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(54) Title: PHARMACEUTICAL COMBINATIONS AND FORMULATIONS WITH IMPROVED STABILITY

(57) Abstract: In combination, at least one therapeutic agent which is susceptible to degradation, and at least one stabilising agent comprising at least one carbonate salt of an amino acid optionally together with one or more saccharides, whereby the stabilising agent can provide a protective stabilising effect for the at least one therapeutic agent susceptible to degradation when present in a pharmaceutical formulation.

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PHARMACEUTICAL COMBINATIONS AND FORMULATIONS WITH IMPROVED STABILITY

The present invention relates to pharmaceutical combinations and formulations with improved stability, uses thereof and processes of preparing the same.

Degradation of a drug can happen through physical, chemical or biological means. The degraded compound is a new moiety generally exhibiting new properties. Such new properties may render the new moiety either inactive or toxic. In both cases there is loss of active ingredient and thus a decrease in therapeutic activity associated therewith.

There are several compounds that are particularly susceptible to degradation and these compounds become difficult to formulate. Such compounds include HMG-CoA reductase inhibitors, ACE inhibitors, anti-histaminics, benzimidazoles and anti-viral agents, including nucleoside reverse transcriptase inhibitors, amongst others well known in the art. It is well known that these molecules degrade easily and therefore pose a great challenge in their formulation development.

HMG-CoA reductase inhibitors are the lipid lowering agents that inhibit the HMG-CoA reductase enzyme and thereby reduce elevated blood pressure. The compounds of this class include pravastatin, lovastatin, simvastatin, fluvastatin, rosuvastatin and the like. These compounds are particularly susceptible to hydrolysis and oxidation. The compounds show immediate discolouration on degradation.

US 5,030,447 discloses a pharmaceutical formulation in the form of a tablet, which has enhanced stability comprising a medicament which is sensitive to a low pH environment, namely pravastatin, one of more fillers, one or more binders, one or more disintegrants, one of more lubricants and one or more basifying agents to impart a desired pH of at least

9 to an aqueous dispersion of said formulation. The basifying agent can be MgO, $Mg(OH)_2$, $Ca(OH)_2$, NaOH, KOH, LiOH, NH_4OH, $Al(OH)_3$ or magaldrate.

WO 01/97800 discloses a method of stabilising pravastatin by adding one or more acid magnesium compounds or acid aluminum compounds, such as magnesium aluminate silicate and magnesium aluminate metasilicate, and medicinal formulations containing thus stabilised pravastatin.

WO 01/93860 discloses stabilisation of a HMG-CoA reductase inhibitor with a buffering substance or basifying substance present in a homogeneous mixture in an amount of about 1% by weight or less, wherein the buffering or basifying agent is selected from the group consisting of salts of inorganic acids, salts of organic bases and salts of organic acids. The process is carried out using co-crystallisation and / or co-precipitation.

Proton pump inhibitors include benzimidazoles, such as omeprazole, rabeprazole, pantoprazole, lansoprazole and the like, which act by preventing the proton pump, the common pathway for acid secretion. These benzimidazoles are highly sensitive to acidic pH. They degrade easily in water and their rate of degradation is increased as the pH of water is decreased.

US 6,379,705 discloses stable pellet pharmaceutical preparations containing substituted benzimidazoles or their salts, present in an amount of 1 to 50 mg. The preparations are characterised in that they comprise an inert core constituting inert excipients having a spherical symmetry with a diameter of 600-1000μm, and which is coated with an active layer containing at least one substituted benzimidazole or its salt in micronised form. Sodium tetraborate is employed to improve the stability of the benzimidazole or its salt. Various pharmaceutically acceptable inert excipients, mixed in suitable proportions to allow the disaggregation of the formulations and dissolution of the active ingredient, are also employed. A further insulating coating layer is also present which consists of a water soluble polymer and any residual water, and being free from alkaline and / or

alkaline-earth metallic salts, and has a minimum thickness of 15μm. Finally, there is also present a gastro-resistant or enteric layer of a minimum thickness of 30μm.

US 6,248,758 discloses stabilising a benzimidazole compound by complexing it with beta and gamma cyclodextrin.

US 2002054913 discloses stabilising a benzimidazole compound by coating the core with an emollient and then coating with a gastric juice resistant layer.

US 6,013,281 discloses a process for preparing an oral pharmaceutical formulation comprising the steps of forming a core material comprising a proton pump inhibitor and at least one alkaline reacting compound, applying an enteric coating polymer layer so as to surround the core material, and thereby forming in situ a separating layer as a water soluble salt product between the alkaline compound and the enteric coating polymer. The concentration of the alkaline reacting compound is about 0.1mmol/g dry ingredients in the alkaline containing part of the core material.

The prior art methods as described herein to stabilise the above compounds are difficult and tedious to perform and the stabilisers are very difficult to obtain and expensive.

Anti-histaminics such as cetirizine, loratidine, desloratidine, terfenadine, astemizole, acrivastine, and other H_1 receptor antagonists, act by blocking the effects of histamine at the various sites of actions and therefore prevent the body from harmful effects of histamine.

US 6,100,274 discloses a method of stabilising the antihistaminic compounds by formulating along with a DCL (descarbonylethoxyloratadine) - protective amount of a pharmaceutically acceptable basic salt and at least one pharmaceutically acceptable disintegrant. The pharmaceutically acceptable basic salt is a calcium, magnesium or aluminum salt, or mixtures thereof, preferably dibasic calcium phosphate. In practical terms, however, the formulation can result in a very hard tablet due to the presence of

dibasic calcium phosphate and as such the formulation requires high amounts of disintegrating agents to be incorporated. Furthermore, the disintegration time of the tablet is increased to about 9-10 minutes.

Anti-viral agents, particularly nucleoside reverse transcriptase inhibitors, such as azidothymidine, didanosine, zalcitabine, stavudine, amongst the others of this class, act by inhibiting the chain synthesis of viral DNA. These anti-viral agents are susceptible to acidic pH environments and like benzimidazoles are often enteric coated to prevent degradation.

US 6,569,463, discloses a pharmaceutical formulation in the form of a solid carrier comprising a substrate and an encapsulation coat on the substrate, wherein the encapsulation coat comprises an admixture of a therapeutically effective amount of a hydrophobic pharmaceutically active ingredient, an effective solubilising amount of at least one hydrophilic surfactant, and a lipophilic additive selected from the group consisting of lipophilic surfactants, triglycerides, and combinations thereof. The effective solubilising amount of the at least one hydrophilic surfactant is an amount effective to partially or fully solubilise the pharmaceutically active ingredient in the encapsulation coat.

US 6,569,457 discloses an enteric coated pharmaceutical formulation comprising: (a) a core in the form of a tablet consisting essentially of an acid labile medicament, and optionally a binder, a lubricant and a disintegrant, and (b) an enteric coating surrounding the tablet. The enteric coating includes an alkalising agent whereby the core is afforded protection in a low pH environment of 3 or less, whilst being capable of releasing a medicament at a pH of 4.5 or higher. The formulation is devoid of a protective subcoat between the core and the enteric coating.

ACE inhibitors act on the enzyme ACE and prevent the formation of angiotensin-II, which is responsible for increasing blood pressure. It is a well-documented fact that ACE inhibitors are highly susceptible to degradation by undergoing the chemical reactions of

cyclisation, hydrolysis and oxidation. The active ingredients readily degrade in the dosage form itself to their diketopiperazine derivatives, which is the internal cyclisation product, and other diacid derivatives.

US 4,793,998 discloses a method of stabilising an ACE inhibitor by combining it with about 1% to 90% by weight of an ascorbic acid-containing stabiliser, with ascorbic acid being at least 10% by weight of the pharmaceutical formulation. The ascorbic acid containing stabilisers are a combination of ascorbic acid with citric acid, fumaric acid, and maleic acid. A disadvantage associated with this formulation is that the ascorbic acid itself gets oxidized on long-term storage and towards the end of its shelf life, is not available to protect the ACE inhibitor.

US 6,509,350 also describes the stabilisation of ACE inhibitors by employing a hydrochloric acid donor selected from an amino acid hydrochloride, or a Lewis acid chloride, along with suitable excipients. The amino acid hydrochloride is selected from glycine hydrochloride, betaine hydrochloride, lysine hydrochloride and the like, whereas the Lewis acid chlorides can be ferric chloride, zinc chloride and aluminum chloride.

US 6,300,361 and US 6,300,362 describe a method of increasing the stability of ACE inhibitors by including the ACE inhibitor along with betaine hydrochloride and the other excipients in the formulation.

US 6,509,350, US 6,300,361 and US 6,300,362 describe that the use of amino acid hydrochlorides, or Lewis acid chlorides, pose several formulation difficulties, in view of the highly hygroscopic nature thereof.

Various prior art documents, such as US 6,417,196 and US 4,743,450, describe stabilisation of ACE inhibitors using a metal containing stabiliser selected from metals from Group I and II of the periodic table, such as magnesium, calcium and sodium, along with a saccharide. This prior art use of such inorganic metal salts has, however, posed formulation difficulties, as a result of being very light and fluffy.

It will be appreciated from the above that although numerous attempts have been made in the prior art to solve the problem of instability, there still remains a long-standing need for a method of stabilising formulations of such compounds, which is inexpensive, time-efficient and minimises compound degradation.

There is provided by the present invention, therefore, the use of carbonate salts of amino acids as stabilisers for unstable therapeutic agents substantially as discussed above, and which carbonate salts can either be employed alone or together with one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, and pharmaceutical combinations and formulations containing stabilising amounts of such carbonate salts of amino acids and optionally one or more saccharides. The carbonate salts of amino acids can include arginine carbonate, lysine carbonate, and the like, their enantiomers, derivatives, or salts thereof, and may suitably be employed as group I or II alkali or alkali earth metal salts of carbonate salts of amino acids, enantiomers, derivatives, or salts thereof. These group I or II alkali or alkali earth metal salts of carbonate salts of amino acids can include compounds such as monosodium glycine carbonate, disodium glycine carbonate, magnesium glycine carbonate, lithium glycine carbonate, calcium glycine carbonate and the like.

Sodium glycine carbonate has previously been used in various pharmaceutical formulations, but the extent of its prior art use is as an effervescent. US 6,077,536 discloses an effervescent formulation comprising amoxicillin trihydrate along with an effervescent couple, the couple comprising an acid component consisting of citric acid, tartaric acid and maleic acid and mixtures thereof, and where the alkaline component of the effervescent couple is selected from the group consisting of sodium bicarbonate, sodium glycine carbonate and sodium carbonate, the corresponding potassium salts, and mixtures thereof.

US 6,444,198 discloses a formulation of effervescent laxatives wherein the effervescence is provided by the combination of acids such as citric acid, maleic acid, and fumaric acid

along with carbonate salts of amino acids such as lysine carbonate, arginine carbonate and the like.

However, nowhere in the prior art is there any disclosure, or suggestion, as to the use of these carbonate salts of amino acids, and their alkali or alkali earth metal salts, of group I or II, as stabilisers in pharmaceutical formulations. It has been found surprisingly that these classes of compounds protect therapeutic agents susceptible to degradation, and therefore increase their stability, their associated therapeutic activity and bioavailability in a formulation. These carbonate salts are also easy to handle, store and do not pose any formulation difficulties.

The present invention is, therefore, aimed at the provision of pharmaceutical combinations and formulations with increased stability by employing stabilisers such as carbonate salts of amino acids, their derivatives, enantiomers and salts thereof, and which carbonate salts can either be employed alone or together with one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor. Further to the above, the present invention can provide a stabilised pharmaceutical combination, and a formulation comprising the same, which provides improved therapeutic activity and increased bioavailability until the end of its shelf life. The present invention also provides a process of preparing such combinations and formulations and the use of such carbonate salts and optionally one or more saccharides as referred to above, as stabilisers in pharmaceutical combinations and formulations including one or more therapeutic agents susceptible to degradation.

The present invention provides, therefore, in combination, at least one therapeutic agent which is susceptible to degradation, and at least one stabilising agent comprising at least one carbonate salt of an amino acid, wherein at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilising agent further comprises one or more saccharides, whereby said stabilising agent can provide a protective stabilising effect for said therapeutic agent susceptible to degradation when present in a pharmaceutical formulation.

There is also provided by the present invention a pharmaceutical formulation comprising one or more therapeutic agents at least one of which is susceptible to degradation, at least one stabilising agent comprising a stabilising amount of at least one carbonate salt of an amino acid, wherein at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilising agent further comprising one or more saccharides, and a pharmaceutically acceptable carrier or excipient therefor.

The term "susceptible to degradation" as used herein is used to characterise one or more classes of therapeutic agents that in use can convert to one or more new moieties as a result of physical, chemical or biological means. These one or more classes of therapeutic agents can include HMG-CoA reductase inhibitors, ACE inhibitors, anti-histaminics, benzimidazoles and anti-viral agents, including nucleoside reverse transcriptase inhibitors, amongst others well known in the art. These therapeutic agents are known to generally degrade easily in use and, therefore, have hitherto posed a great challenge in their formulation development. Degradation can involve cyclisation, hydrolysis, oxidation and several other chemical, microbiological or physical reactions, thereby resulting in the formation of degradation products, and an associated reduced therapeutic activity and decreased bioavailability of the active therapeutic agent.

Specific examples of therapeutic agents susceptible to degradation of the above referred to therapeutic classes of compounds and suitable for use in pharmaceutical combinations and formulations according to the present invention can include but are not limited to the following.

The HMG-CoA reductase inhibitors may be selected from the group consisting of pravastatin, fluvastatin, simvastatin, lovastatin and atorvastatin, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

The ACE inhibitors may be carboxyalkyldipeptides selected from the group consisting of ramipril, quinapril, fosinopril, captopril, enalapril, lisinopril, perindopril, trandolapril,

benazepril and moexipril, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

The anti-histaminics may be H_1 receptor antagonists selected from the group consisting of cetirizine, desloratidine, terfenadine and aestimazole, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

The benzimidazoles may be selected from the group consisting of omeprazole, rabeprazole, pantoprazole and lansoprazole, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

Anti-viral agents, in particularly nucleoside reverse transcriptase inhibitors, may be selected from the group consisting of didanosine, azidothymidine, zalcitabine and stavudine, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

Particularly preferred therapeutic agents for use according to the present invention and as illustrated by the Examples include any of the following: quinapril hydrochloride, pravastatin sodium, captopril, captopril hydrochloride, omeprazole, cetirizine, desloratidine and didanosine.

Formulations according to the present invention can further comprise, in addition to at least one therapeutic agent susceptible to degradation substantially as described above, at least one further therapeutic agent so as to provide a pharmaceutically acceptable stable drug combination. Illustrative categories and specific examples of such further therapeutic agents include but are not limited to:

a) Diuretics such as hydrochlorthiazide, potassium sparing diuretics such as triamterene and amiloride, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof;

b) Antitussives such as dextromorphan hydrobromide, noscapine, carbetantane citrate and chlophedianol hydrochloride, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof;

c) Decongestants such as phenylephidrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephidrine hydrochloride and ephedrine, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof;

d) Various alkaloids such as codeine phosphate, codeine sulphate and morphine, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof;

e) Mineral supplements such as potassium chloride;

f) Calcium channel blockers such as digitalis, amlodipine, nifedipine and the like, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof;

g) The beta adrenergic blockers such as propanolol, atenolol, timolol, sotalol, metoprolol and the like, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof;

h) Aldosterone antagonists such as spironolactone and the like, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

The term "amino acid" as used herein can include any one of the 20 naturally occurring amino acids, their enantiomers, derivatives or salts thereof. Particularly suitable amino acids include glycine, arginine and lysine, either present as carbonate salts *per se* or more preferably as group I or II alkali or alkali earth metal salts of carbonate salts of amino acids, their enantiomers, derivatives or salts thereof, such as monosodium glycine carbonate, disodium glycine carbonate, magnesium glycine carbonate, lithium glycine carbonate and calcium glycine carbonate. Suitable carbonate salts of amino acids that can be employed according to the present invention and are illustrated by the Examples can be selected from the group consisting of monosodium glycine carbonate, disodium glycine carbonate, magnesium glycine carbonate, calcium glycine carbonate, arginine carbonate and lysine carbonate.

In a first embodiment of the present invention, the stabilising agent can consist essentially of at least one carbonate salt of an amino acid and more particularly can consist

essentially of a stabilising amount of at least one carbonate salt of an amino acid as described herein. The term "stabilising amount" as used herein can denote an amount of a carbonate salt of an amino acid whereby the amino acid carbonate salt can provide a protective effect for the at least one therapeutic agent which is susceptible to degradation, and thereby increase the stability, associated therapeutic activity and bioavailability of the therapeutic agent when present in a formulation according to the present invention. Typically, the amino acid carbonate salt may be used in the range of 0.01% to 75% by weight based on the total weight of the formulation and more preferably in the range of 0.01% to 50% by weight based on the total weight of the formulation. Therapeutic agents particularly suitable for use according to the first embodiment of the present invention include benzimidazoles, anti-viral agents and anti-histaminics, but not HMG-CoA reductase inhibitors, or ACE-inhibitors.

In a second embodiment of the present invention, the stabilising agent can comprise one or more amino acid carbonate salts, together with one or more saccharides, and more particularly can comprise a stabilising amount at least one carbonate salt of an amino acid as described herein, and at least one saccharide to enhance the stability provided by the carbonate salt of an amino acid. A suitable saccharide for use according to the second embodiment of the present invention may be selected from the group consisting of lactose, sucrose, glucose, mannitol, xylitol, maltitol, sorbitol and erythritol, either present in anhydrous or hydrated form. Typically a saccharide can be included in a formulation according to the present invention in the range of 5% to 80% by weight based on the total weight of the formulation. Therapeutic agents suitable for use according to the second embodiment of the present invention can include HMG-CoA reductase inhibitors, ACE inhibitors, anti-histaminics, benzimidazoles and anti-viral agents, but in the case where the therapeutic agent comprises a HMG-CoA reductase inhibitor, or ACE-inhibitor, then it is required that one or more saccharides are present to enhance the stabilising effect of a carbonate salt of an amino acid.

Preferred combinations of therapeutic agents, carbonate salts of amino acids and where required one or more saccharides, for use in pharmaceutical combinations and in

pharmaceutical formulations according to the present invention, and as illustrated by the Examples, include any of the following: quinapril hydrochloride, monosodium glycine carbonate and lactose; pravastatin sodium, arginine carbonate and sorbitol; captopril, disodium glycine carbonate and lactose; omeprazole and l-lysine carbonate; cetirizine and calcium glycine carbonate; desloratidine and monosodium glycine carbonate; captopril hydrochloride, magnesium glycine carbonate and lactose; didanosine, l-arginine carbonate, mannitol and sucrose; didanosine and sodium glycine carbonate; and desloratidine, sodium glycine carbonate and sorbitol.

Formulations according to the present invention can be administered in the form of solids, which can be administered orally in form of tablets, capsules, pills, powders and granules, either as conventional or modified release dosage forms. The formulations can further comprise excipients, diluents, carriers, fillers, colourants, binders, disintegrating agents, lubricants, pigments, adjuvants for preserving, wetting or emulsifying, and dispersing agents, which are all well known in the pharmaceutical art.

The fillers may be selected from sugars, sugar alcohols, starches, inert materials such as kaolin, and the like, and can provide bulk to, for example, tablets so as to render the formulations suitable for compression.

Disintegrating agents may be selected from celluloses and their derivatives, alginates, agar-agar, certain complex silicates, starches, modified starches and their derivatives, polyvinylpyrolidones and the like.

The binders may be selected from natural and synthetic gums, celluloses, starches, gelatins, povidones and the like.

Lubricants may be selected from talc, magnesium stearate, microcrystalline cellulose, hydrogenated vegetable oils, polyethylene glycols and their derivatives, sodium lauryl sulphate and the like.

The excipients to be used for directly compressible tablets may include the various excipients known in the art in their DC grade for direct compression.

Tablets as provided by the present invention may be coated for the purpose of retarding the release of therapeutic agents. The coating material can be selected from celluloses and their derivatives, polyethylene glycols and their derivatives, fatty acids such as stearic acid and their derivatives, waxes and polymers, amongst other coating materials well known in the pharmaceutical art. The coating materials may further comprise pharmaceutically acceptable plasticisers to obtain desired mechanical properties, such as flexibility and hardness of the coating layer. Suitable plasticisers can for example include, but are not limited to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates, or any other suitable plasticisers. Tablets as provided by the present invention can be prepared by methods well known in the art.

For capsule preparation, the excipients such as fillers, binders, disintegrating agents, lubricants and the like may be selected from those known in the art. The capsules may be hard or soft gelatin capsules. The capsules can be prepared by methods well known in the art. The capsules may also be coated for delayed or modified release.

For sachets, suitable ingredients may be mixed and dried thoroughly. The ingredients may be packed into sachets for improved stability.

In the case where fast releasing dosage forms are required, a therapeutic agent or agents for use in formulations according to the present invention substantially as hereinbefore described can suitably be combined or coated with sugars, polyols that act as sweetners and disintegrating agents. The polyols may also act as cooling agents. The formulations may further comprise additional agents that may act as binders and lubricants. Manufacture of such formulations can be carried out under conditions well known in the art for such fast dissolving dosage forms. The polyols will also render the advantage of

providing a negative heat of solution, providing a cooling effect when chewed and thus masking the bitter taste of the dosage form.

Formulations as provided by the present invention may also be administered as liquid oral formulations, such as solutions, suspensions or emulsions, employing excipients well known in the art. Antimicrobial preservative agents may also be employed and may, for example, be selected one or more of the following - benzoic acid, sodium benzoate, methyl parabens, ethyl parabens, propyl parabens, butyl parabens and the like, and may be added in the range of 0.001% to 0.1% by weight of the formulation. Colouring agents may also be added for aesthetic appearance. Flavouring agents can be added to mask the bitterness of the formulation and to increase palatability of the formulation. The colour and the flavours are generally selected so as to be complementary to each other.

There is further provided by the present invention a process of preparing a pharmaceutical combination substantially as hereinbefore described, which process comprises providing as a combined preparation at least one therapeutic agent which is susceptible to degradation, and at least one stabilising agent comprising at least one carbonate salt of an amino acid, wherein at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilising agent further comprises one or more saccharides, whereby said stabilising agent can provide a protective stabilising effect for said therapeutic agent susceptible to degradation when present in a pharmaceutical formulation.

The present invention also provides a process of preparing a pharmaceutical formulation substantially as hereinbefore described, which process comprises admixing a pharmaceutically acceptable carrier or excipient with one or more therapeutic agents at least one of which is susceptible to degradation and at least one stabilising agent comprising a stabilising amount of at least one carbonate salt of an amino acid and also one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor. Further and / or preferred ingredients substantially as hereinbefore described for use in a formulation as provided by the present

invention may further be admixed with the above in a process as provided by the present invention.

The present invention also provides a process of stabilising at least one therapeutic agent which is susceptible to degradation, which process comprises admixing said at least one therapeutic agent and at least one stabilising agent comprising a stabilising amount of at least one carbonate salt of an amino acid and also one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor.

There is also provided by the present invention for use in stabilising at least one therapeutic agent susceptible to degradation when present in a pharmaceutical formulation, at least one carbonate salt of at least one amino acid in combination with one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor. Further and / or preferred ingredients substantially as hereinbefore described for use in a pharmaceutical formulation as provided by the present invention may also be employed in the above described use according to the present invention.

There is also provided by the present invention for use in the manufacture of a formulation, one or more therapeutic agents at least one of which is susceptible to degradation when present in a pharmaceutical formulation, and at least one stabilising agent comprising a stabilising amount of at least one carbonate salt of an amino acid together with one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor. Further and / or preferred ingredients substantially as hereinbefore described for use in a formulation as provided by the present invention may also be employed in the above described use according to the present invention.

There is also provided by the present invention a method of treatment comprising administering to an animal patient a pharmaceutical formulation substantially as hereinbefore described.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be falling within the scope of the invention.

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the invention.

Example 1

SR. NO.	INGREDIENTS	QTY/TAB (mg)	QTY/TAB (mg)
	DRY MIX		
1.	Quinapril Hydrochloride	10.83	10.83
2.	Monosodium Glycine Carbonate	100.00	20.00
3.	Lactose	76.17	156.17
4.	Crosspovidone	8.00	8.00
	BINDER SOLN		
5.	Povidone	4.00	4.00
6.	Purified Water	QS	QS
	LUBRICATION		
7.	Magnesium Stearate	1.0	1.0
	COATING		
8.	Opadry AMB	6.0	6.0
9.	Purified water	q.s.	q.s.
	TOTAL	206.0	206.0

PROCESS:

Quinapril hydrochloride and monosodium glycine carbonate were mixed in geometric proportions and sifted. Lactose and crospovidone were then added, mixed and sifted. The above dry mix was blended and granulated with povidone solution. After getting the wet mass consistency the blend was sieved and dried. The dried granules were milled and lubricated with magnesium stearate. The lubricated granules were compressed into tablets and coated.

Example 2

SR. NO.	INGREDIENTS	QTY/TAB (mg)
	DRY MIX	
1.	Pravastatin Sodium	10.0
2.	Sorbitol	74.9
3.	Crosspovidone	12.00
	BINDER SOLN	
4.	Hydroxy propyl cellulose-L	2
5.	Arginine carbonate	0.1
6.	Purified Water	QS to 5%
	LUBRICATION	
7.	Magnesium Stearate	1.0
	TOTAL	100.00

PROCESS:

Pravastatin sodium, sorbitol and crosspovidone were mixed and sifted. The resulting dry mix was then blended for 5 minutes. HPC-L and arginine carbonate were dissolved in water and the dry mix was granulated. After getting the wet mass consistency the blend

was sieved and dried. The dried granules were milled and lubricated with magnesium stearate. The lubricated granules were compressed into tablets.

Example 3

SR. NO.	INGREDIENTS	QTY/TAB (mg)
	DRY MIX	
1.	Captopril	10.00
2.	Disodium Glycine Carbonate	30.00
3.	Tablettose 80	50.00
4.	Avicel PH112	98.00
5.	Crosspovidone	12.00
	TOTAL	200.0

PROCESS:

Captopril, disodium glycine carbonate, tablettose 80 and avicel PH112 were mixed well and sifted. The blend was blended for 15 minutes. After mixing the blend was filled in capsule shells.

Example 4

SR. NO.	INGREDIENTS	QTY/TAB (mg)
1	Pellets	141.0
	Drug Solution.	
2	Omeprazole	12.5
3	L-lysine Carbonate	5.0
4	HPMC-2910	1.5

5	Ethanol	QS
6	Purified Water	QS
	Seal coating	
7	HPMC-2910	3.0
8	Methylene Chloride	QS
	Functional coating	
9	Surerelease	10.0
10	Purified Water	QS
11	Talc	2.0
	Total	175.0

PROCESS:

Pre-sifted pellets were loaded in a fluidised bed processor and the fluidisation pattern was adjusted to optimum level. Omeprazole was dissolved in ethanol and L-lysine carbonate and HPMC-2910 was dissolved in purified water. Both the solutions were mixed and sprayed on the pellets. The drug loaded pellets were seal coated with HPMC-2910 solution. After seal coating the pellets were coated with surerelease and dried. Talc was added to remove the static charge developed during the process.

The dried pellets were filled in capsule shells.

Example 5

SR. NO.	INGREDIENTS	QTY/TAB (mg)
	DRY MIX	
1.	Cetirizine	10.00
2.	Calcium Glycine Carbonate	30.00
3.	Microcrystalline cellulose	66.5

	BINDER SOLN	
4.	Povidone	3.00
5.	Purified Water	QS to 5%
	LUBRICATION	
6.	Magnesium Stearate	5.00
	COATING	
7.	Opadry	4.0
8.	Purified Water	q.s.
	TOTAL	114.00

PROCESS:

Cetirizine, sodium glycine carbonate and MCC were sifted, mixed and blended. The blend was granulated using povidone solution. After getting the wet mass consistency the blend was sieved and dried in a fluidised bed drier. The dried granules were milled and lubricated with magnesium stearate.

The lubricated granules were compressed into tablets and coated.

Example 6

SR. NO.	INGREDIENTS	QTY/TAB (mg)
	DRY MIX	
1.	Desloratidine	5.00
2.	Monosodium Glycine Carbonate.	20.00
3.	Microcrystalline cellulose	151.00
4.	L-HPC	16.00
	BINDER SOLN	
5.	HPC-L	2.00

6.	Purified Water	QS
	LUBRICATION	
7.	Siliconised Talc	6.0
	COATING	
8.	Opadry	5.0
9.	Purified Water	QS
	TOTAL	205.0

PROCESS:

Desloratidine, monosodium glycine carbonate, microcrystalline cellulose and L-HPC were mixed and sifted. This dry mix was blended for 5 minutes. HPC-L was dissolved in water and the dry mix was granulated. After getting the wet mass consistency the blend was sieved and dried in a fluidised bed drier. The dried granules were milled and lubricated with siliconised talc. The lubricated granules were compressed into tablets and coated.

Example 7

SR. NO.	INGREDIENTS	QTY/TAB (mg)
	DRY MIX	
1.	Captopril Hydrochloride	10.00
2.	Magnesium Glycine Carbonate	87.50
3.	Hydrochlorthiazide	12.5
4.	Lactose	76.17
5.	Crosspovidone	8.00
	BINDER SOLN	
6.	Povidone	4.00
7.	Purified Water	QS

	LUBRICATION	
8.	Magnesium Stearate	1.0
	COATING	
8.	Opadry AMB	6.0
9.	Purified water	q.s.
	TOTAL	200.0

PROCESS:

Quinapril hydrochloride and magnesium glycine carbonate and hydrochlorthiazide were mixed in geometric proportions and sifted. The resulting mixture was again mixed with lactose, crospovidone and sifted. The above dry mix was granulated with povidone solution. After getting the wet mass consistency the blend was sieved and dried in a fluidised bed drier. The dried granules were milled and lubricated with magnesium stearate.

The lubricated granules were compressed into tablets and coated.

Example 8

SR. NO.	INGREDIENTS	QTY/SACHET
	DRY MIX	
1.	Didanosine	100.0 mg
2.	Mannitol	250.0 mg
3.	L-arginine carbonate	250.0 mg
4.	Sucrose	390.0 mg
5.	Aspartame	5.0 mg
6.	Orange flavour	5.0 mg
	TOTAL	1000.0 mg.

PROCESS:

Didanosine, mannitol and l-arginine carbonate were mixed and sifted. Sucrose was added and sifted. Finally the blend was mixed with aspartame and orange flavour. The blend was packed in a unit dose sachet and sealed.

Example 9

SR. NO.	INGREDIENTS	QTY/TABLET (mg)	QTY/TABLET (mg)
1.	Didanosine	25.0	100
2.	Sodium glycine carbonate	200	200
3.	Starch (for paste)	50.0	50
4.	Starch	375.0	250
5.	Microcrystalline cellulose	300	300
6.	Avicel PH 102	930.00	980
7.	Sodium Starch Glycollate	50.0	50
8.	Aspartame	25.0	25
9.	Flavour pineapple	15.0	15
10	Talc	20.0	20
11	Magnesium Stearate	10	10
	TOTAL	2000.0	2000.0

PROCESS:

Didanosine, mannitol, sodium starch glycollate, sodium glycine carbonate and starch were mixed and granulated using starch (for paste). Avicel, aspartame, flavour, talc and magnesium stearate were added and blended for 15 minutes and compressed.

Example 10

SR. NO.	INGREDIENTS	QTY %W/V
1	Desloratidine	0.05
2	Methyl paraben	0.2
3	Propyl paraben	0.02
4	Edetate disodium	0.05
5	Sodium Glycine Carbonate	0.05
6	Saccharide sodium	0.2
7	Sorbitol	40.0
8	Propylene glycol	10.0
9	Flavour mixed fruit	0.1
10	Purified water	q.s to 100 ml

Process:

Desloratidine was dissolved in propylene glycol and sorbitol was added. Methyl paraben and propyl paraben were added to purified water and heated to dissolve. Both the solutions were mixed and to this sodium glycine carbonate, edetate disodium, saccharide sodium and flavour were added. Purified water was added to make up the volume.

Example 11

The stability of the formulation of the present invention can be demonstrated as against the prior art as follows:

(I) The stability of a formulation containing pravastatin sodium using a carbonate salt of an amino acid and a saccharide (Example 11B) can be demonstrated initially after preparation thereof and after 2 months at 40° C / 75%RH as compared to the prior art formulation (Example 11A):

	Example 11A			Example 11B		
	Assay	Total related Substances	pH of the Aqueous dispersion	Assay	Total related Substances	pH of the Aqueous dispersion
Initial	100.1	0.55	10.3	101.5	0.24	8.5
After 2 months at 40° C / 75%RH	99.3	1.4	10.4	99.6	0.29	8.3

where Example A and B are as follows:

Sr. No.	Example 11A		Example 11B	
	Ingredients	Quantity (mg)	Ingredients	Quantity (mg)
1.	Pravastatin Sodium	10	Pravastatin Sodium	10
2.	Magnesium Carbonate	53.6	Sodium Glycine Carbonate	0.1
3.	Mannitol	76.2	Mannitol	74.9
4.	Gelatin	5.0	Crospovidone NF	12
5.	Polyplasdone	4.0	Povidone IP (PVP K-30)	4.00
6.	Magnesium stearate	1.0	Magnesium Stearate IP	1.0

CLAIMS

1. In combination, at least one therapeutic agent which is susceptible to degradation, and at least one stabilising agent comprising at least one carbonate salt of an amino acid, wherein at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilising agent further comprises one or more saccharides, whereby said stabilising agent can provide a protective stabilising effect for said therapeutic agent susceptible to degradation when present in a pharmaceutical formulation.

2. A combination according to claim 1, wherein said therapeutic agent susceptible to degradation is selected from HMG-CoA reductase inhibitors, ACE inhibitors, anti-histaminics, benzimidazoles and anti-viral agents.

3. A combination according to claim 2, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of pravastatin, fluvastatin, simvastatin, lovastatin and atorvastatin, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

4. A combination according to claim 2, wherein the ACE inhibitor is selected from the group consisting of ramipril, quinapril, fosinopril, captopril, enalapril, lisinopril, perindopril, trandolapril, benazepril and moexipril, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

5. A combination according to claim 2, wherein the anti-histaminic is selected from the group consisting of cetirizine, desloratidine, terfenadine and aestimazole, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

6. A combination according to claim 2, wherein the benzimidazole is selected from the group consisting of omeprazole, rabeprazole, pantoprazole and lansoprazole, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

7. A combination according to claim 2, wherein the anti-viral agent is selected from the group consisting of didanosine, azidothymidine, zalcitabine and stavudine, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

8. A combination according to claim 2, wherein the therapeutic agent susceptible to degradation is selected from the group consisting of quinapril hydrochloride, pravastatin sodium, captopril, captopril hydrochloride, omeprazole, cetirizine, desloratidine and didanosine.

9. A combination according to any of claims 1 to 8, wherein said carbonate salt of said amino acid is present as either the group I or II alkali or alkali earth metal salt thereof.

10. A combination according to any of claims 1 to 9, wherein said amino acid is selected from the group consisting of glycine, arginine and lysine.

11. A combination according to claims 9 and 10, wherein said carbonate salt of said amino acid is selected from the group consisting of monosodium glycine carbonate, disodium glycine carbonate, magnesium glycine carbonate, lithium glycine carbonate and calcium glycine carbonate.

12. A combination according to claims 9 and 10, wherein said carbonate salt of said amino acid is selected from the group consisting of monosodium glycine carbonate, disodium glycine carbonate, magnesium glycine carbonate, calcium glycine carbonate, arginine carbonate and lysine carbonate.

13. A combination according to any of claims 1 to 12, wherein said stabilising agent consists essentially of a stabilising amount of at least one carbonate salt of an amino acid and said therapeutic agent is selected from the group consisting of anti-histaminics, benzimidazoles and anti-viral agents.

14. A combination according to any of claims 1 to 12, wherein the stabilising agent further comprises one or more saccharides to enhance the stability provided by said at least one carbonate salt of said amino acid and said therapeutic agent is selected from the group consisting of HMG-CoA reductase inhibitors, ACE inhibitors, anti-histaminics, benzimidazoles and anti-viral agents, in particular HMG-CoA reductase inhibitors, or ACE inhibitors.

15. A combination according to claim 15, wherein the saccharide is selected from the group consisting of lactose, sucrose, glucose, mannitol, xylitol, maltitol, sorbitol and erythritol, either in anhydrous or hydrated form.

16. In combination, at least one therapeutic agent which is susceptible to degradation, and at least one stabilising agent comprising at least one carbonate salt of an amino acid, wherein at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilising agent further comprises one or more saccharides, whereby said stabilising agent can provide a protective stabilising effect for said therapeutic agent susceptible to degradation when present in a pharmaceutical formulation, wherein said at least one therapeutic agent and said at least one stabilising agent are selected from the following combinations: quinapril hydrochloride, monosodium glycine carbonate and lactose; pravastatin sodium, arginine carbonate and sorbitol; captopril, disodium glycine carbonate and lactose; omeprazole and l-lysine carbonate; cetirizine and calcium glycine carbonate; desloratidine and monosodium glycine carbonate; captopril hydrochloride, magnesium glycine carbonate and lactose; didanosine, l-arginine carbonate, mannitol and sucrose; didanosine and sodium glycine carbonate; and desloratidine, sodium glycine carbonate and sorbitol.

17. A pharmaceutical formulation comprising one or more therapeutic agents at least one of which is susceptible to degradation, at least one stabilising agent comprising a stabilising amount of at least one carbonate salt of an amino acid, wherein at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilising agent further comprising one or more saccharides, and a pharmaceutically acceptable carrier or excipient therefor.

18. A formulation according to claim 17, wherein said therapeutic agent susceptible to degradation is selected from HMG-CoA reductase inhibitors, ACE inhibitors, anti-histaminics, benzimidazoles and anti-viral agents.

19. A formulation according to claim 18, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of pravastatin, fluvastatin, simvastatin, lovastatin and atorvastatin, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

20. A formulation according to claim 18, wherein the ACE inhibitor is selected from the group consisting of ramipril, quinapril, fosinopril, captopril, enalapril, lisinopril, perindopril, trandolapril, benazepril and moexipril, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

21. A formulation according to claim 18, wherein the anti-histaminic is selected from the group consisting of cetirizine, desloratidine, terfenadine and aestimazole, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

22. A formulation according to claim 18, wherein the benzimidazole is selected from the group consisting of omeprazole, rabeprazole, pantoprazole and lansoprazole, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

23. A formulation according to claim 18, wherein the anti-viral agent is selected from the group consisting of didanosine, azidothymidine, zalcitabine and stavudine, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

24. A formulation according to claim 18, wherein the therapeutic agent susceptible to degradation is selected from the group consisting of quinapril hydrochloride, pravastatin sodium, captopril, captopril hydrochloride, omeprazole, cetirizine, desloratidine and didanosine.

25. A formulation according to any of claims 17 to 24, wherein said carbonate salt of said amino acid is present as either the group I or II alkali or alkali earth metal salt thereof.

26. A formulation according to any of claims 17 to 25, wherein said amino acid is selected from the group consisting of glycine, arginine and lysine.

27. A formulation according to claims 25 and 26, wherein said carbonate salt of said amino acid is selected from the group consisting of monosodium glycine carbonate, disodium glycine carbonate, magnesium glycine carbonate, lithium glycine carbonate and calcium glycine carbonate.

28. A formulation according to claims 25 and 26, wherein said carbonate salt of said amino acid is selected from the group consisting of monosodium glycine carbonate, disodium glycine carbonate, magnesium glycine carbonate, calcium glycine carbonate, arginine carbonate and lysine carbonate.

29. A formulation according to any of claims 17 to 28, which further comprises a further therapeutic agent selected from the group consisting of diuretics, antitussives, decongestants, alkaloids, mineral supplements, calcium channel blockers, beta adrenergic blockers and aldosterone antagonists, including enantiomers, racemic mixtures, salts, prodrugs and derivatives thereof.

30. A formulation according to any of claims 17 to 29, wherein said carbonate salt of said amino acid is present in the range of 0.01% to 75% by weight based on the total weight of the formulation.

31. A formulation according to claim 30, wherein said carbonate salt of said amino acid is present in the range of 0.01% to 50% by weight based on the total weight of the formulation.

32. A formulation according to any of claims 17 to 31, wherein said stabilising agent consists essentially of a stabilising amount of said at least one carbonate salt of said amino acid and said therapeutic agent is selected from the group consisting of anti-histaminics, benzimidazoles and anti-viral agents.

33. A formulation according to any of claims 17 to 31, wherein the stabilising agent further comprises one or more saccharides to enhance the stability provided by said at least one carbonate salt of said amino acid and said therapeutic agent is selected from the group consisting of HMG-CoA reductase inhibitors, ACE inhibitors, anti-histaminics, benzimidazoles and anti-viral agents, in particular HMG-CoA reductase inhibitors, or ACE inhibitors.

34. A formulation according to claim 33, wherein the saccharide is selected from the group consisting of lactose, sucrose, glucose, mannitol, xylitol, maltitol, sorbitol and erythritol, either in anhydrous or hydrated form.

35. A formulation according to claim 33 or 34, wherein said saccharide is present in the range of 5% to 80% by weight based on the total weight of the formulation.

36. A pharmaceutical formulation comprising one or more therapeutic agents at least one of which is susceptible to degradation, at least one stabilising agent comprising a stabilising amount at least one carbonate salt of an amino acid, wherein at least in the

case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilising agent further comprises one or more saccharides, and a pharmaceutically acceptable carrier or excipient therefor, wherein said at least one therapeutic agent and said at least one stabilising agent are selected from the following combinations: quinapril hydrochloride, monosodium glycine carbonate and lactose; pravastatin sodium, arginine carbonate and sorbitol; captopril, disodium glycine carbonate and lactose; omeprazole and l-lysine carbonate; cetirizine and calcium glycine carbonate; desloratidine and monosodium glycine carbonate; captopril hydrochloride, magnesium glycine carbonate and lactose; didanosine, l-arginine carbonate, mannitol and sucrose; didanosine and sodium glycine carbonate; and desloratidine, sodium glycine carbonate and sorbitol.

37. A process of preparing a pharmaceutical combination according to any of claims 1 to 16, which process comprises providing as a combined preparation at least one therapeutic agent which is susceptible to degradation, and at least one stabilising agent comprising at least one carbonate salt of an amino acid, wherein at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor, the stabilising agent further comprises one or more saccharides, whereby said stabilising agent can provide a protective stabilising effect for said therapeutic agent susceptible to degradation when present in a pharmaceutical formulation.

38. A process of preparing a pharmaceutical formulation according to any of claims 17 to 36, which process comprises admixing a pharmaceutically acceptable carrier or excipient with one or more therapeutic agents at least one of which is susceptible to degradation and at least one stabilising agent comprising a stabilising amount of at least one carbonate salt of an amino acid and also one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor.

39. A process of stabilising at least one therapeutic agent which is susceptible to degradation when present in a pharmaceutical formulation, which process comprises admixing said at least one therapeutic agent and at least one stabilising agent comprising a stabilising amount of at least one carbonate salt of an amino acid and also one or more

saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor.

40. A process according to claim 39, which comprises providing a pharmaceutical combination according to any of claims 1 to 16, or a pharmaceutical formulation according to any of claims 17 to 36.

41. For use in stabilising at least one therapeutic agent susceptible to degradation when present in a pharmaceutical formulation, at least one carbonate salt of at least one amino acid in combination with one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor.

42. Use according to claim 41, which comprises providing a pharmaceutical combination according to any of claims 1 to 16, or a pharmaceutical formulation according to any of claims 17 to 36.

43. For use in the manufacture of a formulation, one or more therapeutic agents at least one of which is susceptible to degradation when present in a pharmaceutical formulation, and at least one stabilising agent comprising a stabilising amount of at least one carbonate salt of an amino acid together with one or more saccharides at least in the case where the therapeutic agent is a HMG-CoA reductase inhibitor, or an ACE inhibitor.

44. Use according to claim 43, which comprises providing a formulation according to any of claims 17 to 36.

45. A method of treatment comprising administering to an animal patient a pharmaceutical formulation according to any of claims 17 to 36.