risk of or treating a cardiovascular event or disease, coronary artery disease or cerebrovascular disease.

US Patent Application 20040138274 (Novel Pharmaceuticals) describe a pharmaceutical composition comprising a cyclopentyl substituted glutaramide derivatives with one or more

angiotensin receptor blockers; calcium channel blockers, statins; beta blockers; ACE inhibitors; alpha-blockers; selective aldosterone receptor antagonists; and the like.

US Patent Application 2003114497 (Warner-Lambert Co.) discloses pharmaceutical composition comprising two components: (a) one component comprising a granulation of atorvastatin or salts thereof and a carrier including an alkalizing agent that forms a pH greater than 5; and (b) a second component comprising amlodipine or salts thereof and a carrier excluding an alkalizing agent that forms a pH greater than 5, wherein the two components are combined to form a final composition for a solid dosage form is described as well as methods to prepare the compositions, kits for containing such compositions, and a method of treating angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and/or hypercholesterolemia, and symptoms of cardiac risk using the pharmaceutical composition.

US Patent Application 20030175344 (Wald, Nicholas et al.) describes a formulation comprising at least two blood pressure lowering agents, each selected from a diuretic, a beta blocker, an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, and a calcium channel blocker with an active agent from at least two of the three categories (i) a lipid regulating agent (ii) one platelet function altering agent and (iii) one serum homocysteine lowering agent. The application also describes the use and method of treatment for reducing the risk of cardiovascular disease of the active principals by simultaneous, separate or sequential administration of the said combination therapy.

In WO-A-97/38694 (Merck & Co., Inc) describes a method for preventing or reducing the risk of developing atherosclerotic disease comprising the administration of a lipid reducing drug, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (HMG-CoA RI-a statin) formulated together with folic acid (a homocysteine reducing drug) to a person at risk of developing atherosclerotic disease which is said to be more convenient for patient compliance as it is reasonably easy to add the small amount of folic acid necessary to an existing daily HMG-CoA RI unit dosage form. The patent neither demonstrates nor suggests any additional physiological benefit of the combination. It also suggests very generally that other active agents may be

added, listing a large and varied range of active agents with no specificity or indication of their intended purpose. Most significantly, there is no indication whatsoever of administering a combined formulation to individuals without measuring, or if measured regardless of the level, of any of the risk factors associated with cardiovascular disease.

WO-A-98/11896 (Merck & Co., Inc) parallels this disclosure proposing a combination of an HMG-CoA RI with a platelet aggregation inhibitor. Neither the rationale for the combination nor any indication of advantage is disclosed. WO-A-98/19690 (Bristol-Myers Squibb Company) discloses combinations of folic acid (with or without vitamin B12) together with an agent selected to dilate the brain vasculature.

Thus, it will be appreciated from prior art discussed above that many different combinations formulations for simultaneous, separate or sequential oral or systemic administration of cardiovascular drugs have been described.

The physiological effects of antihypertensives such as calcium channel blockers, β -adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors together with lipid-regulators and serum homocysteine lowering agents in reducing the risk of cardiovascular disease have been found to be independent of each other. The recognition of the combined effect using these four different categories of drug together is novel. At preferred dosages of these drugs and in specific pharmaceutical drug delivery form, the prevalence of ratio of reduction in the incidence of cardiovascular disease to the prevalence of the adverse effects of the drugs is high. Also, the effect of modified release methylcobalamin is another novel feature of the present invention.

In general, humans ingest about 10 - 20 μg / day of vitamin B₁₂ in the diet. Of this, 2 to 3 μg of vitamin B₁₂ is absorbed with the help of intrinsic factor (IF) in the lower ileum. (Intrinsic factor (IF) dependent absorption during normal doses).

However, when vitamin B₁₂ is administered orally in large doses, it is in part absorbed through a mechanism of diffusion. i.e., large oral doses are concentration-dependently absorbed in the upper and lower ileum. Total serum B₁₂ levels are found to increase significantly 10 hours after a small dose of methycobalamin. This suggests an intrinsic factor dependent absorption between 8 and 12 hrs after administration.

Total serum B₁₂ levels also increase slightly with 1500 µg (single dose), but absorption, which appears to be attributable to the intrinsic factor, contributes to the increase only slightly. With doses still higher, no intrinsic factor dependent absorption is seen. Increase in serum total B₁₂ levels are not necessarily proportional to dosage levels, probably because free B₁₂ is promptly excreted in the urine. Generally with a dose of up to 1 mcg the rate of absorption is 60 % or more. That is, about 0.6 mcg of cobalamin is absorbed after a dose of 1 mcg, whereas after high oral doses of 500 to 1000 mcg the rate of absorption is as low as 2 to 5 %, the amount of absorption ranging from 10 to 50 mcg. Therefore, a sustained/ extended release formulation of methylcobalamin (1500 mcg) with release of the active vitamin over longer period of time will be superior to the conventional or immediate release preparation.

Thus one can infer from the above that Vitamin B₁₂ is absorbed better at a smaller dose compared to a higher dose because at lower doses the absorption is mediated by the Intrinsic factor whereas at higher doses it is concentration dependent and mediated less by the Intrinsic factor. Also since there is a saturation effect of the intrinsic factor at higher doses the absorption is lower. By the time the intrinsic factor is free to transport the remaining Vitamin B₁₂ available, parallel processes of metabolism and elimination decrease the levels of Vitamin B₁₂ and hence there is no vitamin B₁₂ available for the intrinsic factor to ferry across for the process of absorption.

An ideal way to overcome this problem would be to limit the amount of Vitamin B₁₂ by using a sustained / controlled or modified release Vitamin B₁₂ so that lower concentrations of Vitamin B₁₂ are available at the site of absorption intermittently due to controlled release to

make the absorption predominantly intrinsic factor dependent as a result achieving higher concentrations.

This is achieved by the present invention by providing the Vitamin B12 in a controlled or modified release fashion thus increasing absorption and patient compliance (no necessity for taking vitamin B12 thrice a day as an immediate release formulation).

As used herein, the term "controlled or modified release" means the rate at which a drug is released from a matrix or reservoir. The release rate from the matrix or reservoir is sufficiently slow that the resulting effect is an extended or sustained release over many hours albeit at an ever-changing concentration. More particularly, it refers to a property of the pharmaceutical composition wherein the absorption and bioavailability of the active medicament is maintained in a time-release pattern such that therapeutically effective amounts of active agents are available over an extended period of time.

The term "immediate release" refers to a property of the pharmaceutical composition wherein the entire dose of active medicament is made available without substantial delay. Thus the term "controlled or modified release" here means all types of release from a formulation except "immediate release".

Thus, a combination of drugs comprising serum homocysteine lowering agents such as methylcobalamin preferably as modified release alongwith antihypertensive agents such as calcium channel blockers, β -adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors together with lipid-regulators and folic acid and vitamin B6 as immediate release as disclosed hereinafter in the claimed invention are unrevealed.

Furthermore, for the oral administration of the said combination of a controlled release methylcobalamin with calcium channel blockers or β -adrenergic blockers or angiotensin converting enzyme (ACE) inhibitors together with lipid-regulators and optionally folic acid and vitamin B6 for synergistic effect in the treatment of cardiovascular disorders, the individual and double and triple commercially available combination products have been heretofore

administered in the present invention together. Hence, the said combination therapy would fill a highly desirable gap in the medical armamentarium. The present invention therefore would significantly improve the treatment of cardiovascular disorders through significantly enhanced patient compliance because of ease of administration and a reduced frequency of dosing. There is also a possibility of significant reduction in the doses of the drug substances used in combination because of synergistic action, reducing in possible reduction to the toxicity.

The art of formulating various different classes of drugs diverse in their physicochemical properties and belonging to unrelated chemical classes is an invention as because of the presence of active ingredients and the other excipients, one has to ensure that such a combination composition is stable physicochemically and also achieves the desired characteristics "*in-vivo*" when administered to patients. Frequently there is an incompatibility between the active ingredients themselves or between the excipients and each of the active ingredients or between the excipients and the combination of active ingredients. To overcome this it becomes very important for the formulator to study the detailed aspects before formulation and the ratios of drug to excipients to be used so that it results in a stable combination composition physicochemically, even during storage and to ensure the release of all the therapeutic ingredients after administration to the patient. This becomes all the more difficult especially when one of the therapeutically active ingredients has to be given in a controlled or modified release fashion with the others being in an immediate release form. The task becomes onerous further when the dose of the therapeutically active ingredient to be administered, as a controlled or modified release is significantly low compared to the other components.

Hence, the present invention is directed towards combination therapy comprising methylcobalamin as controlled release alongwith with calcium channel blockers or β -adrenergic blockers or angiotensin converting enzyme (ACE) inhibitors together with lipid-regulators and optionally folic acid and/or vitamin B6 preferably in a single dosage form for prophylactic and therapeutic treatment of hyperhomocysteinemia associated with hypertension, dyslipidemia, diabetic neuropathy, angina pectoris and similar other cardiovascular disorders.

SUMMARY OF THE INVENTION

The present invention provides a formulation comprising an oral pharmaceutical combination composition comprising methylcobalamin preferably as controlled or modified release alongwith at least one active agent each selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or angiotensin converting enzyme (ACE) inhibitors together with lipid-regulators and optionally with folic acid and/or vitamin B6 preferably in a single dosage form and method of its preparation and use in the prophylactic and/or therapeutic treatment of hyperhomocysteinemia coupled with hypertension, dyslipidemia, diabetic neuropathy, angina pectoris and similar other cardiovascular disorders.

Accordingly, it is an object of the present invention to provide a pharmaceutical composition and a process of manufacturing the same for combination comprising methylcobalamin preferably as controlled or modified release alongwith at least one active agent each selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or angiotensin converting enzyme (ACE) inhibitors together with lipid-regulators, folic acid and vitamin B6 preferably in a single dosage form.

It is also an object of the present invention to provide a pharmaceutical composition and a process of manufacturing the same for combination comprising methylcobalamin preferably as controlled or modified release alongwith at least one cardiovascular agent optionally with folic acid and/or vitamin B6 preferably in a single dosage form. The cardiovascular agents may be selected from lipid-regulators and antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or angiotensin converting enzyme (ACE) inhibitors.

The present invention therefore also provides a pharmaceutical combination composition comprising methylcobalamin preferably as controlled or modified release alongwith at least one active agent each selected from antihypertensive agents such as calcium channel blockers or β -

adrenergic blockers or angiotensin converting enzyme (ACE) inhibitors together with lipid-regulators, folic acid and vitamin B6 preferably in a single dosage form alongwith suitable pharmaceutically suitable excipients thereof.

It is further object of the present invention to provide an oral drug delivery system for the combination of controlled release drug with a controlled/immediate release drugs.

Another object of the present invention is to provide a delivery system for oral administration constituting of release in the body of mammal, a sustained or controlled release drug such as methylcobalamin, alongwith at least one immediate release active agent each selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or ACE inhibitors together with lipid-regulators optionally with folic acid and/or vitamin B6 preferably in a single dosage form alongwith suitable pharmaceutically suitable excipients thereof.

Yet another object of the present invention is to provide a delivery system for oral administration constituting of release in the body of mammal, a sustained or controlled release drug such as methylcobalamin, alongwith at least one cardiovascular agent optionally with folic acid and/or vitamin B6 preferably in a single dosage form. The cardiovascular agents may be selected from lipid-regulators and antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or angiotensin converting enzyme (ACE) inhibitors.

There is further provided by the present invention an oral delivery system kit comprising a sustained or controlled release drug such as methylcobalamin, alongwith at least one immediate release active agent each selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or ACE inhibitors together with lipid-regulators optionally with folic acid and/or vitamin B6 alongwith suitable excipients thereof.

Yet another aspect of the present invention is to provide a method of use of this combination therapy for the treatment of various cardiovascular diseases coupled with hyperhomocysteinemia formulated such that the components of tablet or kit in any order are consumed within 0-24 hours after administration of the drugs comprised in the formulation.

Yet another aspect of the present invention is that the invention relates to an oral delivery system that selectively delivers drugs at an optimal rate to patients over a period of time during treatment and aims to achieve a reduction in the dose of the drugs administered after an initial therapy with this regimen. The reduction in the dosage shall be beneficial to the patient and will be at discretion of the physician depending upon the pathological profile obtained after treatment with this combination therapy.

Yet another aspect of the present invention is the process of manufacturing the pharmaceutical dosage form for oral administration. In other words, the invention provides an oral combination composition comprising sustained or controlled release drug such as methylcobalamin, alongwith at least one immediate release active agent each selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or ACE inhibitors together with lipid-regulators optionally with folic acid and/or vitamin B6 alongwith suitable excipients thereof blended suitably and granulated with suitable binders that may be dissolved in aqueous and/or organic solvents and/or hydroalcoholic solvents thereof, dried and lubricated. The resultant granules are then compressed using suitable double or triple layer compressing machines. Alternatively, the granules of the said composition can also be prepared by using direct compression or fluidized bed granulation technique.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes a formulation comprising an oral pharmaceutical combination composition comprising methylcobalamin preferably as controlled or modified release alongwith at least one active agent each selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or ACE inhibitors together with lipid-regulators and optionally with folic acid and/or vitamin B6 preferably in a single dosage form and method of its preparation and use in the prophylactic and/or therapeutic treatment of

hyperhomocysteinemia coupled with hypertension, dyslipidemia, diabetic neuropathy, angina pectoris and similar other cardiovascular disorders.

The said medicament according to the present invention comprises a formulation substantially as herein described, and in particular a tablet or a kit, typically a tablet formulation substantially as hereinafter further described.

Suitably, a combination composition according to the present invention provides an oral formulation comprising sustained or controlled release drug such as methylcobalamin, alongwith at least one immediate release active agent each selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or ACE inhibitors together with lipid-regulators and optionally with folic acid and/or vitamin B6 alongwith suitable excipients thereof blended suitably and granulated with suitable binders that may be dissolved in aqueous and/or organic solvents and/or hydroalcoholic solvents thereof, dried, lubricated and compressed using suitable double or triple layer compressing machines.

In a preferred embodiment of the present invention, a combination composition comprises pharmaceutically active agents together with suitable excipients for oral administration. In particular, the present invention provides composition comprising a sustained or controlled release source of methylcobalamin alongwith at least one active agent selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or ACE inhibitors together with lipid-regulators, folic acid and vitamin B6 alongwith suitable excipients thereof.

A preferred calcium channel blocker may be selected from amlodipine, diltiazem, felodipine, nifedipine, nimodipine, nisoldipine, isradipine, nicardipine, bepridil, and verapamil and their salts, esters, lactones forms thereof. Most preferred active is amlodipine and/or its salts, solvates and derivatives thereof.

Preferred β -adrenergic agents may include acebutolol, atenolol, metoprolol, betaxolol, bisoprolol, labetalol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol and salts,

solvates and derivatives thereof. Most preferred β -adrenergic agent might be atenolol or metoprolol and salts, solvates and derivatives thereof.

Numerous ACE inhibitors have been synthesized. Most of these compounds can be classified into three groups based on their chemical structure: (1) sulfhydryl-(also called mercapto-) containing ACE inhibitors, including captopril and agents that are structurally related to captopril, such as fentiapril, pivalopril, zofenopril and alacepril; (2) dicarboxyl-containing ACE inhibitors, including enalapril and agents that are structurally related to enalapril, such as lisinopril, benazepril, quinapril, moexipril, ramipril, spirapril, perindopril, indolapril, pentopril, indalapril and cilazapril; and (3) phosphorus-containing ACE inhibitors, structurally related to fosinopril.

Preferred ACE inhibitors are captopril, cilazapril, delapril, enalapril, enalaprilat, fentiapril, fosinopril, indolapril, libenzapril, rentiapril, zabicipril, moveltipril, spiraprilat, lisinopril, perindopril, pivopril, quinapril, ramipril, spirapril, trandolapril, and zofenopril; particularly preferred are captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril, and trandolapril; and most preferred is ramipril and its salts, solvates and derivatives thereof.

Preferred cholesterol-lowering agents or lipid regulating agents are HMG CoA reductase inhibitors. The members of this class of compounds inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. This enzyme catalyzes the conversion of HMG CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Examples of HMG CoA reductase inhibitors that may be used are selected from the group comprising lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, fluindostatin, velostatin and the salts, solvates and derivatives thereof. Most preferred HMG CoA reductase inhibitor is atorvastatin and/or its salts, solvates and derivatives thereof.

Preferably the serum homocysteine-lowering agents are folic acid, vitamin B6, vitamin B12, methylcobalamin, or a combination of two or three of these. Preferably the composition may comprise of combination of these active agents where methylcobalamin may be formulated in sustained or controlled release form. Preferably the active principals are administered orally to

a patient. The invention further provides formulations for use in the treatment of cardiovascular disease.

In a preferred embodiment of the present invention, there is provided a formulation comprising at least one antihypertensive agent selected from a beta blocker, an angiotensin converting enzyme (ACE) inhibitor, a calcium channel blocker and at least one active agent from the following:

- i) at least one lipid-regulating agent, and optionally
- ii) at least one serum homocysteine lowering agent

alongwith sustained or controlled release methylcobalamin and suitable pharmaceutical excipients.

Preferably the formulation has active agents from both the categories i) and ii) alongwith sustained or controlled release methylcobalamin and suitable pharmaceutical excipients. Optionally the formulation comprises more than one active agent from one or more of the three categories.

More particularly there is now provided by the present invention a pharmaceutically acceptable oral formulation comprising a therapeutically effective amount of methylcobalamin alongwith therapeutically effective amount of at least one active agent each selected from antihypertensive agents such as calcium channel blockers or β -adrenergic blockers or ACE inhibitors together with lipid-regulators, or pharmaceutically acceptable salts, solvates or derivatives thereof and optionally folic acid and/or vitamin B6 which is further provided with suitable excipients thereof.

As used herein, the term "therapeutically effective amount" means an amount of the drug which is capable of eliciting a physiological response in a human patient substantially as hereinafter described in greater detail. More particularly, the term "therapeutically effective amount" means the amount of drugs, which is capable of treating cardiovascular and related disorders associated with hyperhomocysteinemia.

The β -adrenergic blockers, ACE inhibitors, calcium channel blockers and lipid-regulators are preferably those referred to above, preferably in their therapeutically effective amount. Similarly the serum homocysteine lowering agents are preferably those referred to above, preferably in their therapeutically effective amount.

In general, the present invention provides a combination composition comprising the drugs from at least two of the following three categories:

- i) at least one antihypertensive drug
- ii) at least one lipid-regulating agent, optionally
- iii) at least one serum homocysteine lowering agent,
with a controlled or modified release methylcobalmin

The suitable antihypertensive drug may be selected from the class of β -adrenergic blockers or ACE inhibitors or calcium channel blockers, the lipid regulating agent selected from the class of HMG CoA Inhibitors and the optional serum homocysteine lowering agent selected from Vitamin B2, B6 and folic acid.

The suitable antihypertensive agent, lipid-regulator and homocysteine lowering agents are preferably those referred to above in their therapeutically effective amounts along with sustained or controlled release methylcobalamin and suitable excipients.

The formulation of the present invention is provided in a form suitable for oral administration. For oral administration, the formulation of the present invention is preferably in the form of a tablet, a capsule, a pill, a powder or granules. Most preferred dosage form is tablet.

According to a preferred embodiment of the present invention there is provided, therefore a tablet formulation comprising a tablet core or layers provided with a sustained or controlled release methylcobalamin or a pharmaceutically acceptable salt, or solvate thereof, together with at least one drug each from antihypertensive agents such as β -adrenergic blockers or ACE

inhibitors or calcium channel blockers alongwith lipid-regulators and optionally serum homocysteine lowering agents.

Suitably the tablet formulation as provided by the present invention can further comprise suitable excipients selected so as to provide the required properties for pharmaceutical usage, such as the required hardness, friability, dissolution, disintegration time and the like. Preferred excipients may include inert diluents, disintegrating agents, binding agents, lubricating agents, and sweetening agents, flavoring agents, coloring agents and preservatives. Suitable diluents employed in a formulation according to present invention should typically be selected based on desired pharmaceutical properties as referred to above, such as dissolution, content uniformity, hardness, friability, disintegration time and the like. Preferred diluents can be selected from the group consisting of sodium and calcium carbonate, sodium and calcium phosphate, lactose either present in anhydrous or hydrated form, or spray dried, and microcrystalline cellulose, starch and the like. The appropriate choice of diluents would be well known to one of ordinary skill in the art, in order to achieve the desired pharmaceutical properties of a pharmaceutical formulation according to present invention.

Suitably, the tablet formulation according to the present invention may further comprise of a disintegrant. There are a variety of grades of disintegrants available, and the grade may be selected based on the acceptable batch variability. The preferred disintegrants include starch, hydroxypropylcellulose, microcrystalline cellulose, croscarmellose sodium alginic acid and other known disintegrants.

Suitable binders may also be employed using known methods. Such binders should be selected to provide satisfactory compressibility. The preferred binders may include starch, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose and other cellulose derivatives, gums and gelatin, and the like. Other binders known in the art may also be selected.

Appropriate lubricants and glidants may also be employed, for example to prevent sticking of tablets to compression tooling. Examples of suitable lubricants include magnesium stearate, calcium stearate, zinc stearate, glyceryl behenate, light mineral oil, polyethylene glycol, sodium steryl fumarate, stearic acid, talc, hydrogenated vegetable oil, calcium silicate, magnesium silicate and colloidal silicon dioxide. The most preferred lubricants are calcium stearate and magnesium stearate.

Methylcobalamin, folic acid, vitamin B6 and cardiovascular agents, in particular β -adrenergic blockers or calcium channel blockers or ACE inhibitors alongwith lipid-regulators have their applicability for use in the treatment of hyperhomocysteinemia associated with cardiovascular and related disorders. There is further provided by the present invention, therefore, a method of treating a condition prevented, ameliorated or eliminated by administration of these agents as combined composition, which method comprises administering to a human patient suffering from or susceptible to such a condition therapeutically effective amount of formulation according to the present invention substantially as hereinbefore described. The term "treatment" as used herein encompasses both prophylaxis, and the treatment of established conditions. The "treatment" can also include the management and care of a human patient for the purpose of combating, the disease conditions as referred to above and can include the administration of a formulation according to present invention to prevent the onset of symptoms or complications associated with such conditions.

Substantially as hereinbefore described, folic acid and vitamin B6 are preferred serum homocysteine lowering agents for use according to the present invention and are effective over a wide dosage range, with actual dose administered being dependent on the condition being treated and also the patient. Single doses of 1-5 mg and 20 mg of folic acid and vitamin B6 respectively have been shown to be effective for the acute treatment of hyperhomocysteinemia in adults. Similarly, a preferred formulation according to the present invention is an oral formulation comprising about 1000-1500 mcg of methylcobalamin as sustained or controlled release drug, releasing methylcobalamin over extended periods of therapy, suitably with oral

administration at intervals of about 12-18 hours. The controlled release is thus achieved by formulation substantially as hereinbefore described.

A tablet according to the present invention comprises a combination of drugs together with pharmaceutically acceptable excipients such as one or more suitable diluents, polymers, binders, and lubricants. These excipients are combined with drugs in the following therapeutically effective amounts to achieve the beneficial characteristics of the present invention:

- a) about 5-80 mg atorvastatin as a lipid-regulating agent
- b) about 1 to 10 mg amlodipine, and about 10-100 mg of atenolol as antihypertensive agents,
- c) about 1000-1500 mcg of methylcobalamin as controlled release, 1-5 mg folic acid, and 5-20 mg vitamin B6 as homocysteine lowering agents

Alternatively, the formulation comprises:

- a) about 5-80 mg atorvastatin as a lipid-regulating agent
- b) about 1 to 10 mg amlodipine as antihypertensive agent,
- c) about 1000-1500 mcg of methylcobalamin as controlled release, 1-5 mg folic acid, and 5-20 mg vitamin B6 as homocysteine lowering agents

Alternatively, the formulation comprises:

- a) about 5-80 mg atorvastatin as a lipid-regulating agent
- b) about 10-100 mg of atenolol as antihypertensive agent,
- c) about 1000-1500 mcg of methylcobalamin as controlled release, 1-5 mg folic acid, and 5-20 mg vitamin B6 as homocysteine lowering agents

Alternatively, the formulation comprises:

- a) about 5-80 mg atorvastatin as a lipid-regulating agent
- b) about 10-100 mg of atenolol as antihypertensive agent,

- c) about 1000-1500 mcg of methylcobalamin as controlled release, 1-5 mg folic acid as homocysteine lowering agents

Alternatively, the formulation comprises:

- a) about 5-80 mg atorvastatin as a lipid-regulating agent
- b) about 5-19 mg of amlodipine as antihypertensive agent,
- c) about 1000-1500 mcg of methylcobalamin as controlled release homocysteine lowering agent

Alternatively, the formulation comprises:

- a) about 5-80 mg atorvastatin as a lipid-regulating agent
- b) about 10-100 mg of atenolol as antihypertensive agent,
- c) about 1000-1500 mcg of methylcobalamin as controlled release as homocysteine lowering agent

Alternatively, the formulation comprises:

- a) about 5-80 mg atorvastatin as a lipid-regulating agent
- b) about 10-100 mg of atenolol as antihypertensive agent,
- c) about 1000-1500 mcg of methylcobalamin as controlled release and 5-20 mg vitamin B6 as homocysteine lowering agents

Alternatively, the formulation comprises:

- (a) about 5-40 mg of simvastatin as a lipid-regulating agent
- (b) about 1 to 10 mg amlodipine, and about 10-100 mg of atenolol as antihypertensive agents,
- (c) about 1000-1500 mcg of methylcobalamin as controlled release, 1-5 mg folic acid, and 5-20 mg vitamin B6 as homocysteine lowering agents

Alternatively, the formulation comprises:

- (a) about 5-40 mg of pravastatin as a lipid-regulating agent

- (b) about 1 to 10 mg amlodipine, and about 10-100 mg of atenolol as antihypertensive agents,
- (c) about 1000-1500 mcg of methylcobalamin as controlled release, 1-5 mg folic acid, and 5-20 mg vitamin B6 as homocysteine lowering agents.

Alternatively, the formulation comprises:

- (a) about 5-80 mg of atorvastatin as a lipid-regulating agent,
- (b) about 1 to 10 mg ramipril as antihypertensive agent,
- (c) about 1000-1500 mcg of methylcobalamin as controlled release, 1-5 mg folic acid, and 5-20 mg vitamin B6 as homocysteine lowering agents.

Alternatively, the formulation comprises:

- (a) about 5-80 mg of atorvastatin as a lipid-regulating agent,
- (b) about 1 to 10 mg ramipril as antihypertensive agent,
- (c) about 1000-1500 mcg of methylcobalamin as controlled release as homocysteine lowering agents.

It will be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different pharmaceutical formulations, or separately or sequentially. If there is separate or sequential administration, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimize, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

In a preferred embodiment of the present invention, an oral combination composition comprises a multilayer system including the pharmaceutically active agents effective for the treatment of cardiovascular and related disorders associated with hyperhomocystenemia, with suitable pharmaceutically acceptable excipients. More particularly, a multilayer formulation according to the present invention comprises the first immediate release layer comprising a

formulation core comprising lipid-regulating agents such as atorvastatin or its salts, solvates and derivatives thereof alongwith suitable diluents, binders and lubricants and a second immediate release layer comprising at least one antihypertensive agent such as amlodipine, atenolol, ramipril or its salts, solvates and derivatives thereof optionally with serum homocysteine lowering agents such as folic acid and/or vitamin B6 with the third sustained release layer comprising methylcobalamin and further comprising or being provided with suitable polymers together with suitable diluents, binders and lubricants. The suitable polymers help to delay the release of methylcobalamin from the core of the third layer over a controlled period of time, whereas the first and second layer releases drugs conventionally (i.e. immediate release) to have the desired therapeutic effect.

There is still further provided by the present invention a process of preparing a pharmaceutically acceptable oral combination composition substantially as hereinbefore described, which process comprises providing a multilayer system which comprises a therapeutically effective amount of methylcobalamin alongwith other cardiovascular agents and suitable pharmaceutical excipients.

Direct compression process, dry granulation processes, wet granulation processes or fluidized bed processing technology could provide suitable processes for preparing pharmaceutical oral formulations according to present invention. The present invention further provides, therefore, a process of preparing a pharmaceutical formulation substantially as hereinbefore described, which process may comprise wet granulation or direct compression techniques.

Substantially as hereinbefore described the tablets of the present invention comprise multilayer tablets, of which, a first layer comprising a lipid regulator, such as atorvastatin or its salts, solvates or derivatives thereof, may be prepared by mixing the atorvastatin with binder and diluent. Alternatively, the first layer may comprise of combination of lipid regulator such as atorvastatin or its salts, solvates or derivatives thereof and amlodipine or its salts, solvates and derivatives thereof may be prepared by mixing the drugs with binder and diluents. The resulting mixture may then be blended and wet granulated with a film former, such as

hydroxypropylcellulose and polysorbate 80. The granulate may then be sized through a sieve of optimum mesh, mixed with the disintegrants, and a lubricant. Preferably a second layer comprising an antihypertensive agent such as atenolol or ramipril or its salts, solvates and derivatives thereof optionally with folic acid and/or vitamin B6 i.e. pyridoxine hydrochloride, is prepared by mixing the drugs with the diluents and binder. The resulting mixture may then be blended and wet granulated with a suitable binder such as polyvinylpyrrolidone dissolved in aqueous or nonaqueous solvents. The granulate may then be sized through a sieve of optimum mesh, mixed with the disintegrants, and a lubricant. Preferably the third layer comprises of methylcobalamin, may be prepared by mixing methylcobalamin with diluents and binder in suitable mixer blending well and mixing with a lubricant. These three granulates are then compressed using suitable triple layer compression machine. The first and second layer may alternatively be prepared by using direct compression processes or fluid bed granulation processes and the third layer may alternatively prepared by using wet granulation or fluid-bed granulation techniques to achieve homogenous distribution of a drug within the formulation.

The tablets of the invention are orally administered in the amounts necessary to achieve a particular blood level. Once the blood level is achieved, it can be maintained by repeated oral administration of the tablet at a dose interval of 24 hours i.e. one tablet administered daily. An optimum dosage size may be determined by observing the therapeutic results achieved and the side effects encountered and / or by blood serum analysis.

The present invention will now be further illustrated by the following examples, which does not limit the scope of the invention in any way. Further different strengths of the formulation may be achieved by proportionately using a dose-weight scale-up or scale-down formula. The selection and concentration of the excipients may also be varied or modified to achieve the desired dissolution profile by a skilled artisan.

EXAMPLES**Example-1**

Sr No.	Ingredient	Quantity/tab (mg)
<i>Layer-1</i>		
1.	Atorvastatin calcium	10.00
2.	Calcium carbonate	20.00
3.	Croscarmellose sodium	5.00
4.	Microcrystalline cellulose (Avicel PH 102)	43.00
5.	Pregelatinised starch	10.00
6.	Polysorbate-80	5.00
7.	Hydroxypropyl cellulose	5.00
8.	Colloidal silicon dioxide	2.00
9.	Magnesium stearate	5.00
Total weight of layer 1		105.00 mg
<i>Layer-2</i>		
10.	Ramipril	2.50
11.	Folic acid	5.00
12.	Vitamin B-6 (Pyridoxine)	20.00
13.	Maize starch	35.00
14.	Microcrystalline cellulose (Avicel PH 102)	30.00
15.	Povidone K-30	4.00
16.	Sodium starch glycollate	2.00
17.	Magnesium stearate	2.00
Total weight of layer 2		100.50 mg
<i>Layer-3</i>		
18.	Mecobalamin	1.80
19.	Microcrystalline cellulose (Avicel PH 102)	50.00
20.	Lactose (DCL-21)	48.20
21.	Corn starch	8.00
22.	Calcium stearate	2.00

23.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure:**Layer 1**

Mix Atorvastatin calcium, microcrystalline cellulose, Pregelatinized starch and calcium carbonate. Dissolve hydroxypropylcellulose and polysorbate 80 in purified water and granulate above mixture till wet mass forms. Dry the wet mass in suitable dryer. Pass the granular through mesh of suitable size. Add Croscarmellose sodium, magnesium stearate and colloidal silicon dioxide and blend in suitable blender.

Layer 2

Mix Ramipril, folic acid, pyridoxine hydrochloride, Maize starch, and microcrystalline cellulose in suitable mixer. Dissolve polyvinylpyrrolidone K30 in isopropyl alcohol and granulate till wet mass forms. Dry the wet mass in suitable dryer. Pass the granules through suitable sieve. Add sodium starch glycollate, magnesium stearate and blend in suitable blender.

Layer 3

Mix Methylcobalamin and cornstarch in suitable mixer sieved through suitable mesh size, blended again in suitable mixer & resieved through suitable mesh. Mix the above drug concentrate with hydroxypropyl methylcellulose, microcrystalline cellulose and lactose and blend in suitable blender. Add calcium Stearate and blend again in suitable blender.

Compress the above granules of all three layers by using suitable triple layer tablet compression machine.

Example-2

Sr No.	Ingredient	Quantity/tab (mg)
Layer-1		
1.	Atorvastatin calcium	10.00
2.	Calcium carbonate	20.00
3.	Croscarmellose sodium	5.00
4.	Microcrystalline cellulose (Avicel PH 102)	43.00
5.	Pregelatinised starch	10.00
6.	Polysorbate-80	5.00
7.	Hydroxypropyl cellulose	5.00
8.	Colloidal silicon dioxide	2.00
9.	Magnesium stearate	5.00
Total weight of layer 1		105.00 mg
Layer-2		
10.	Mecobalamin	1.80
11.	Microcrystalline cellulose (Avicel PH 102)	50.00
12.	Lactose (DCL-21)	48.20
13.	Corn starch	8.00
14.	Calcium stearate	2.00
15.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure:**Layer 1**

Mix Atorvastatin calcium, microcrystalline cellulose, Pregelatinized starch and calcium carbonate. Dissolve hydroxy propyl cellulose and polysorbate 80 in purified water and granulate above mixture till wet mass forms. Dry the wet mass in suitable dryer. Pass the granular through mesh of suitable size. Add Croscarmellose sodium, magnesium stearate and colloidal silicon dioxide and blend in suitable blender.

Layer 2

Mix Methylcobalamin and cornstarch in suitable mixer sieved through suitable mesh size, blended again in suitable mixer & resieved through suitable mesh. Mix the above drug concentrate with hydroxy propyl methylcellulose, microcrystalline cellulose and lactose and blend in suitable blender. Add calcium Stearate and blend again in suitable blender. Compress the above granules of all three layers by using suitable triple layer tablet compression machine.

Example-3

Sr No.	Ingredient	Quantity/tab (mg)
Layer-1		
1.	Atorvastatin calcium	10.00
2.	Calcium carbonate	20.00
3.	Folic acid	5.00
4.	Vitamin B6	20.00
5.	Croscarmellose sodium	5.00
6.	Microcrystalline cellulose (Avicel PH 102)	43.00
7.	Pregelatinised starch	10.00
8.	Polysorbate-80	5.00
9.	Hydroxypropyl cellulose	5.00
10.	Colloidal silicon dioxide	2.00
11.	Magnesium stearate	5.00
Total weight of layer 1		130.00 mg
Layer-2		
12.	Ramipril	2.50
13.	Maize starch	35.00
14.	Microcrystalline cellulose (Avicel PH 102)	55.00
15.	Povidone K-30	4.00
16.	Sodium starch glycollate	2.00
17.	Magnesium stearate	2.00
Total weight of layer 2		100.50 mg
Layer-3		
18.	Methylcobalamin	1.80
19.	Microcrystalline cellulose (Avicel PH 102)	50.00

20.	Lactose (DCL-21)	48.20
21.	Corn starch	8.00
22.	Calcium stearate	2.00
23.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure:**Layer 1**

Mix Atorvastatin calcium, microcrystalline cellulose, Pregelatinized starch and calcium carbonate, folic acid and vitamin B6 in suitable mixer. Dissolve hydroxy propyl cellulose and polysorbate 80 in purified water and granulate above mixture till wet mass forms. Dry the wet mass in suitable dryer. Pass the granular through mesh of suitable size. Add Croscarmellose sodium, magnesium stearate and colloidal silicon dioxide and blend in suitable blender.

Layer 2

Mix Ramipril, Maize starch and microcrystalline cellulose in suitable mixer. Dissolve polyvinylpyrrolidone K30 in isopropyl alcohol and granulate till wet mass forms. Dry the wet mass in suitable dryer. Pass the granules through suitable sieve. Add sodium starch glycollate, magnesium stearate and blend in suitable blender.

Layer 3

Mix Methylcobalamin and cornstarch in suitable mixer sieved through suitable mesh size, blended again in suitable mixer & resieved through suitable mesh. Mix the above drug concentrate with hydroxy propyl methylcellulose, microcrystalline cellulose and lactose and blend in suitable blender. Add calcium Stearate and blend again in suitable blender.

Compress the above granules of all three layers by using suitable triple layer tablet compression machine.

Example-4

Sr No.	Ingredient	Quantity/tab (mg)
<i>Layer-1</i>		
1.	Atorvastatin calcium	10.00
2.	Ramipril	2.50
3.	Calcium carbonate	20.00
4.	Croscarmellose sodium	5.00
5.	Microcrystalline cellulose (Avicel PH 102)	43.00
6.	Pregelatinised starch	10.00
7.	Polysorbate-80	5.00
8.	Hydroxypropyl cellulose	5.00
9.	Colloidal silicon dioxide	2.00
10.	Magnesium stearate	5.00
Total weight of layer 1		107.50 mg
<i>Layer-2</i>		
11.	Folic acid	5.00
12.	Vitamin B-6 (Pyridoxine)	20.00
13.	Maize starch	35.00
14.	Microcrystalline cellulose (Avicel PH 102)	32.5
15.	Povidone K-30	4.00
16.	Sodium starch glycollate	2.00
17.	Magnesium stearate	2.00
Total weight of layer 2		100.50 mg
<i>Layer-3</i>		
18.	Methylcobalamin	1.80
19.	Microcrystalline cellulose (Avicel PH 102)	50.00
20.	Lactose (DCL-21)	48.20
21.	Corn starch	8.00
22.	Calcium stearate	2.00
23.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure:**Layer 1**

Mix Atorvastatin calcium, ramipril, microcrystalline cellulose, pregelatinized starch and calcium carbonate in suitable mixer. Dissolve hydroxy propyl cellulose and polysorbate 80 in purified water and granulate above mixture till wet mass forms. Dry the wet mass in suitable dryer. Pass the granular through mesh of suitable size. Add Croscarmellose sodium, magnesium stearate and colloidal silicon dioxide and blend in suitable blender.

Layer 2

Mix folic acid, pyridoxine hydrochloride, Maize starch, and microcrystalline cellulose in suitable mixer. Dissolve polyvinylpyrrolidone K30 in isopropyl alcohol and granulate till wet mass forms. Dry the wet mass in suitable dryer. Pass the granules through suitable sieve. Add sodium starch glycollate, magnesium stearate and blend in suitable blender.

Layer 3

Mix Methylcobalamin and cornstarch in suitable mixer sieved through suitable mesh size, blended again in suitable mixer & resieved through suitable mesh. Mix the above drug concentrate with hydroxy propyl methyl cellulose, microcrystalline cellulose and lactose and blend in suitable blender. Add calcium Stearate and blend again in suitable blender.

Compress the above granules of all three layers by using suitable triple layer tablet compression machine.

Example-5

Sr No.	Ingredient	Quantity/tab (mg)
<i>Layer-1</i>		
1.	Atorvastatin calcium	10.00
2.	Calcium carbonate	20.00
3.	Croscarmellose sodium	5.00
4.	Microcrystalline cellulose (Avicel PH 102)	43.00
5.	Pregelatinised starch	10.00
6.	Polysorbate-80	5.00
7.	Hydroxypropyl cellulose	5.00
8.	Colloidal silicon dioxide	2.00
9.	Magnesium stearate	5.00
Total weight of layer 1		105.00 mg
<i>Layer-2</i>		
10.	Ramipril	5.00
11.	Folic acid	5.00
12.	Vitamin B-6 (Pyridoxine)	20.00
13.	Maize starch	35.00
14.	Microcrystalline cellulose (Avicel PH 102)	30.00
15.	Povidone K-30	4.00
16.	Sodium starch glycollate	2.00
17.	Magnesium stearate	2.00
Total weight of layer 2		103.00 mg
<i>Layer-3</i>		
18.	Methylcobalamin	1.80
19.	Microcrystalline cellulose (Avicel PH 102)	50.00
20.	Lactose (DCL-21)	48.20
21.	Corn starch	8.00
22.	Calcium stearate	2.00
23.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure: As described in Example-1.

Example-6

Sr No.	Ingredient	Quantity/tab (mg)
<i>Layer-1</i>		
1.	Atorvastatin calcium	10.00
2.	Calcium carbonate	20.00
3.	Folic acid	5.00
4.	Vitamin B6	20.00
5.	Croscarmellose sodium	5.00
6.	Microcrystalline cellulose (Avicel PH 102)	43.00
7.	Pregelatinised starch	10.00
8.	Polysorbate-80	5.00
9.	Hydroxypropyl cellulose	5.00
10.	Colloidal silicon dioxide	2.00
11.	Magnesium stearate	5.00
Total weight of layer 1		130.00 mg
<i>Layer-2</i>		
12.	Ramipril	5.00
13.	Maize starch	35.00
14.	Microcrystalline cellulose (Avicel PH 102)	52.00
15.	Povidone K-30	4.00
16.	Sodium starch glycollate	2.00
17.	Magnesium stearate	2.00
Total weight of layer 2		100.00 mg
<i>Layer-3</i>		
18.	Methylcobalamin	1.80
19.	Microcrystalline cellulose (Avicel PH 102)	50.00
20.	Lactose (DCL-21)	48.20
21.	Corn starch	8.00
22.	Calcium stearate	2.00
23.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure: As described in Example-2.

Example-7

Sr No.	Ingredient	Quantity/tab (mg)
<i>Layer-1</i>		
1.	Atorvastatin calcium	10.00
2.	Ramipril	5.00
3.	Calcium carbonate	20.00
4.	Croscarmellose sodium	5.00
5.	Microcrystalline cellulose (Avicel PH 102)	43.00
6.	Pregelatinised starch	10.00
7.	Polysorbate-80	5.00
8.	Hydroxypropyl cellulose	5.00
9.	Colloidal silicon dioxide	2.00
10.	Magnesium stearate	5.00
Total weight of layer 1		135.00 mg
<i>Layer-2</i>		
11.	Folic acid	5.00
12.	Vitamin B-6 (Pyridoxine)	20.00
13.	Microcrystalline cellulose (Avicel PH 102)	67.00
14.	Povidone K-30	4.00
15.	Sodium starch glycollate	2.00
16.	Magnesium stearate	2.00
Total weight of layer 2		100.00 mg
<i>Layer-3</i>		
17.	Methylcobalamin	1.80
18.	Microcrystalline cellulose (Avicel PH 102)	50.00
19.	Lactose (DCL-21)	48.20
20.	Corn starch	8.00
21.	Calcium stearate	2.00
22.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure: As described in Example-III.

Example-8

Sr.No.	Ingredient	Quantity/tab (mg)
Layer 1		
1.	Amlodipine besylate	2.50
2.	Atorvastatin calcium	10.00
3.	Calcium carbonate	20.00
4.	Crosscarmellose sodium	5.00
5.	Microcrystalline cellulose (Avicel PH 102)	43.00
6.	Pregelatinised starch	10.00
7.	Polysorbate-80	5.00
8.	Hydroxypropyl cellulose	5.00
9.	Colloidal silicon dioxide	2.00
10.	Magnesium stearate	5.00
Total weight of layer 1		107.50 mg
Layer 2		
11.	Atenolol	50.00
12.	Folic acid	5.00
13.	Vitamin B-6 (Pyridoxine)	20.00
14.	Magnesium carbonate heavy	15.00
15.	Maize starch	35.00
16.	Microcrystalline cellulose (Avicel PH 102)	30.00
17.	Povidone K-30	4.00
18.	Sodium starch glycollate	2.00
19.	Magnesium stearate	2.00
Total weight of layer 2		163.00 mg
Layer 3		
20.	Methylcobalamin	1.80
21.	Microcrystalline cellulose (Avicel PH 102)	50.00
22.	Lactose (DCL-21)	48.20

23.	Corn starch	8.00
24.	Calcium stearate	2.00
25.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure:**Layer 1**

Mix Amlodipine besylate, Atorvastatin calcium, microcrystalline cellulose and calcium carbonate in a suitable mixer. Dissolve hydroxy propyl cellulose and polysorbate-80 in purified water and granulate above mixture till wet mass forms. Dry the wet mass in suitable dryer. Sieve the granules using suitable mesh size. Add croscarmellose sodium, magnesium stearate and colloidal silicon dioxide to the granules and blend in suitable blender.

Layer 2

Mix Atenolol, Folic acid, Vitamin B6 i.e. Pyridoxine hydrochloride, magnesium carbonate, maize starch and PVPK 30 in suitable mixer. Granulate the mix using purified water. Dry the wet mass in suitable dryer. Sieve the granules using suitable mesh size. Add sodium starch glycollate, microcrystalline cellulose and magnesium stearate to the granules and blend in suitable blender.

Layer 3

Mix Methylcobalamin with cornstarch in suitable mixer. Sieve through suitable mesh, again mix the blend in suitable mixer & resieve using suitable mesh. Mix the above drug concentrate with hydroxy propyl methylcellulose, microcrystalline cellulose and lactose in suitable blender homogenize. Add calcium stearate to the resultant blend and blend in suitable blender.

Compress the above granules of all three layers by using suitable triple layer tablet compression machine.

Example-9

Sr.No.	Ingredient	Quantity/tab (mg)
<i>Layer 1</i>		
1.	Amlodipine besylate	2.50
2.	Folic acid	5.00
3.	Vitamin B6	20.00
4.	Crosscarmellose sodium	5.00
5.	Microcrystalline cellulose (Avicel PH 102)	63.00
6.	Pregelatinised starch	10.00
7.	Polysorbate-80	5.00
8.	Hydroxypropyl cellulose	5.00
9.	Colloidal silicon dioxide	2.00
10.	Magnesium stearate	5.00
Total weight of layer 1		122.50 mg
<i>Layer 2</i>		
11.	Atenolol	50.00
12.	Atorvastatin calcium	10.00
13.	Calcium carbonate	15.00
14.	Maize starch	35.00
15.	Microcrystalline cellulose (Avicel PH 102)	30.00
16.	Povidone K-30	4.00
17.	Sodium starch glycollate	2.00
18.	Magnesium stearate	2.00
Total weight of layer 2		148.00 mg
<i>Layer 3</i>		
19.	Methylcobalamin	1.80
20.	Microcrystalline cellulose (Avicel PH 102)	50.00
21.	Lactose (DCL-21)	48.20
22.	Corn starch	8.00
23.	Calcium stearate	2.00
24.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure:**Layer 1**

Mix Amlodipine besylate, folic acid, vitamin B6, microcrystalline cellulose and pregelatinized starch in a suitable mixer. Dissolve hydroxypropylcellulose and polysorbate-80 in purified water and granulate above mixture till wet mass forms. Dry the wet mass in suitable dryer. Sieve the granules using suitable mesh size. Add croscarmellose sodium, magnesium stearate and colloidal silicon dioxide to the granules and blend in suitable blender.

Layer 2

Mix Atenolol, atorvastatin calcium, calcium carbonate, maize starch and PVPK 30 in suitable mixer. Granulate the mix using purified water. Dry the wet mass in suitable dryer. Sieve the granules using suitable mesh size. Add sodium starch glycolate, microcrystalline cellulose and magnesium stearate to the granules and blend in suitable blender.

Layer 3

Mix Methylcobalamin with cornstarch in suitable mixer. Sieve through suitable mesh, again mix the blend in suitable mixer & resieve using suitable mesh. Mix the above drug concentrate with hydroxypropyl methylcellulose, microcrystalline cellulose and lactose in suitable blender homogenize. Add calcium stearate to the resultant blend and blend in suitable blender.

Compress the above granules of all three layers by using suitable triple layer tablet compression machine.

Example-10

Sr.No.	Ingredient	Quantity/tab (mg)
Layer 1		
1.	Amlodipine besylate	5.00
2.	Atorvastatin calcium	10.00
3.	Calcium carbonate	20.00
4.	Crosscarmellose sodium	5.00
5.	Microcrystalline cellulose (Avicel PH 102)	43.00
6.	Pregelatinised starch	10.00
7.	Polysorbate-80	5.00
8.	Hydroxypropyl cellulose	5.00
9.	Colloidal silicon dioxide	2.00
10.	Magnesium stearate	5.00
Total weight of layer 1		110.00 mg
Layer 2		
11.	Atenolol	50.00
12.	Folic acid	5.00
13.	Vitamin B-6 (Pyridoxine)	20.00
14.	Magnesium carbonate heavy	15.00
15.	Maize starch	35.00
16.	Microcrystalline cellulose (Avicel PH 102)	30.00
17.	Povidone K-30	4.00
18.	Sodium starch glycollate	2.00
19.	Magnesium stearate	2.00
Total weight of layer 2		163.00 mg
Layer 3		
20.	Methylcobalamin	1.80
21.	Microcrystalline cellulose (Avicel PH 102)	50.00
22.	Lactose (DCL-21)	48.20
23.	Corn starch	8.00
24.	Calcium stearate	2.00
25.	Hydroxypropyl methyl cellulose	50.00

Total weight of layer 3	160.00 mg
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Procedure: As described in Example-7.

Example-11

Sr.No.	Ingredient	Quantity/tab (mg)
Layer 1		
1.	Atorvastatin calcium	10.00
2.	Calcium carbonate	25.00
3.	Crosscarmellose sodium	5.00
4.	Microcrystalline cellulose (Avicel PH 102)	43.00
5.	Pregelatinised starch	10.00
6.	Polysorbate-80	5.00
7.	Hydroxypropyl cellulose	5.00
8.	Colloidal silicon dioxide	2.00
9.	Magnesium stearate	5.00
Total weight of layer 1		110.00 mg
Layer 2		
10.	Atenolol	50.00
11.	Folic acid	5.00
12.	Vitamin B-6 (Pyridoxine)	20.00
13.	Magnesium carbonate heavy	15.00
14.	Maize starch	50.00
15.	Microcrystalline cellulose (Avicel PH 102)	50.00
16.	Povidone K-30	4.00
17.	Sodium starch glycollate	2.00
18.	Magnesium stearate	2.00
Total weight of layer 2		128.0 mg
Layer 3		
19.	Methylcobalamin	1.80
20.	Microcrystalline cellulose (Avicel PH 102)	50.00
21.	Lactose (DCL-21)	48.20
22.	Corn starch	8.00

23.	Calcium stearate	2.00
24.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure: As described in Example-7.

Example-12

Sr.No.	Ingredient	Quantity/tab (mg)
Layer 1		
1.	Amlodipine besylate	5.00
2.	Folic acid	5.00
3.	Vitamin B6	20.00
4.	Crosscarmellose sodium	5.00
5.	Microcrystalline cellulose (Avicel PH 102)	63.00
6.	Pregelatinised starch	10.00
7.	Polysorbate-80	5.00
8.	Hydroxypropyl cellulose	5.00
9.	Colloidal silicon dioxide	2.00
10.	Magnesium stearate	5.00
Total weight of layer 1		125.00 mg
Layer 2		
11.	Atenolol	50.00
12.	Atorvastatin calcium	10.00
13.	Calcium carbonate	15.00
14.	Maize starch	35.00
15.	Microcrystalline cellulose (Avicel PH 102)	30.00
16.	Povidone K-30	4.00
17.	Sodium starch glycollate	2.00
18.	Magnesium stearate	2.00
Total weight of layer 2		148.00 mg
Layer 3		
19.	Methylcobalamin	1.80
20.	Microcrystalline cellulose (Avicel PH 102)	50.00

21.	Lactose (DCL-21)	48.20
22.	Corn starch	8.00
23.	Calcium stearate	2.00
24.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure: As described in Example-8.

Example-13

Sr.No.	Ingredient	Quantity/tab (mg)
Layer 1		
1.	Amlodipine besylate	5.00
2.	Calcium carbonate	30.00
3.	Crosscarmellose sodium	5.00
4.	Microcrystalline cellulose (Avicel PH 102)	43.00
5.	Pregelatinised starch	10.00
6.	Polysorbate-80	5.00
7.	Hydroxypropyl cellulose	5.00
8.	Colloidal silicon dioxide	2.00
9.	Magnesium stearate	5.00
Total weight of layer 1		110.00 mg
Layer 2		
10.	Atenolol	50.00
11.	Folic acid	5.00
12.	Vitamin B-6 (Pyridoxine)	20.00
13.	Magnesium carbonate heavy	15.00
14.	Maize starch	35.00
15.	Microcrystalline cellulose (Avicel PH 102)	30.00
16.	Povidone K-30	4.00
17.	Sodium starch glycollate	2.00
18.	Magnesium stearate	2.00
Total weight of layer 2		163.00 mg
Layer 3		
19.	Methylcobalamin	1.80

20.	Microcrystalline cellulose (Avicel PH 102)	50.00
21.	Lactose (DCL-21)	48.20
22.	Corn starch	8.00
23.	Calcium stearate	2.00
24.	Hydroxypropyl methyl cellulose	50.00
Total weight of layer 3		160.00 mg

Procedure: As described in Example-7.

We Claim:

1. A pharmaceutical composition comprising
 - (a) A slow release therapeutic agent as one of the components preferably a serum homocysteine lowering agent
 - (b) An immediate release therapeutic agent belonging to antihypertensive agents selected from β -adrenergic blockers or calcium channel blockers or angiotensin converting enzyme inhibitors and
 - (c) An immediate release therapeutic agent belonging to lipid lowering agents for simultaneous, separate or sequential use in the treatment of cardiovascular and its associated or related disorders.
2. A pharmaceutical combination composition comprising
 - (a) A slow release therapeutic agent as one of the components preferably a serum homocysteine lowering agent
 - (b) An immediate release therapeutic agent belonging to antihypertensive agents selected from β -adrenergic blockers or calcium channel blockers or angiotensin converting enzyme inhibitors
 - (c) An immediate release therapeutic agent belonging to lipid lowering agents and
 - (d) Optionally one or more serum homocysteine-lowering agent in immediate release form, for simultaneous, separate or sequential use in the treatment of cardiovascular and related disorders associated with homocystinuria alongwith suitable pharmaceutically acceptable excipients.
3. A pharmaceutical combination composition comprising
 - (a) A slow release therapeutic agent as one of the components preferably a serum homocysteine lowering agent
 - (b) An immediate release therapeutic agent belonging to antihypertensive agents selected from β -adrenergic blockers or calcium channel blockers or angiotensin converting enzyme inhibitors
 - (c) An immediate release therapeutic agent belonging to lipid lowering agents and

- (d) Optionally one or more serum homocysteine lowering agent in immediate release form for use in the treatment of cardiovascular and related disorders together with suitable pharmaceutically acceptable excipients.
4. A pharmaceutical composition of claim 1 wherein the disorder is either cardiovascular and its associated disorders.
 5. A pharmaceutical composition of claim 2 wherein the disorder is either cardiovascular and its associated disorders.
 6. A pharmaceutical composition of claim 3 wherein the disorder is either cardiovascular and its associated disorders.
 7. A pharmaceutical composition of claim 1 wherein the disorder is cardiovascular and related disorders associated with homocystinuria.
 8. A pharmaceutical composition of claim 2 wherein the disorder is cardiovascular and related disorders associated with homocystinuria.
 9. A pharmaceutical composition of claim 3 wherein the disorder is cardiovascular and related disorders associated with homocystinuria.
 10. A kit containing the pharmaceutical agents defined in claim 1 to 3, either as single or as dual or as triple or quadruple entities for administration to humans suffering from cardiovascular and related disorders associated with homocystinuria.
 11. A pharmaceutical composition of claim 1 to 3, wherein said slow release therapeutic agent is selected from serum homocysteine lowering agent such as, cyanocobalamin, methylcobalamin, and pharmaceutically acceptable salt, a solvate, an isomer or derivatives thereof.
 12. A pharmaceutical composition of claim 1 to 3, wherein said slow release therapeutic agent is methylcobalamin or a pharmaceutically acceptable salt, a solvate or derivative thereof.
 13. A pharmaceutical composition of claim 1 to 3, wherein said antihypertensive agent is selected from β -adrenergic blockers such as Acebutol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Esmolol, Labetalol, Metoprolol, Nadolol, Penbutolol, Pindolol, Propranolol, Sotalol, Timolol and pharmaceutically acceptable salts, solvates, isomers and derivatives thereof.

14. A pharmaceutical composition of claim 9, wherein said β -adrenergic blocker is Atenolol or a pharmaceutically acceptable salt, a solvate, an isomer or derivative thereof.

15. A pharmaceutical composition of claim 1 to 3, wherein said antihypertensive agent is selected from calcium channel blockers such as amlodipine, diltiazem, felodipine, nifedipine, nimodipine, nisoldipine, isradipine, bepridil, and verapamil, and its salts, esters, lactones, isomers and derivatives thereof.

16. A pharmaceutical composition of claim 11, wherein said calcium channel blocker is amlodipine besylate or a pharmaceutically acceptable salt, a solvate, an isomer or derivative thereof.

17. A pharmaceutical composition of claim 1 to 3, wherein said antihypertensive agent is selected from angiotensin converting enzyme (ACE) inhibitors such as captopril, cilazapril, delapril, enalapril, enalaprilat, fentiapril, fosinopril, indolapril, libenzapril, rentiapril, zabicipril, moveltipril, spiraprilat, lisinopril, perindopril, pivopril, quinapril, ramipril, spirapril,trandolapril, zofenopril, and pharmaceutically acceptable salts, solvates, isomers and derivatives thereof.

18. A pharmaceutical composition of claim 13, wherein said angiotensin converting enzyme (ACE) inhibitor is ramipril or a pharmaceutically acceptable salt, a solvate, an isomer or derivative thereof.

19. A pharmaceutical composition of claim 1 to 3, wherein said lipid regulators are selected from 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors such as lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, fluindostatin, velostatin and the salts, solvates, isomers and derivatives thereof.

20. A pharmaceutical composition of claim 2 and 3, wherein said serum homocysteine lowering agents are selected from vitamin B2, vitamin B6, folic acid and the salts, solvates, isomers and derivatives thereof.

21. A pharmaceutical composition of any of the claims 1 to 15, which comprises a controlled or sustained release source of methylcobalamin and immediate release source of at least one antihypertensive agent, at least one lipid regulator and optionally one or more serum homocysteine lowering agents.

22. A pharmaceutical composition of any of the claims 1 to 17, wherein at least one of the therapeutically active ingredients is present in the core of a tablet composition.
23. A pharmaceutical composition of any of the claims 1 to 17, wherein said core material is present in the form of granules.
24. A pharmaceutical composition of any of the claims 1 to 17, wherein said core material is present in the core of capsule composition.
25. A pharmaceutical composition of any of the claims 1 to 17, wherein said core material is present in the form of a combination of tablets and/or granules in capsules.
26. A process of preparing a pharmaceutical combination composition according to any of the claims 1 to 21, which process comprises providing a therapeutically effective amount of methylcobalamin together with at least one lipid regulator and at least one antihypertensive agent or a pharmaceutically active salt, a solvate or derivative thereof optionally with folic acid, vitamin B6, alongwith suitable pharmaceutical excipients and prepared by either wet granulation, dry granulation, direct compression or fluidized bed granulation techniques or a suitable combination of these.
27. A tablet formulation comprising a controlled or sustained release source of methylcobalamin together with combination of immediate release source of at least one antihypertensive agent, at least one lipid regulator and optionally at least one serum homocysteine lowering agent.
28. A tablet formulation comprising a controlled or sustained release source of methylcobalamin together with combination of immediate release source of at least one antihypertensive agent, at least one lipid regulator and at least one serum homocysteine lowering agent.
29. A tablet formulation of claim 23 and 24, wherein controlled or sustained release source comprises methylcobalamin or its salt, a solvate or derivative thereof.
30. A tablet formulation of claim 23 and 24, wherein methylcobalamin or its salt, a solvate or derivative thereof is in immediate release form alongwith other cardiovascular agents.
31. A tablet formulation of claim 23 and 24, wherein the source of serum homocysteine lowering agents may be released immediately.

32. A tablet formulation of claim 23 to 24, wherein said antihypertensive agents are selected from β -adrenergic blockers or calcium channel blockers or angiotensin converting enzyme (ACE) inhibitors.
33. A tablet formulation of claim 28, wherein said β -adrenergic blocker is atenolol.
34. A tablet formulation of claim 28, wherein said calcium channel blocker is amlodipine besylate.
35. A tablet formulation of claim 23 and 24, wherein said lipid regulator belongs to HMG CoA reductase inhibitors such as lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, fluindostatin, velostatin and the salts, solvates and derivatives thereof.
36. A tablet formulation of claim 23 and 24, wherein said serum homocysteine lowering agents are folic acid and vitamin B6.
37. A pharmaceutical composition of any of the claims 1 to 31, wherein the composition comprises a multilayer system.
38. A pharmaceutical composition of any of the claims 1 to 32, wherein composition comprises at least more than a single layer system.
39. A pharmaceutical composition of any of the claims 1 to 34, wherein composition comprises a triple layer system comprising one sustained or controlled release layer comprising methylcobalamin and suitable pharmaceutically acceptable excipients, and the second and third immediate release layers comprising of at least one antihypertensive agent, at least one lipid regulator and optionally at least one serum homocysteine lowering agent.
40. A pharmaceutical composition of claim 35, wherein the composition comprises
- The first immediate release layer comprising combination of at least one calcium channel blocker together with at least one lipid regulator with suitable pharmaceutically acceptable excipients, and
 - The second immediate release layer comprising at least one β -adrenergic blocker and optionally at least one serum homocysteine agents such as folic acid and/or vitamin B6, with suitable pharmaceutically acceptable excipients and

- c. The third sustained or controlled release layer comprising methylcobalamin with pharmaceutically acceptable excipients.
41. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one calcium channel blocker together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising combination of at least one β -adrenergic blocker and at least one lipid regulator with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients.
42. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one lipid regulator with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising combination of at least one angiotensin converting enzyme (ACE) inhibitor together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin and with suitable pharmaceutically acceptable excipients.
43. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one lipid regulator together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising at least one angiotensin converting enzyme (ACE) inhibitor with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin and with suitable pharmaceutically acceptable excipients.

44. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one β -adrenergic blocker together with at least one lipid regulator with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising at least one calcium channel blocker together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients.
45. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one angiotensin converting enzyme (ACE) inhibitor together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising at least one lipid regulator with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients.
46. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one β -adrenergic blocker together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising at least one calcium channel blocker together with at least one lipid regulator with suitable pharmaceutical excipients and

- c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients
47. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one angiotensin converting enzyme (ACE) inhibitor with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising at least one lipid regulator together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients
48. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one calcium channel blocker together with at least one β -adrenergic blocker with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising at least one lipid regulator together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients
49. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one lipid regulator together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and

- b. The second immediate release layer comprising at least one calcium channel blocker together with at least one β -adrenergic blockers with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients
50. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one β -adrenergic blocker together with at least one lipid regulator with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising at least one calcium channel blocker together with serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutical excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients
51. A pharmaceutical composition of claim 35, wherein the composition comprises
- a. The first immediate release layer comprising combination of at least one calcium channel blocker together with serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and
 - b. The second immediate release layer comprising at least one β -adrenergic blocker together with at least one lipid regulator with suitable pharmaceutically acceptable excipients and
 - c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients.
52. A method of treating a condition prevented, ameliorated or eliminated by administration of a combination composition comprising sustained or controlled release methylcobalamin, at least one antihypertensive agent, at least one lipid regulator and

optionally at least one serum homocysteine lowering agent which method comprises administering to a human patient suffering from or susceptible to such a condition a therapeutically effective amount of a composition according to any of the claims 35 to 47.

53. A method of treating cardiovascular and related disorders in a subject in need of treatment, which method comprises administering to the subject a pharmaceutical composition according to any of the claims 35 to 47.
54. A method of claim 53, wherein the cardiovascular and related disorders are associated with homocystinuria.
55. A tablet formulation comprising a controlled or sustained release source of methylcobalamin together with combination of immediate release source of at least one lipid regulator and at least one serum homocysteine lowering agent.
56. A tablet formulation of claim 55, wherein controlled or sustained release source comprises methylcobalamin or its salt, a solvate or derivative thereof.
57. A tablet formulation of claim 55, wherein said lipid regulator belongs to HMG CoA reductase inhibitors such as lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, fluindostatin, velostatin and the salts, solvates and derivatives thereof.
58. A tablet formulation of claim 55, wherein said serum homocysteine lowering agents are folic acid and vitamin B6.
59. A pharmaceutical composition of any of the claims 35 to 55, wherein the composition comprises a multilayer system.
60. A pharmaceutical composition of any of the claims 35 to 55, wherein composition comprises at least more than a single layer system.
61. A pharmaceutical composition of any of the claims 35 to 60, wherein composition comprises double or triple layer system comprising one sustained or controlled release layer comprising methylcobalamin and suitable pharmaceutically acceptable excipients, and the second and third immediate release layers comprising of at least one lipid regulator and at least one serum homocysteine lowering agent.
62. A pharmaceutical composition of claim 55 and 61, wherein the composition comprises

- a. The first immediate release layer comprising at least one calcium channel blocker with suitable pharmaceutically acceptable excipients, and
- b. The second immediate release layer comprising at least one serum homocysteine agents such as folic acid and/or vitamin B6, with suitable pharmaceutically acceptable excipients and
- c. The third sustained or controlled release layer comprising methylcobalamin with pharmaceutically acceptable excipients.

63. A pharmaceutical composition of claim 55 and 61, wherein the composition comprises

- a. The first immediate release layer comprising combination of at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and
- b. The second immediate release layer comprising at least one lipid regulator with suitable pharmaceutical excipients and
- c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients.

64. A pharmaceutical composition of claim 55 and 61, wherein the composition comprises

- a. The first immediate release layer comprising combination of at least one lipid regulator together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutical excipients and
- b. The second sustained or controlled release layer comprising methylcobalamin and with suitable pharmaceutically acceptable excipients.

65. A method of treating a condition prevented, ameliorated or eliminated by administration of a combination composition comprising sustained or controlled release methylcobalamin, at least one lipid regulator and at least one serum homocysteine lowering agent which method comprises administering to a human patient suffering from or susceptible to such a condition a therapeutically effective amount of a composition according to any of the claims 55 to 64.

66. A method of treating cardiovascular and related disorders in a subject in need of treatment, which method comprises administering to the subject a pharmaceutical composition according to any of the claims 55 to 64.
67. A method of claim 66, wherein the cardiovascular and related disorders are associated with homocystinuria.
68. A method of claim 67, wherein the cardiovascular disorder is hyperlipidemia associated with homocystinuria.
69. A tablet formulation comprising a controlled or sustained release source of methylcobalamin together with combination of immediate release source of at least one antihypertensive agent and at least one serum homocysteine lowering agent.
70. A tablet formulation of claim 69, wherein controlled or sustained release source comprises methylcobalamin or its salt, a solvate or derivative thereof.
71. A tablet formulation of claim 70, wherein said antihypertensive agents are selected from β -adrenergic blockers or calcium channel blockers or angiotensin converting enzyme (ACE) inhibitors.
72. A tablet formulation of claim 71, wherein said β -adrenergic blocker is atenolol.
73. A tablet formulation of claim 71, wherein said calcium channel blocker is amlodipine besylate.
74. A pharmaceutical composition of claim 71, wherein said antihypertensive agent is selected from angiotensin converting enzyme (ACE) inhibitors such as captopril, cilazapril, delapril, enalapril, enalaprilat, fentiapril, fosinopril, indolapril, libenzapril, rentiapril, zabicipril, moveltipril, spiraprilat, lisinopril, perindopril, pivopril, quinapril, ramipril, spirapril, trandolapril, zofenopril, and pharmaceutically acceptable salts, solvates and derivatives thereof.
75. A tablet formulation of claim 69, wherein said serum homocysteine lowering agents are folic acid and vitamin B6.
76. A pharmaceutical composition of any of the claims 69 to 75, wherein the composition comprises a multilayer system.
77. A pharmaceutical composition of any of the claims 69 to 75, wherein composition comprises at least more than a single layer system.

■ A pharmaceutical composition of any of the claims 69 to 75, wherein composition comprises double or triple layer system comprising one sustained or controlled release layer comprising methylcobalamin and suitable pharmaceutically acceptable excipients, and the second and third immediate release layers comprising of at least one antihypertensive agent and at least one serum homocysteine lowering agent.

79. A pharmaceutical composition of claim 69 and 78, wherein the composition comprises

- a. The first immediate release layer comprising at least one calcium channel blocker with suitable pharmaceutically acceptable excipients, and
- b. The second immediate release layer comprising at least one β -adrenergic blocker and at least one serum homocysteine agents such as folic acid and/or vitamin B6, with suitable pharmaceutically acceptable excipients and
- c. The third sustained or controlled release layer comprising methylcobalamin with pharmaceutically acceptable excipients.

80. A pharmaceutical composition of claim 69 and 78, wherein the composition comprises

- a. The first immediate release layer comprising combination of at least one calcium channel blocker together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and
- b. The second immediate release layer comprising at least one β -adrenergic blocker with suitable pharmaceutical excipients and
- c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients.

81. A pharmaceutical composition of claim 69 and 78, wherein the composition comprises

- a. The first immediate release layer comprising at least one β -adrenergic blocker or at least one calcium channel blocker or at least one angiotensin converting

enzyme (ACE) inhibitor together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutical excipients and

- b. The second sustained or controlled release layer comprising methylcobalamin and with suitable pharmaceutically acceptable excipients.

82. A pharmaceutical composition of claim 69 and 78, wherein the composition comprises

- a. The first immediate release layer comprising combination of at least one β -adrenergic blocker together with at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutically acceptable excipients and
- b. The second immediate release layer comprising at least one calcium channel blocker with suitable pharmaceutical excipients and
- c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients

83. A pharmaceutical composition of claim 69 and 78, wherein the composition comprises

- a. The first immediate release layer comprising combination of at least one calcium channel blocker together with at least one β -adrenergic blocker with suitable pharmaceutically acceptable excipients and
- b. The second immediate release layer comprising at least one serum homocysteine agents such as folic acid and vitamin B6 with suitable pharmaceutical excipients and
- c. The third sustained or controlled release layer comprising methylcobalamin with suitable pharmaceutically acceptable excipients

84. A therapeutically effective amount of a pharmaceutical composition according to any of the claims 1,17,23,24,35,55 and 69, which allows reduction in the dosing regimen of any of the individual agents for cardiovascular and related disorders associated with homocystinuria

85. A therapeutically effective amount of a pharmaceutical composition according to any of the claims 1,17,23,24,35,55 and 69 which allows reduction in the dosing regimen of any of the individual agents for hypertension and related disorders associated with homocystinuria.
86. A therapeutically effective amount of a pharmaceutical composition according to any of the claims 1,17,23,24,35,55 and 69, which allows reduction in the dosing regimen of any of the individual agents for related disorders associated with homocystinuria.
87. A therapeutically effective amount of a pharmaceutical composition according to any of the claims 1,17,23,24,35,55 and 69 which allows reduction in the dosing regimen of any of the individual agents for hyperlipidemia and related disorders associated with homocystinuria.
88. A pharmaceutical composition of any of the claims 1,17,23,24,35,55 and 69 wherein the formulation is administered as multilayer system for the treatment of cardiovascular and related disorders associated with homocystinuria.
89. A pharmaceutical composition of any of the claims 1,17,23,24,35,55 and 69 wherein the formulation is in the form of one or more tablets for simultaneous, separate or sequential use in the treatment of cardiovascular and related disorders associated with homocystinuria.
90. A pharmaceutical composition of any of the claims 1,17,23,24,35,55 and 69 to 71, wherein the formulation is in the form of one or more capsules for simultaneous, separate or sequential use in the treatment of cardiovascular and related disorders associated with homocystinuria.
91. A composition of any of the claims 1,17,23,24,35,55 and 69 wherein the formulation is in the form of one or more tablets and/or capsules and/or granules for simultaneous, separate or sequential use in the treatment of cardiovascular and related disorders associated with homocystinuria.
92. A process of preparing a pharmaceutical composition according to any of the claims 69 to 78, which process comprises providing a therapeutically effective amount of methylcobalamin, folic acid, vitamin B6 together with lipid regulators and antihypertensive agents or a pharmaceutically active salt, solvate or derivatives thereof,

alongwith suitable pharmaceutical excipients prepared by wet granulation, dry granulation, direct compression or fluidized bed granulation techniques or a suitable combination of these.

93. A method of treating a condition prevented, ameliorated or eliminated by administration of a combination composition comprising sustained or controlled release methylcobalamin, at least one antihypertensive agent, at least one lipid regulator and at least one serum homocysteine lowering agent which method comprises administering to a human patient suffering from or susceptible to such a condition a therapeutically effective amount of a composition according to any of the claims 69 to 92.
94. A method of claim 93, wherein the antihypertensive agent is selected from β -adrenergic blockers or calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors or salts, solvates and derivatives thereof.
95. A method of treating cardiovascular and related disorders in a subject in need of treatment, which method comprises administering to the subject a pharmaceutical composition according to any of the claims 69-94.
96. A method of claim 95, wherein the cardiovascular and related disorders are associated with homocystenuria.
97. A method of claim 96, wherein the cardiovascular disorder is hypertension associated with homocystenuria
98. Use of sustained or controlled release methylcobalamin, at least one antihypertensive agent, at least one lipid regulator and at least one serum homocysteine lowering agent, in the manufacture of a medicament for the treatment of cardiovascular and related disorders associated with homocystenuria.
99. Use of the pharmaceutical combination composition according to claim 80, wherein the antihypertensive agent is selected from β -adrenergic blockers or calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors or salts, solvates and derivatives thereof, in the manufacture of a medicament for the treatment of cardiovascular and related disorders associated with homocystenuria.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB05/00346

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 9/20(2006.01),9/22(2006.01),9/24(2006.01),9/26(2006.01),9/48(2006.01),9/52(2006.01),9/54(2006.01)

USPC: 424/451,457,458,464,468,469,470,472

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/451, 457, 458, 464, 468, 469, 470, 472

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,004,582 A (FAOUR et al.) 21 December 1999 (21.12.1999), see reference.	1-3
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Y	US 2002/0077348 A1 (DEAN et al.) 20 June 2002 (20.06.2002), see reference.	4-10, 13-28, 30-39
Y	US 2002/0172721 A1 (BOULOS et l.) 21 November 2002 (21.11.2002) see reference.	11, 12, 29, 40-99



Further documents are listed in the continuation of Box C.



See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

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