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SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

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REF: EXPEDIENTE 03-113-785

TÍTULO SOLICITADO: "Composiciones farmacéuticas de amlodipina y atorvastatina"

PUBLICACIÓN: Gaceta 554 de 29-07-2005, número de publicación 287

PRIORIDAD: US 60/309.133 de 31/06/2001

SOLICITANTE: WARNER-LAMBERT COMPANY LLC

APODERADO: CARLOS R. OLARTE

TRÁMITE: COMPLEMENTO DE INFORMACIÓN

JOSÉ LUIS REYES VILLAMIZAR, conocido apoderado de la sociedad opositora Tecnoquímicas S.A., de manera respetuosa me permito hacer breve referencia a la respuesta a la oposición que ha sido presentada por el apoderado del solicitante el 27/07/2006, en los siguientes términos:

1. Pese a que el solicitante intenta desvirtuar los fundamentos de la oposición cuando afirma que *"Aún cuando D1 reclama una composición de amlodipino y atorvastatina, no reconoce el problema técnico particular que resuelve este invento. En particular D1, no revela o siquiera sugiere la aplicación de un agente alcalinizante que produce un pH mayor que 5 usado en el componente que incluye la atorvastatina y excluido del componente que comprende el amlodipino"*, basta tener en cuenta nuevamente que la solicitud internacional WO 99/11259 en su página 33, incluye para las tabletas propuestas, excipientes tales como citrato de sodio, carbonato de calcio y fosfato de calcio junto con otros excipientes adecuados.

Aunque la tesis del solicitante en el sentido de que únicamente las revelaciones textuales de la materia reivindicada pueden ser consideradas para evaluar la Novedad haría inútil cualquier análisis de patentabilidad (pues todo lo no-textual sería nuevo), cabe reiterar aquí que aún si D1 no revelara textualmente dicho objeto, su conocimiento sí permitiría a cualquier persona medianamente versada en la materia técnica respectiva derivar el mismo objeto que nos ocupa.

2. De otro lado, es importante resaltar que el documento GB 2 262 229A "Stabilised HMG-CoA reductase inhibitor compositions" publicada el 16 de junio de 1993 y con prioridad US 07805667 de diciembre 12 de 1991, revela, una forma de dosificación farmacéutica que comprende un inhibidor de HMG-CoA reductasa como es Fluvastatina sódica, la cual es estabilizada contra la degradación relacionada con el pH por un medio alcalino estabilizado capaz de impartir un pH de al menos 8 a una solución acuosa o a la dispersión de la composición por ejemplo, añadiendo carbonato o bicarbonato de sodio o carbonato de calcio.

En la parte descriptiva de dicho documento GB 2 262 229 A se revela: *la Fluvastatina Sódica → [R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt, es inestable debido a la extrema labilidad de los grupos β, δ-hidroxi sobre la cadena de ácido heptenóico y la presencia del doble enlace, tal que en pH neutro a ácido, los compuestos fácilmente sufren la eliminación o la isomerización o reacciones de oxidación para formar compuestos aromáticos conjugados insaturados, así como el isómero threo, las correspondientes lactonas, y otros productos de degradación (Pág 2); luego, en la página 3 dice: Las composiciones comprenden la sustancia activa y "un medio alcalino", dicho medio alcalino es capaz de estabilizar la composición por impartir un pH de al menos 8 a una solución acuosa o dispersión de la composición; y por último en la página 4 menciona: ejemplos de sustancias alcalinas solubles en agua capaces de impartir la basicidad requerida incluye ciertas sales inorgánicas de carbonato farmacéuticamente aceptables tales como carbonato de sodio o potasio, bicarbonato de sodio, o potasio hidrógeno carbonato; sales de fosfatos seleccionadas de, por ejemplo, fosfato dibásico de sodio anhidro, de potasio o*

de calcio, o fosfato trisódico; así como hidróxidos de metales alcalinos como hidróxido de sodio, potasio o litio; y mezclas de los anteriores; teniendo en mente lo anteriormente descrito, me permito comparar lo revelado en la GB 2 262 229 A con la materia revelada en la solicitud colombiana en trámite 03-113-785 así:

GB 2 262 229 A	CO 03-113-785
Fluvastatina Sódica $C_{24}H_{25}FNO_4 \cdot Na$ Mol. wt. 433.46 Nombre químico: $[R^*, S^*-(E)]-(\pm)-7-[3-(4\text{-fluorophenyl})-1-(1\text{-methylethyl})-1H\text{-indol-2-yl}]-3,5\text{-dihydroxy-6-heptenoic acid}$, monosodium salt.	Atorvastatina Cálcica Nombre químico: $[R-(R^*, R^*)]-2-(4\text{-fluorophenyl})-\beta, \delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-}[(\text{phenylamino})\text{ carbonyl}]-1H\text{-pyrrole-1-heptanoic acid}$ calcium SALT (2:1) trihydrate.
La composición comprende una sustancia activa (Inhibidor de la HMG-CoA reductasa) y un <u>medio alcalino</u> capaz de estabilizar la composición y proporcionar una vida extendida de almacenamiento.	Composición farmacéutica que comprende a) un componente que comprende una granulación de atorvastatina o sus sales farmacéuticamente aceptables y un vehículo que incluye un <u>agente alcalinizante</u> que forma un pH mayor 5, y b) un segundo componente...
El medio alcalino puede ser: sales inorgánicas de carbonato farmacéuticamente aceptables tales como carbonato de sodio o potasio, bicarbonato de sodio, o potasio hidrógeno carbonato; sales de fosfatos seleccionadas de, por ejemplo, <u>fosfato dibásico</u> de sodio anhidro, de potasio o de calcio, o fosfato trisódico; así como hidróxidos de metales alcalinos como hidróxido de sodio, potasio o litio; y mezclas de los anteriores	El agente alcalinizante en el componente a) se selecciona entre el grupo que consiste en: carbonato de calcio, <u>fosfato de dicalcio</u> y fosfato de tricalcio.

Como se observa, tanto la Fluvastatina como la Atorvastatina son compuestos inhibidores de la HMG-CoA reductasa y que cuentan con una cadena de ácido

heptenóico, esto, en consecuencia, hace que las dos moléculas presenten una similitud enorme desde el punto de vista estructural y que probablemente por cambios en el pH de la formulación, posean una labilidad extrema en los grupos β , δ -hidroxi, y que exista la posibilidad de sufrir reacciones de oxidación, isomerización, eliminación y lactonización.

Por lo tanto, es necesario mejorar tanto la estabilidad del principio activo como de la formulación y en el caso que nos ocupa como en el de la anterioridad, vemos que como elemento de estabilización se hace uso de una sal inorgánica multivalente o de un medio alcalino o agente alcalinizante, respectivamente, que como nos damos cuenta juegan el mismo papel dentro de la formulación "Proteger la molécula".

Es evidente, por lo expuesto, que las reivindicaciones de la solicitud en curso incumplen a primera vista los preceptos de la Decisión 486 de la Comunidad Andina especialmente en materia de Nivel Inventivo y, se reitera, aún de Novedad, pues aunque pueda resultar cierto que la anterioridad no haga referencia expresa a la sustancia Atorvastatina, no lo es menos su referencia a otro inhibidor de la HMG-CoA reductasa (Fluvastatina), sustancia que posee un grupo estructural idéntico (cadena de ácido heptenóico) y por ello es igualmente susceptible al medio que la rodea, requiere de protección para asegurar su estabilidad en presencia de un medio alcalino, en particular mediante el empleo de una sal inorgánica multivalente o un agente alcalinizante, como sea que se le quiera llamar.

3. También es importante concluir que si se presenta algún tipo de incompatibilidad entre el amlodipino y la atorvastatina dadas las características fisicoquímicas de las mismas (naturaleza básica y naturaleza ácida, respectivamente), lo más lógico para una persona medianamente versada en la materia sería, teniendo en cuenta las anterioridades explicadas (composiciones de inhibidores de HMG-CoA con agentes inorgánicos multivalentes) y sus conocimientos básicos en materia farmacéutica, incluir en la formulación un agente capaz de regular, neutralizar o cambiar el pH, con el fin de estabilizar o evitar la degradación de la formulación.

En conclusión, ruego a este Despacho tenga en cuenta los argumentos presentados por el suscrito dentro de los términos permitidos en el escrito de oposición y de sustentación, así como los demostrados en esta oportunidad, y que basado en ellos proceda a negar la solicitud en curso en todas sus reivindicaciones.

PRUEBAS

Ruego que se tenga como prueba adicional de los argumentos de la oposición y del presente memorial, la materia revelada en la publicación de patente británica GB 2 262 229a, páginas 1 a 10.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

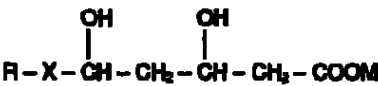
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(12) UK Patent Application (18) GB (11) 2 262 229 (19) A
(48) Date of A publication 18.08.1999

(21) Application No 8235688.3 (22) Date of filing 08.12.1992 (30) Priority data (31) 07805087 (32) 12.12.1991 (33) US	(51) INT CL⁸ A61K 47/02 31/405 (52) UK CL (Edition L) A58 BJB BLM B180 B27Y B27Z B28Y B28S B44Y B441 B442 B446 B45Y B480 B50Y B50S B55Y B551 B57Y B57S B58Y B58S B61Y B61S B65Y B65S B68S B82S U18 S2415 (58) Documents cited None (59) Field of search UK CL (Edition L) A58 BJB BLM INT CL⁸ A61K 31/405 47/02 Online databases: DIALINDEX (MEDICINE), WPI, CAS-ONLINE
(71) Applicant Sandoz Ltd (Incorporated in Switzerland) 35 Lichtstrasse, CH-4002 Basle, Switzerland (72) Inventors Mohan B Khabadi Richard Victor Vivianichia (74) Agent and/or Address for Service B A Yaris & Co Coomb House, 7 St John's Road, Isleworth, Middlesex, TW7 6RH, United Kingdom	

- (54) Stabilised HMG-CoA reductase inhibitor compositions
- (57) A pharmaceutical dosage form comprising an HMG-CoA reductase inhibitor compound of general formula



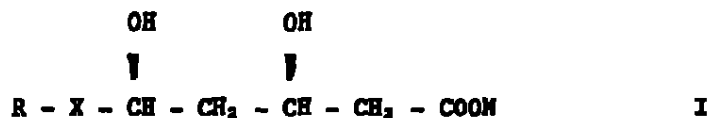
where R is an organic radical, X is -CH=CH- and M is a physiologically acceptable cation, e.g., fluvastatin sodium, is stabilized against pH-related degradation by an alkaline stabilizing medium capable of imparting a pH of at least 8 to an aqueous solution or dispersion of the composition e.g. by adding sodium carbonate or bicarbonate or calcium carbonate.

GB 2 262 229 A

Stabilized Pharmaceutical Compositions
Comprising an HMG-CoA Reductase Inhibitor Compound

The present invention relates to a pharmaceutical composition comprising a pH sensitive medicament, which has enhanced storage stability.

Certain HMG-CoA reductase compounds, i.e. cholesterol biosynthesis inhibitors, are useful in the treatment of hyperlipoproteinemia and atherosclerosis, which are compounds of the formula



wherein

R is an organic radical,

X is -CH=CH-, preferably (E)-CH=CH-, and

M is a physiologically acceptable cation, such as an alkali metal cation or ammonium, preferably sodium or potassium, and especially sodium,

are extremely susceptible to degradation at pH below about 8. An example of such a compound comprises the compound having the USAN designation fluvastatin sodium (hereinafter "fluvastatin"), of the chemical designation:

R',S'-(E)-(+)-7-[3-(4-Fluorophenyl)-1-(1-methyl-ethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt, [see European Patent Application EP-A-114027].

For example, we have found the degradation kinetics of fluvastatin in aqueous solution at various pH are as illustrated below:

% fluvastatin remaining at 37°C

<u>pH</u>	<u>after 1 hour</u>	<u>after 24 hrs</u>
7.8	98.3	98.0
6.0	99.6	97.1
4.0	86.7	25.2
1.0	10.9	0

The above-indicated instability of fluvastatin and related HMG-CoA reductase compounds we believe is due to the extreme lability of the β , δ -hydroxy groups on the heptenoic acid chain and the presence of the double bond, such that at neutral to acidic pH, the compounds readily undergo elimination or isomerization or oxidation reactions to form conjugated unsaturated aromatic compounds, as well as the threo isomer, the corresponding lactones, and other degradation products.

In order to achieve marketable dosage forms comprising such a compound, it is essential to adequately protect it against pH-related destabilization.

Additionally, the heat and light sensitivity as well as hygroscopicity of the subject compounds impose particular requirements in the manufacture and storage of pharmaceutical dosage forms.

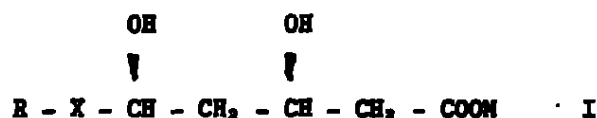
We have surprisingly been able to prepare such compositions having extended periods of storage stability, e.g., whereby at least about 95% of the initial amount of the drug is active after 2 years at +25°C and +30°C and for longer periods.

Compositions of the invention on oral administration can provide rapid and essentially complete intestinal absorption of drug substance.

It is a further advantage that the stabilized compositions of the

invention can be readily prepared by aqueous or other solvent-based techniques, e.g. wet granulation.

In one aspect the present invention provides a pharmaceutical composition comprising an HMG-CoA compound of the formula



wherein

R is an organic radical,

X is -CH=CH-, and

H is a physiologically acceptable cation, and an alkaline medium capable of imparting a pH of at least 8 to an aqueous solution or dispersion of the composition.

The compositions comprise the drug substance and an "alkaline medium," said alkaline medium being capable of stabilizing the composition by imparting a pH of at least 8 to an aqueous solution or dispersion of the composition. Preferably the compounds of formula I and the alkaline medium are in intimate contacting association in the composition to achieve optimal stability of the medicament.

The resulting composition has been found to provide an extended storage life of the compounds of formula I, even in the presence of moisture or when such compositions additionally comprise otherwise potentially reactive excipients, such as lactose. The stability of the drug substance in compositions of the invention can be at least 95%, and is typically between 98% and 99%, after 18 months at 25°C., and for even longer periods.

The term "alkaline medium" or "base" employed herein shall refer to one or more pharmaceutically acceptable substances capable of imparting a pH of at least 8, and preferably at least 9, and up to about pH 10, to an aqueous solution or dispersion of the composition of the invention. More particularly, the alkaline medium creates a "micro-pH" of at least 8 around the particles of the composition when water is adsorbed thereon or when water is added in small amounts to the composition. The alkaline medium should otherwise be inert to the compounds of formula I. The pH may be determined by taking a unit dosage of the composition containing e.g. 20 mg of fluvastatin or the equivalent amount of another compound falling under formula I and dispersing or dissolving the composition in 10 to 100 ml of water.

The pharmaceutically acceptable alkaline substance(s) which comprise the alkaline medium may range from water-soluble to sparingly soluble to essentially water-insoluble.

Examples of water-soluble alkaline substances capable of imparting the requisite basicity include certain pharmaceutically acceptable inorganic carbonate salts such as sodium or potassium carbonate, sodium bicarbonate, or potassium hydrogen carbonate; phosphate salts selected from, e.g., anhydrous sodium, potassium or calcium dibasic phosphate, or trisodium phosphate; as well as alkali metal hydroxides such as sodium, potassium, or lithium hydroxide; and mixtures of the foregoing.

An example of a stabilized composition according to the invention may comprise: 0.5 to 60 wt.% (weight %), typically 0.5 to 40 wt.%, drug substance (e.g., fluvastatin); and 0.1 to 35 wt.%, preferably 1-15 wt.%, of soluble carbonate compound, for example, selected from sodium bicarbonate, sodium carbonate and mixtures thereof.

Examples of water-insoluble or sparingly soluble alkaline substances also potentially useful to comprise the stabilizing alkaline medium in

the compositions comprise compounds commonly employed in antacid formulations (e.g., magnesium oxide, hydroxide or carbonate; magnesium hydrogen carbonate; aluminum or calcium hydroxide or carbonate; composite aluminum-magnesium compounds, such as magnesium aluminum hydroxide); as well as pharmaceutically acceptable salts of phosphoric acid such as tribasic calcium phosphate; and mixtures thereof.

Of the above-mentioned alkaline substances, the "pharmaceutically acceptable carbonate salts," by which is meant pharmaceutically acceptable inorganic carbonate and bicarbonate salts, e.g., sodium carbonate, sodium bicarbonate, calcium carbonate, and mixtures thereof, have been found particularly effective to comprise the alkaline medium.

Compositions also having particularly attractive storage stability comprise, as an alkaline medium, both a water-soluble alkaline excipient and a water-insoluble or sparingly soluble alkaline excipient.

For example, substantial improvements in stability and other advantages have been achieved by employing an alkaline medium comprising a water-soluble carbonate salt and a water-insoluble carbonate salt, especially, the combination of sodium bicarbonate (or carbonate) with calcium carbonate.

Sodium bicarbonate advantageously serves to neutralize acidic groups in the composition in the presence of moisture which may adsorb onto particles of the composition during storage. The calcium carbonate exerts a buffering action in the stored composition, without apparent effect on drug release upon ingestion. It has further been found that the carbonate salts sufficiently stabilize the drug substance such that conventional water-based preparative techniques, e.g. trituration with water or wet granulation, can be utilized to prepare stabilized compositions of the invention.

— The calcium carbonate can be a precipitated or ground material, but is preferably precipitated.

The alkaline medium will be present in the compositions in an amount sufficient to impart a pH of e.g. at least 8, and preferably at least 9, and as high as pH 10, to an aqueous solution or dispersion of the composition. In general, the compositions of the invention comprise from about 0.1 to 60 wt.% (typically, 0.5 to 40 wt.%) drug substance; and from about 0.1 to 60 wt.%, preferably 20 to 35 wt.%, alkaline medium.

The amount of a particular stabilizing excipient to be employed will depend to some extent on the intended manufacturing process. In compositions to be tableted, for example, calcium carbonate should not exceed an amount which can be conveniently subjected to compression, and will generally be used in combination with a more readily compressible alkaline substance, e.g., sodium bicarbonate. On the other hand, capsule dosage forms may comprise higher levels of poorly compressible excipients, provided that the overall composition remains sufficiently free-flowing and processible.

A solid unit dosage composition may have the ratio of water soluble carbonate to insoluble carbonate from e.g. 1:40 to 2:1.

An exemplary tablet of the invention may comprise about 2:1 to 1:2 by weight calcium carbonate to sodium bicarbonate. A capsule composition may comprise these excipients in a ratio of, for example, 25:1 to 35:1 by weight.

In addition to the drug substance and alkaline medium, a filler is also generally employed in the compositions to impart processability. Potentially suitable filler materials are well-known to the art (see, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990), Mack

Publishing Co., Easton, PA, pp. 1635-1636), and include lactose and other carbohydrates, pregelatinized starch, e.g., starch 1500[®] (Colorcon Corp.), corn starch, dicalcium phosphate, cellulose, microcrystalline cellulose, sugars, sodium chloride, and mixtures thereof, of which lactose, microcrystalline cellulose, pregelatinized starch, and mixtures thereof, are preferred.

Owing to its superior disintegration and compression properties, microcrystalline cellulose (Avicel[®], FMC Corp.), and mixtures comprising microcrystalline cellulose and one or more additional fillers, e.g., pregelatinized starch, are particularly useful.

The total filler is present in the compositions in an amount of about 1 to 65 wt.%, based on the total composition.

Other ingredients which may be incorporated into the compositions to facilitate processing and/or provide enhanced properties of the product dosage form, include well-known tableting binders (e.g., gelatin, sugars, natural and synthetic gums, such as carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, hydroxypropylmethyl-cellulose), microcrystalline cellulose, and mixtures of the foregoing); disintegrants (e.g., cross-linked carboxymethyl-cellulose, croscarmellose, crospovidone, sodium starch glycolate), lubricants (e.g., magnesium stearate, hydrogenated vegetable oil, carnauba wax and the like); flow agents (e.g., silicon dioxide), anti-adherents or glidants (e.g., talc) as well as sweeteners, coloring mediums (e.g., iron oxide, aluminum lakes), flavoring mediums, antioxidants, etc. Selection of a particular ingredient or ingredients and the amounts used will be readily determinable by one skilled in the art by reference to standard procedures and practices for preparing tableted or encapsulated or other dosage forms. In general, an effective amount of a tableting binder will comprise about 1 to 10 wt.%, and preferably 1 to 5 wt.%; anti-adherents or glidants, about 1 to 10 wt.%; disintegrants, about 1

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to 5 wt.%, and lubricants, about 0.1 to 2 wt.%, based on the total composition.

Such compositions may be formulated by known means to provide standard unitary oral dosages of compound, e.g., 5 mg, 10 mg, 20 mg, 40 mg, etc., in the form of capsules, tablets, pellets, etc.

Enteric film coating materials may optionally be applied to oral tablets, pellets or capsules to protect against premature degradation of the drug substance by gastric acid prior to reaching the intestinal absorption site. Examples of such materials are well-known and include hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, methylcellulose phthalate, copolymerized methacrylic acid/methacrylic acid methyl esters (e.g., Eudragit[®], Rohm Pharma). The enteric coating is preferably applied to result in about a 5 to 12, preferably 8 to 10, weight percent increase of the capsule, pellet or tablet core.

Tableted compositions of the invention are desirably coated to protect against moisture and light discoloration, and to mask the bitter taste of the drug. Either the enteric coating may contain opacifiers and colorants, or a conventional opaque film coating may be applied to the tablet core, optionally after it has been coated with an enteric substance.

Examples of suitable film formers in film coating formulations to be applied to compositions of the invention comprise, e.g., polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydrophilic polymers such as hydroxypropylcellulose, hydroxymethylcellulose, and hydroxypropylmethylcellulose or the like, of which hydroxypropylmethylcellulose (e.g., Opadry Yellow[®], Colorcon Corp.) is preferred. Hydrophobic film-formers which may be applied using an organic solvent vehicle comprise, for example, ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, etc.

- The film coating may be generally applied to achieve a weight increase of the pellet or core or tablet of about 1 to 10 wt.%, and preferably about 2 to 6 wt.%.

Other conventional enteric or film coating formulation ingredients include plasticizers, e.g., polyethylene glycol (e.g. polyethylene glycol 6000), triethylcitrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, in conventional amounts, as well as the above-mentioned opacifiers such as titanium dioxide, and colorants, e.g. iron oxide, aluminum lakes, etc.

The enteric or film coatings can be applied by conventional techniques in a suitable coating pan or fluidized bed apparatus using water and/or conventional organic solvents (e.g., methyl alcohol, ethyl alcohol, isopropyl alcohol), ketones (acetone, ethylmethyl ketone), chlorinated hydrocarbons (methylene chloride, dichloroethane), etc.

A composition according to the invention comprises the following (in weight percent based on the total composition):

0.1 to 60 wt.% (typically 0.5 to 40 wt.%) compound (e.g., fluvastatin), 0.1 to 60 wt.% alkaline medium (e.g., carbonate salts), and 1 to 65 wt.% filler (e.g., microcrystalline cellulose).

An example of such a composition comprises (in weight percent based on the total composition):

0.5 to 60 wt.% HMG-CoA reductase compound (e.g., fluvastatin), 10 to 55 wt.% alkaline medium (e.g., carbonate salts), and 10 to 65 wt.% filler (e.g., microcrystalline cellulose).

Another example of a composition according to the invention comprises (in weight percent based on the total composition):

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— 0.5 to 60 wt.%, drug compound (e.g., fluvastatin), 5 to 40 wt.% calcium carbonate, 0.5 to 20 wt.% sodium bicarbonate, and 10 to 65 wt.% filler (e.g., microcrystalline cellulose).

An example of a capsule composition according to the invention comprises (in weight percent based on the total composition):

0.5 to 60 wt.% (typically 0.5 to 40 wt.%) drug compound (e.g., fluvastatin), 25 to 40 wt.% calcium carbonate, 0.5 to 10 wt.% sodium bicarbonate, and 20 to 35 wt.% microcrystalline cellulose, and optional additional filler (e.g., pregelatinized starch) in an amount of 15 to 30 wt.%.

An example of an tableted composition according to the invention comprises (in weight percent based on the total composition):

0.5 to 60 wt.% drug compound (e.g., fluvastatin), 5 to 20 wt.% calcium carbonate, 5 to 20 wt.% sodium bicarbonate, and 50 to 65 wt.% microcrystalline cellulose.

The stabilized compositions of the invention may be prepared by various techniques and manufacturing processes generally known to the art.

In preparing the compositions it is important that the drug substance and the alkaline medium be brought into intimate contacting association. Dry blending these components to achieve a substantially homogeneous mixture (preferably prior to addition of filler and remaining excipients), followed by a compression step, can achieve the desired intimate contacting.

However, to obtain very stable formulations, an aqueous or other solvent-based preparative process is preferably utilized, whereby the