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Application No. 14 728 940.9 - 1466	Ref. P2706EP02	Date 13.07.2016
Applicant Ferrer Internacional, S.A., et al		

Communication under Rule 71(3) EPC

1. Intention to grant

You are informed that the examining division intends to grant a European patent on the basis of the above application, with the text and drawings and the related bibliographic data as indicated below.

A copy of the relevant documents is enclosed.

1.1 In the text for the Contracting States:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT
RO RS SE SI SK SM TR

Description, Pages

1-26 filed in electronic form on 10-06-2016

Claims, Numbers

1-11 filed in electronic form on 10-06-2016

Drawings, Sheets

1/3-3/3 as published

With the following amendments to the above-mentioned documents proposed by the division

Description, Pages 6-8, 11

Claims, Numbers 1

Comments

DESCRIPTION

Pages 6-8, 11: Description adapted to amended claims (Art. 84 EPC)

CLAIMS

Page 1, Claim 1: Error(s) in spelling, grammar, typography corrected

1.2 Bibliographic data

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated contracting states, the registered name(s) of the applicant(s) and the other bibliographic data are shown on **EPO Form 2056** (enclosed).

2. Invitation

You are invited, **within a non-extendable period of four months** of notification of this communication,

2.1 to EITHER approve the text communicated above and verify the bibliographic data (Rule 71(5) EPC)

(1) by filing a translation of the claim(s) in the other two official languages of the EPO

Fee code	EUR
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(2a) by paying the fee for grant including the fee for publication:
minus any amount already paid (Rule 71a(5) EPC):

007	925.00
	0.00

Total amount:	925.00
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(3) by paying additional claims fees under Rule 71(4) EPC;
number of claims fees payable: 0
minus any amount already paid (Rule 71a(5) EPC):

016	0.00
	0.00

Total amount:	0.00
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Important: If the translations of the claims and fees have already been filed and paid respectively in reply to a previous communication under Rule 71(3) EPC, e.g. in the case of resumption of examination after approval (see Guidelines C-V, 6), **agreement as to the text to be granted** (Rule 71a(1) EPC) must be expressed within the same time limit (e.g. by approving the text and verifying the bibliographic data, by confirming that grant proceedings can go ahead with the documents on file and/or by stating which translations of the claims already on file are to be used).

Note 1: See "Important notes concerning fee payments" below.

Note 2: Any overpaid "minus" amounts will be refunded when the decision to grant (EPO Form 2006A) has been issued.

Note 3: For the calculation of the grant fee under Article 2(2), No. 7, RFees (old fee structure), the number of pages is determined on the basis of a clean copy of the application documents, in which text deleted as a result of any amendments by the examining division is not shown. Such clean copy is made available via on-line file inspection only.

2.2 OR, in the case of disapproval, to request reasoned amendments or corrections to the text communicated above or keep to the latest text submitted by you (Rule 71(6) EPC).

In this case the translations of the claims and fee payments mentioned under point 2.1 above are NOT due.

The terms "amendment(s)" and "correction(s)" refer only to amendments or corrections of the application documents and not of other documents (e.g. bibliographic data, the designation of the inventor, etc.).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the examining division requesting that you correct this deficiency (Rule 137(4) EPC).

2.3 Bibliographic data

Where you request a change or correction of bibliographic data in response to the Rule 71(3) communication, this will **not** cause the sending of a further communication under Rule 71(3) EPC. You will still have to pay the fees and file translations in reply to the Rule 71(3) communication in the case of 2.1 above, unless you also file a reasoned request for amendments or corrections in response to the Rule 71(3) communication (see case 2.2 above).

3. Loss of rights

If neither of the two possible actions above (see points 2.1 or 2.2) is performed in due time, the European patent application will be deemed to be withdrawn (Rule 71(7) EPC).

4. Further procedure

4.1 In the case of point 2.1 above

- 4.1.1 The decision to grant the European patent will be issued, and the **mention of the grant** of the patent will be published in the European Patent Bulletin, if the requirements concerning the translation of the claims and the payment of all fees are fulfilled and there is agreement as to the text to be granted (Rule 71a(1) EPC).

Note on payment of the renewal fee:

If a renewal fee becomes due before the next possible date for publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (Rule 71a(4) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Note on payment of the designation fee(s):

If the designation fee(s) become(s) due after the communication under Rule 71(3) EPC, the mention of the grant of the European patent will not be published until these fees have been paid (Rule 71a(3) EPC).

- 4.1.2 After publication, the **European patent specification** can be downloaded free of charge from the EPO publication server <https://data.epo.org/publication-server> or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

4.1.3 Filing of translations in the contracting states

As regards translation requirements prescribed by the contracting states under Article 65(1) EPC, please consult the website of the European Patent Office

www.epo.org → Law & practice → Legal texts, National law relating to the EPC

www.epo.org → Law & practice → All Legal texts → London Agreement

In the case of a valid extension or validation

As regards translation requirements prescribed by the extension or validation states, please consult the website of the European Patent Office

www.epo.org → Law & practice → Legal texts, National law relating to the EPC

Failure to supply a prescribed translation in a contracting state, or in an extension or validation state may result in the patent being deemed to be void *ab initio* in the state concerned (Art. 65(3) EPC).

4.2 In the case of 2.2 above

If the present communication under Rule 71(3) EPC is based on an auxiliary request and, within the time limit, you maintain the main request or a higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the examining division gives its consent to the requested amendments or corrections, it will issue a new communication under Rule 71(3) EPC; otherwise, it shall resume the examination proceedings (Rule 71(6) EPC).

5. Filing of a divisional application

Any divisional application relating to this European patent application must be filed directly with the European Patent Office in Munich, The Hague or Berlin and will be in the language of the proceedings for the present application, or if the latter was not in an official language of the EPO, the divisional application may be filed in the language of the present application as filed (see Article 76(1) and Rule 36(2) EPC). Any such divisional application must be filed while the present application is still pending (Rule 36(1) EPC; Guidelines A-IV, 1.1.1).

6. Important notes concerning fee payments

6.1 For all payments, please refer to the relevant **fee code(s)**.

6.2 Automatic debiting procedure

The fee for grant, including the fee for publication, and any additional claims fees due under Rule 71(4) EPC will be debited automatically on the date of filing of the translations of the claims, or on the last day of the period of this communication. However, if the designation fee(s) become(s) due as set out in Rule 71a(3) EPC and/or a renewal fee becomes due as set out in Rule 71a(4) EPC, these should be paid separately by another permitted way of payment in order not to delay the publication of the mention of the grant. The same applies in these circumstances to the payment of extension and validation fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) in Supplementary publication - OJ EPO 3/2015).

Note: If a waiver is expressed in response to a Rule 71(3) communication (see OJ EPO 2015, A52), the fee for grant, including the fee for publication/printing, and any additional claims fees will not be debited automatically. These fees must be paid separately by another means of payment allowed under the Rules relating to Fees.

6.3 Important information relating to fee amounts

Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment**. The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (www.epo.org) and can be found under www.epo.org/schedule-of-fees, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

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Enclosures: Text intended for grant

 EPO Form 2056

Annex to EPO Form 2004, Communication pursuant to Rule 71(3) EPC

Bibliographical data of European patent application No. 14 728 940.9

For the intended grant of the European patent, the bibliographical data are set out below, for information:

Title of invention:

- ORALE FORMULIERUNG ZUR BEHANDLUNG VON HERZ-KREISLAUF-ERKRANKUNGEN
- ORAL FORMULATION FOR THE TREATMENT OF CARDIOVASCULAR DISEASES
- FORMULATION ORALE POUR LE TRAITEMENT DE MALADIES CARDIOVASCULAIRES

Classification: INV. A61K9/20 A61K9/28 A61K9/48 A61K9/50 A61K31/40 A61K31/403 A61K31/60 A61K31/505 A61K31/616 A61P9/00

Date of filing: 05.06.2014

Priority claimed: EP / 06.06.2013 / EPA13170909

Contracting States*
for which fees have been paid:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

Extension States*
for which fees have been paid:

BA ME

Validation States*
for which fees have been paid:

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| <p>*) If the time limit for the payment of designation fees according to Rule 39(1) EPC has not yet expired and the applicant has not withdrawn any designation, all Contracting States/Extension States/Validation States are currently still deemed to be designated. See also Rule 71a(3) EPC and, if applicable, the above Note to users of the automatic debiting procedure.</p> <p>**) If two or more applicants have designated different Contracting States, this is indicated here.</p> |
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ORAL FORMULATION FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

FIELD OF THE INVENTION

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The present invention relates to a pharmaceutical composition which includes a HMG-CoA reductase inhibitor, in particular, a statin and acetylsalicylic acid in a manner to minimize interaction of acetylsalicylic acid with the statin, for use in the prevention or treatment of cardiovascular diseases.

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BACKGROUND OF THE INVENTION

Cardiovascular diseases are one of the leading causes of death in the world and one of the most significant factors for these diseases is total/high density lipoprotein (HDL) cholesterol level. However, recent developments have indicated that only taking the cholesterol level under control is not sufficient for cardiovascular treatment. In line with this need, researchers have found that the use of some active agents in combination provides a more effective treatment method.

20 The use of acetylsalicylic acid for reducing the risk of myocardial infarction and the use of statins for lowering cholesterol and preventing or treating cardiovascular disease and cerebrovascular disease are well documented. In fact, it is not uncommon that patients having elevated cholesterol levels who are at high risk for a myocardial infarction take both a statin and acetylsalicylic acid. However, use of
25 both a statin and acetylsalicylic acid may require special care to insure that drug interaction, including physical and chemical incompatibility, and side effects, are kept to a minimum while achieving maximum benefit from these drugs.

HMG-CoA reductase inhibitors can be divided into two groups: those administered
30 as a prodrug, i.e., the lactone form and those administered in the active form, i.e., the acid form or salts of the acid form (e.g. pravastatin sodium, atorvastatin calcium and rosuvastatin calcium). These compounds are unstable since they are susceptible to heat, moisture, low pH environment and light. Both atorvastatin and rosuvastatin and salts thereof, including calcium and magnesium salts, are

particularly unstable when compared to other statins. In particular, atorvastatin is transformed into the lactone as a result of the intramolecular esterification reaction. Major degradation products (3R, 5S) produced as a result of disintegration of statins are lactones and oxidation products. This fact reduces the stability of atorvastatin and therefore shortens its shelf life.

It is known from the prior art that HMG-CoA reductase inhibitors degrade in the presence of acetylsalicylic acid during storage.

Document WO9738694 discloses pharmaceutical compositions comprising aspirin and a statin. However, the problem of statin-aspirin interaction is not addressed. Document EP1071403 addresses the problem of said interaction and describes a formulation in the form of a bilayered tablet. Aspirin, in the form of granules, is present in the first layer while the statin is present in the second layer. However, combination products produced in bilayer dosage forms can fail to prevent interaction of the active agents with each other. In this case, the product may be degraded during its shelf life. This may result in serious complications to the patient and insufficient dose intake.

Document EP 1581194 relates to multilayer tablet dosage form comprising pravastatin and aspirin as active agents. The layers comprising the active agents are separated by a barrier layer in order to impede their interaction. However, it is quite inconvenient to produce this type of tablet formulations and it is not certainly known if the barrier layer would maintain its effect during the shelf life.

Document WO2011096665 describes that the deterioration in the stability of HMG-CoA reductase can be prevented by coating aspirin with a barrier containing a hydrophobic additive. According to said document, when aspirin is coated with conventional coatings, HMG-CoA reductase inhibitors are degraded. When a hydrophobic additive is added to the coating layer, the degradation of HMG-CoA reductase inhibitors is reduced.

There are other documents in the state of the art which provide compositions combining acetylsalicylic acid and HMG-CoA dosage units.

WO2009/118359A2 discloses a capsule for the prevention of cardiovascular diseases which comprises coated tablets of acetylsalicylic acid, coated tablets of simvastatin or pravastatin, and coated tablets of lisinopriol, ramipril or perindopril.

5 US2012/045505A1 discloses a pharmaceutical composition comprising a cholesterol lowering agent, an inhibitor of the rennin-angiotensin systems, aspirin and a beta-adrenergic receptor blocker or diuretic, which are useful for treating or preventing cardiovascular disease.

10 WO2006/00052A1 discloses an oral composition for treatment or prevention of atherosclerosis comprising a low dose aspirin and a low-dose of statin wherein the aspirin and statin are in a slow-release formulation.

15 US2003/049314 discloses compositions for reducing the risk of cardiovascular events in individuals who are at elevated cardiovascular risk. The compositions comprise a cholesterol-lowering agent, such as an HMG CoA reductase inhibitor, an inhibitor of the renin-angiotensin system, such as an ACE inhibitor, aspirin, and optionally, one or more of vitamin B₆, vitamin B₁₂, and folic acid. In particular, it discloses capsules comprising aspirin in enteric coated granules combined with
20 granules of pravastatin and ramipril.

WO03/02043A1 discloses a pharmaceutical formulation comprising a cholesterol lowering agent, an inhibitor of the renin-angiotensin system and aspirin, where at least one of the active agents is present in a dosage unit that physically separates
25 this active agent from the others.

Finally, US2012/027849 discloses a solid oral pharmaceutical multi-component composition comprising the combination of blood pressure lowering drugs with lipid lowering agent/s and optionally a platelet aggregation inhibitor in a single dosage
30 form.

In view of the above, it is seen that there is a need in patients required to take both a statin and acetylsalicylic acid for a statin-acetylsalicylic acid formulation which provides for maximum effect in cardiovascular diseases prevention and treatment

without the undesirable side effects and drug interaction normally associated with use of such combination.

5 In accordance with the present invention, a pharmaceutical composition is provided which includes a HMG-CoA reductase inhibitor selected from atorvastatin and rosuvastatin and salts thereof, and acetylsalicylic acid, which provides for maximum patient benefits with minimal physical and chemical incompatibility and reduced side effects normally associated with use of such drugs.

10 SUMMARY OF THE INVENTION

The authors of the present invention have found that when acetylsalicylic acid is provided in an oral formulation and the amount of coating for acetylsalicylic acid units is above 6 mg/cm² and said coating contains a water-soluble polymer, the
15 deterioration in the stability of atorvastatin and rosuvastatin can be surprisingly prevented.

Thus, the present invention refers to an orally administrable pharmaceutical dosage form for use in the prevention and/or treatment of a cardiovascular disease
20 comprising:

- (a) acetylsalicylic acid as a first active agent; and
- (b) HMG-CoA reductase inhibitor as a second active agent,
wherein said HMG-CoA reductase inhibitor is selected from atorvastatin and rosuvastatin and salts thereof, and wherein
25 (a) are two or more single separate coated dosage units comprising one or more water-soluble polymer in said coating and being said coating substantially free from a water-insoluble polymer or an enteric polymer which means in an amount ranging between 0 to 5% by weight of the composition of the coating; and wherein the amount of coating is comprised from 8 to 12 mg/cm²; and showing a non-modified
30 release profile; and
- (b) is one or more single separate coated dosage units; and
the dosage units are in the form of tablets, and
the water soluble polymer is present in an amount by weight above 40% of the total weight of the coating and is selected from the group consisting of; a water-soluble

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polyvinyl derivative selected from polyvinyl pyrrolidone, partly hydrolyzed polyvinyl alcohol, polyvinyl alcohol, and mixtures thereof.

BRIEF DESCRIPTION OF THE FIGURES

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Figure 1 represents the dissolution profiles of 100 mg and 50 mg ASA strength formulations (4.3 mg/cm² coating).

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Figure 2 shows the dissolution profile of acetylsalicylic acid 100 mg tablets containing different amounts of film coating agent per cm² (2.17, 4.3 and 8.7).

Figure 3 shows the dissolution profile of 50 mg *versus* 100 mg ASA tablets containing 4.3 and 8.7 mg/cm² of film coating agent.

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Figure 4 shows the dissolution profile of AAR capsules containing ASA 50 mg x 2 film-coated tablets with 8.7 mg/cm² at pH 4.5.

Figure 5 shows the dissolution profile of AAR capsules containing ASA 50 mg x 2 film-coated tablets with 8.7 mg/cm² at pH 6.8.

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DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical dosage form of the present invention exhibits improved storage stability of HMG-CoA reductase inhibitors atorvastatin and rosuvastatin (and salts thereof) in the presence of acetylsalicylic acid, thereby providing useful combinations for the prevention and treatment of cardiovascular diseases.

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The authors of the present invention have developed a new formulation. This new formulation consists of an oral dosage form containing separate coated dosage units for each drug substance, being said units tablets, and being the amount of coating for acetylsalicylic acid units above standard levels. In fact, the authors of the present invention have found that when the amount of coating for acetylsalicylic acid units is comprised from 8-12 mg/cm² and said coating contains a water-soluble polymer in an amount by weight above 40% of the total weight of the coating and

is selected from the group consisting of; a water-soluble polyvinyl derivative selected from polyvinyl pyrrolidone, partly hydrolyzed polyvinyl alcohol, polyvinyl alcohol, and mixtures thereof, the deterioration in the stability of atorvastatin or rosuvastatin can be surprisingly prevented. As it is shown in the examples below, the production of lactone H, which is the major degradation product of atorvastatin, is significantly lower in the formulation of the invention when compared to a formulation containing a standard coating.

Thus, in a first aspect, the present invention refers to an orally administrable pharmaceutical dosage form for use in the prevention and/or treatment of a cardiovascular disease comprising:

(a) acetylsalicylic acid as a first active agent; and

(b) HMG-CoA reductase inhibitor as a second active agent, wherein said HMG-CoA reductase inhibitor is selected from atorvastatin and rosuvastatin and salts thereof, and wherein

(a) are two or more single separate coated dosage units comprising one or more water-soluble polymer in said coating and being said coating substantially free from a water-insoluble polymer or an enteric polymer; and wherein the amount of coating is comprised from 8-12 mg/cm²; and showing a non-modified release profile; and

(b) is one or more single separate coated dosage units; and

the dosage units are in the form of tablets, and where the water-soluble polymer is present in an amount by weight above 40% of the total weight of the coating and is selected from the group consisting of; a water-soluble polyvinyl derivative selected from polyvinyl pyrrolidone, partly hydrolyzed polyvinyl alcohol, polyvinyl alcohol, and mixtures thereof.

As used herein the term "dosage units" refers to dosage forms containing a single dose or a part of a dose of drug substance in each unit. ~~Said~~

~~According to the present~~

~~invention, said~~ dosage units can be in the form of tablets, particles, granules, pellets or capsules.

Multiple dosage forms ~~of the present invention~~ can be prepared by combining one or more dosage units in an oral formulation. These dosage units can be tablets, granules, pellets, capsules or particles or combinations thereof. As it can be understood by the skilled person in the pharmaceutical industry, the term

"granulation" refers to the act or process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Thus, it is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Granulation is extensively used in the manufacturing of tablets and pellets (or spheroids).

As used herein the term "tablet" includes tablets, mini tablets or micro tablets. Similarly, the term "capsule" also can refer to micro capsules. Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, gelatin capsules being preferred. Two-piece hard gelatin capsules are preferably sealed by gelatin bands or the like. In a preferred embodiment, said orally administrable pharmaceutical dosage form according to the invention is in the form of a capsule. 2 ■ Dosage units ■ 2

~~In another preferred embodiment, wherein (a) 2 ■ and ■ 2 and/or (b) dosage units~~
are in the form of tablets.

The term "cardiovascular disease" as used herein refers to a disease such as hypercholesterolemia, atherosclerosis, coronary and cerebral diseases, for instance myocardial infarction, secondary myocardial infarction, myocardial ischemia, angina pectoris, congestive heart diseases, cerebral infarction, cerebral thrombosis, cerebral ischemia and temporary ischemic attacks.

The compositions of the present invention may be used as treatment for acute cardiovascular events, as well as for chronic therapy for prevention or reduction of risk of occurrence of cardiovascular events.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. Thus, for example, "treating" a patient involves prevention of a particular disorder or adverse physiological event in a susceptible individual as well as treatment of a clinically symptomatic individual.

As used herein, the terms "aspirin" or "acetylsalicylic acid (ASA)" are used interchangeably.

This invention employs effective cholesterol-lowering agents that are HMG CoA reductase inhibitors. HMG-CoA reductase inhibitors can be divided into two groups: those administered as the prodrug, i.e., the lactone form and those administered in the active form, i.e., the acid form (e.g. atorvastatin and rosuvastatin).

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Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Pat. No. 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33.

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The HMG-CoA reductase inhibitor for use in the formulation of the invention is selected from atorvastatin and rosuvastatin and salts thereof, in particular calcium and magnesium salts.

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~~The term "HMG-CoA reductase inhibitor" is intended to include all pharmaceutically acceptable salt or ester of the compounds having HMG-CoA reductase inhibitory activity according to the invention, and therefore the use of such salts or esters is included within the scope of this invention.~~

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The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically-acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically-acceptable acid addition salts" is intended to

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define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts. It will also be recognized that it is possible to administer amorphous forms of the statins.

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The pharmaceutically-acceptable cationic salts of statins containing free carboxylic acids may be readily prepared by reacting the free acid form of the statin with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (sodium or potassium ethylhexanoate, magnesium oleate), employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The pharmaceutically acceptable acid addition salts of statins containing free amine groups may be readily prepared by reacting the free base form of the statin with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

A number of mechanisms are likely responsible for the cardiovascular protective activity of acetylsalicylic acid, but its antithrombotic, anti-platelet aggregating activities are probably highly significant in this regard. Acetylsalicylic acid irreversibly acetylates the enzyme cyclooxygenase, rendering it nonfunctional. Cyclooxygenase is essential for the synthesis of (among other compounds) prostaglandins, many of which are proinflammatory; thromboxane A₂, which is synthesized by platelets to promote platelet aggregation and ultimately thrombosis (blood clotting); and prostacyclins, which have anti-platelet aggregating properties. Cyclooxygenases are synthesized in endothelial cells and not in platelets. Low doses of acetylsalicylic acid neutralize cyclooxygenase selectively in the platelets, while allowing continued

cyclooxygenase and prostacyclin synthesis in the endothelial cells. The net effect is to reduce inflammation and platelet aggregation, and thus thrombosis, in the blood vessels.

5 As mentioned above, when the amount of coating for each acetylsalicylic acid dosage unit is above 6 mg/cm^2 and said coating comprises a water-soluble polymer, the deterioration in the stability of HMG-CoA reductase inhibitor, in particular, atorvastatin and rosuvastatin, is surprisingly reduced. Moreover, as it is shown in the Examples accompanying the present invention, a dosage form according to the
10 present invention comprising acetylsalicylic acid in the form of two dosage units, wherein the amount of coating for said acetylsalicylic acid units is above 6 mg/cm^2 , has the effect of reducing the amount of atorvastatin impurities produced in addition to maintaining a non-modified release profile for the acetylsalicylic acid dosage units.

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As used herein, the amount of coating expressed in mg/cm^2 refers to the amount of coating per cm^2 of surface of the core of active ingredient.. In the first aspect of the invention, the amount of coating for acetylsalicylic acid dosage units is comprised from 8 to 12 mg/cm^2 .

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According to the present invention, acetylsalicylic acid dosage units (a) have a non-modified or conventional release profile. According to another particular embodiment, all dosage units in the formulation of the invention have non-modified or conventional release profile.

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As used herein the terms "conventional release" or "non-modified release" profile are used indistinctively and it is to be understood as pertaining a dosage form showing a release of the active substance(s) which is not deliberately modified by a special formulation design and/or manufacturing method. In the case of a solid
30 dosage form the dissolution profile of the active substance depends essentially on its intrinsic properties. It is also understood that non-modified or conventional release is, essentially, immediate release of active ingredients. This is further understood to be traditional or conventional release profile where no slow, delayed or extended release effect is incorporated. Preferably, means that a percentage
35 equal to or greater than 65 % of the active ingredient is dissolved within 60 minutes,

preferably within 30 minutes and more preferably within 15 minutes in a US Pharmacopeia type 1 apparatus in 0.05 M acetate buffer, at pH 4.5, 100 rpm in a volume of 900 ml. More preferably the percentage of active ingredient dissolved is greater than 75 %, more preferably greater than 80%.

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The term "water-soluble polymer" as used herein refers to a wide range of highly varied families of products of natural or synthetic origin. These polymers are often used as thickeners, stabilizers, film formers, rheology modifiers, emulsifiers and lubricity aids. Basically, water soluble polymers are highly hydrophilic as a result of the presence of oxygen and nitrogen atoms: hydroxyl, carboxylic acid, sulfonate, phosphate, amino, imino groups etc. Examples of suitable water soluble polymers ~~according to the present invention~~ include, for instance, water soluble cellulose derivatives such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose carboxymethylcellulose calcium or sodium, methylcellulose or combinations thereof, sugars such as glucose, fructose or polydextrose, polyalcohols such as sorbitol, mannitol, maltitol, xylitol and isomalt, maltodextrin, polyethylene oxide, povidone, copovidone, gelatine, partly hydrolyzed polyvinyl alcohol, polyvinyl alcohol, poloxamer, or combinations thereof. In ~~the present~~ ~~a particular embodiment of the invention~~, said ~~the~~ water-soluble polymer is selected from the group consisting of ~~a water-soluble cellulose ether selected from methylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose and mixtures thereof,~~ a water-soluble polyvinyl derivative selected from polyvinyl pyrrolidone, partly hydrolyzed polyvinyl alcohol and polyvinyl alcohol and mixtures thereof, ~~an alkylene oxide polymer selected from polyethylene glycol and polypropylene glycol, and mixtures thereof.~~

In the first aspect of the invention, said water soluble polymer is present in an amount by weight above 40% of the total weight of the coating.

According to the present invention, the acetylsalicylic acid dosage unit coating is substantially free from a water-insoluble polymer or an enteric polymer. The term "substantially free" as used here in refers to the presence of the substance (s) to which it refers, i.e. a water-insoluble polymer or an enteric polymer, in amounts ranging between 0 to 5% b.w., more preferably in amounts ranging between 0 to 1% by weight of the composition of the coating. In a preferred embodiment, said coating

contains no more than about 0.1% by weight of the composition of the coating of a water-insoluble polymer or enteric polymer.

5 Examples of water-insoluble polymers includesynthetic or semisynthetic hydrophobic polymers such as ethyl cellulose, aminoalkyl methacrylate copolymer RS, ethyl acrylate-methyl methacrylate copolymer, polyvinyl chloride, polyvinyl acetate and cellulose acetate.

10 As it is known in the art, acetylsalicylic acid can lead to stomach diseases in long-term use. Thus, according to the present invention, acetylsalicylic acid units can optionally comprise an enteric coating layer. Said coating layer would preferably be included between the acetylsalicylic acid core and the water-soluble polymer coating. Enteric or gastro-resistant coating is intended to resist the gastric fluid and to release the active substance or substances in the intestinal fluid.

15 Coating materials that can be used in enteric coating of said dosage forms can be selected from methacrylic copolymers for instance methacrylic acid/methyl methacrylate, methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl acrylate/methyl methacrylate copolymers, shellac, hydroxypropyl methylcellulose
20 phthalate, hydroxyl propyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose trimellitate, cellulose acetate phthalates, polyvinyl acetate phthalates or combinations thereof. Commonly used plasticizers as may be suitable for particular enteric polymers can be used. It will be appreciated that any polymer with suitable plasticizer can be used in aqueous or non-aqueous system to form an enteric
25 coating on the acetylsalicylic acid dosage unit. The coating can, and usually does, contain a plasticizer to prevent the formation of pores and cracks that would permit the penetration of the gastric fluids.

30 Enterically coated dosage forms may be manufactured using standard enteric coating procedures and equipment. For example, an enteric coating can be applied using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like.

35 In addition to the active agent(s), the dosage units of the formulation of the invention prepared for oral administration will generally contain other pharmaceutically

acceptable excipients such as binders, diluents, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like. The terms “pharmaceutically acceptable excipients”, “pharmaceutically compatible excipients”, and “excipients” are used interchangeably in this disclosure. They refer to non-API substances such as binders, diluents, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards.

Binders are used to impart cohesive qualities to a dosage form. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose, and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and water-washed smectite clays such as Veegum®.

Diluents are typically used to increase bulk so that a practical size dosage unit, for example a tablet, is ultimately obtained. Suitable diluents include alkali metal carbonates, cellulose derivatives (microcrystalline cellulose, cellulose acetate, etc.), phosphates, maltodextrin, dextrin, fructose, dextrose, glyceryl palmitostearate, lactitol, lactose, including direct compression lactose, maltose, mannitol, sorbitol, starch, talc, xylitol and/or hydrates thereof and/or derivatives thereof.

Examples of suitable lubricants include, for example, metallic stearates (such as magnesium stearate, calcium stearate, aluminum stearate), fatty acid esters (such as sodium stearyl fumarate), fatty acids (such as stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oil, leucine, polyethylene glycols (PEG), metallic lauryl sulfate (such as sodium lauryl sulfate, magnesium lauryl sulfate), sodium chloride, sodium benzoate, sodium acetate, talc, siliconized talc and/or hydrates thereof.

Disintegrants used in the present invention enable the dosage form to disperse in water easily and rapidly. Disintegrants can be selected from a group comprising

polymers having high dispersing characteristics such as cross-linked hydroxypropyl cellulose, polyvinylpyrrolidone, high molecular weight polymers, microcrystalline cellulose, sodium starch glycolate, croscarmellose sodium, crospovidone; the products known under the trademarks Kollidon(R) CL, Polyplasdone(R) or alginic acid, sodium alginate, corn starch.

Basic agents of the present invention are either water-soluble or water-insoluble and selected from a group comprising meglumine, tromethamol, sodium bicarbonate, sodium carbonate, sodium citrate, calcium gluconate, disodium hydrogen phosphate, dipotassium hydrogen phosphate, tripotassium phosphate, sodium tartrate, sodium acetate, calcium glycerophosphate, magnesium oxide, magnesium hydroxide, aluminum hydroxide, dihydroxy aluminum, sodium carbonate, calcium carbonate, aluminum carbonate, dihydroxy aluminum amino acetate, diethanolamine, triethanolamine, N-methyl-glucamine, glucosamine, ethylenediamine, triethyleneamine, isopropylamine, di-isopropyl amine or combinations thereof.

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

Surfactants may be anionic, cationic, amphoteric, or nonionic surface-active agents. Surfactants that can optionally be used in the present invention are selected from a group comprising sodium lauryl sulfate, dioctyl sulfosuccinate, gelatin, casein, lecithin, dextran, sorbitan esters, polyoxy ethylene alkyl ethers, polyethylene glycols, polyethylene stearates, colloidal silicon dioxide.

Anti-adhesive agents can be used in the present invention in order to prevent the mixture comprising active agents to adhere onto device and machine surfaces and create rough surfaces. The substances used for this purpose can comprise one or more components selected from a group comprising talc, colloidal silicone dioxide (Aerosil, Syloid, Cab-OSil), magnesium stearate and corn starch.

Release rate determinant polymers that can be used in the formulations of the present invention can be pH-dependant polymers, non pH-dependant polymers, swellable polymers, non-swellable polymers, hydrophilic polymers, hydrophobic

polymers and/or one or more hydrophobic substances; ionic polymers such as sodium alginate, carbomer, calcium carboxy methyl cellulose or carboxy methyl cellulose; non-ionic polymers such as hydroxy propyl methyl cellulose; natural or/synthetic polysaccharides such as alkyl celluloses, hydroxyl alkyl celluloses, cellulose ethers, nitrocellulose, dextrin, agar, carrageenan, pectin, starch and starch derivatives or mixtures thereof; cellulosic polymers; methacrylate polymers, methacrylate copolymers, polyvinylpyrrolidone, polyvinylpyrrolidone-polyvinyl acetate copolymer, ethyl cellulose, cellulose acetate, cellulose propionate (high, medium and low molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, polyvinyl acetate, polyvinyl chloride and mixtures thereof.

As mentioned above, acetylsalicylic acid dosage units (a) show a non-modified or conventional release profile. However, release rate determinant polymers as the ones mentioned in the paragraph above, can also be used in the dosage form of the present invention for the other dosage units. Therefore, the dosage units according to the invention may show a modified release profile. The term "modified release" as used herein includes all types of modified release profiles such as controlled release, sustained release, delayed release, and the like.

The film coating materials of the present invention can contain the following components and/or combinations thereof: lactose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, triacetine, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate phthalate, polyvinyl acetate phthalate, diethyl phthalate, sugar derivatives, polyvinyl derivatives, waxes, fats and gelatins, triethyl citrate, glyceride, titanium oxide, talc, sodium alginate, stearic acid, lecithin.

The term "therapeutically effective amount" as used herein is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The dosage regimen utilizing an HMG-CoA reductase inhibitor in combination with acetylsalicylic acid will be selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and

the particular compound or salt or ester thereof employed. Since two or more different active agents are being used together in a combination therapy, the potency of each of the agents and the enhanced effects achieved by combining them together must also be taken into account. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective amounts of the drug combination needed to prevent, counter, or arrest the progress of the condition.

In a particular embodiment of the invention the amount of acetylsalicylic acid in the formulation is in the range of 10 - 400 mg per dosage unit. More preferable, the amount of acetylsalicylic acid is in the range of 30 - 100 mg per dosage unit. In a more preferred embodiment, the amount of acetylsalicylic acid per dosage unit is in the range of 40 - 85, more preferably 40 - 60 mg per dosage unit, even more preferably 50 mg.

The pharmaceutical dosage form of the invention will contain a HMG-CoA reductase inhibitor, in particular a statin selected from atorvastatin and rosuvastatin and salts thereof in an amount as normally employed for such statin. Thus, depending upon the particular statin, it may be employed in amounts within the range from about 0.1 mg to 2000 mg per day in single or divided doses, and preferably from about 0.2 to about 200 mg per day. The clinical dosage range for atorvastatin is 10 - 80 mg per day. Therefore, in a particular embodiment of the invention the amount of HMG-CoA reductase inhibitor in the dosage form of the invention can be in the range of 1 - 40 mg per dosage unit, more preferably, from 5 - 40, even more preferably from 5 - 20 mg per dosage unit. In a preferred embodiment of the invention, the HMG-CoA reductase inhibitor is in the form of two or more dosage units in the dosage form of the invention.

In a particular embodiment of the invention, the composition further comprises one or more single separate dosage units comprising an inhibitor of the rennin-angiotensin system as a third active agent.

The renin aldosterone angiotensin system (RAAS) plays an important role in the regulation of blood pressure and volume homeostasis, and pivotal roles in the pathophysiology of cardiovascular, renal, and metabolic diseases. Renin is secreted

by the kidney in response to a decrease in circulating volume and blood pressure, and cleaves the substrate angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by angiotensin converting enzyme (ACE). Ang II interacts with cellular receptors, in particular ATI receptors, inducing vasoconstriction and release of catecholamines from the adrenal medulla and pre-junctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. In addition, Ang II inhibits renin release, thus providing a negative feedback to the system. Accordingly, Ang II acts at various levels (e.g. vasculature, sympathetic nervous system, cortex and medulla of the adrenal gland) to increase vascular resistance and blood pressure.

The RAAS can be blocked at various levels. Renin inhibitors, ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) represent major drug classes that block the RAAS. Each individual drug class has a different mode of action and thus blocks the RAAS at a different level: Renin inhibitors block the first, rate-limiting step of RAAS cascade by competitively inhibiting the enzyme renin, thereby preventing the formation of Ang I from angiotensinogen. ACEi block the second step of the RAAS cascade by competitively inhibiting the enzyme ACE, thereby preventing the formation of Ang II. Finally, ARBs block the third and last step of the RAAS cascade by binding to and occupying the ATI receptors without activating them. Thereby, ARBs prevent binding and activation of said ATI receptors by Ang II. It has been disclosed that certain gene polymorphisms reflecting on cardiovascular systems are useful as biomarkers for predicting disease susceptibility or progression, or as a guide for individualized therapy, including drug therapy.

The renin inhibitors to which the present invention applies are any of those having renin inhibitory activity *in vivo*. Renin inhibitors for use herein include, but are not limited to, those disclosed in EP 678.503, WO 00/64887, WO 00/064873, WO 2005/051895, WO 2006/095020, US 2009/0076062, WO 2011/056126, Yokokawa et al. (Expert Opin. Ther. Patents 18(6):581-602, 2008), and Maibaum et al. (Expert Opin. Ther. Patents 13(5):589-603, 2003). Moreover, suitable renin inhibitors include compounds having different structural features. In one embodiment, the renin inhibitor is preferably selected from aliskiren, ditekiren, terlakiren, zankiren, RO 66-1132, RO 66-1168, VTP27999, ACT-280778, and TAK-272, and pharmaceutically acceptable salts, prodrugs, derivatives and isomers thereof.

An ARB according to the invention is any molecule that can specifically antagonize or block the action of angiotensin II type 1 receptors (AT₁ receptors). ARBs suitable for use herein include, but are not limited to, losartan, valsartan, irbesartan, candesartan, telmisartan, eprosartan, tasosartan, zolarsartan, azilsartan, olmesartan, saprisartan, forasartan, E-4177, and ZD-8731, and pharmaceutically acceptable salts, prodrugs, derivatives and isomers thereof.

In a preferred embodiment, the inhibitor of the rennin-angiotensin system is an angiotensin-converting enzyme (ACE) inhibitor. An ACEi according to the invention is any molecule that can specifically inhibit the enzymatic activity of angiotensin converting enzyme. ACEi suitable for use herein include, but are not limited to, benazepril, benazeprilat, captopril, zofenopril, enalapril, enaprilat, fosinopril, ceronapril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril, alacepril, cilazapril, delapril, imidapril, rentiapril, spirapril, temocapril, and moveltipril, and pharmaceutically acceptable salts, prodrugs, derivatives and isomers thereof. In one embodiment, the preferred ACEi is ramipril and pharmaceutically acceptable salts thereof.

Ramipril is a prodrug, which is rapidly hydrolysed after absorption to the active metabolite ramiprilat. Ramipril and ramiprilat inhibit angiotensin-converting enzyme (ACE). ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. The effect of ramipril on hypertension appears to result at least in part from inhibition of both tissue and circulating ACE activity, thereby reducing angiotensin II formation in tissue and plasma. Administration of ramipril to patients with mild to moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted. Ramipril can significantly reduce the incidence of MI, stroke or death from cardiovascular causes in patients aged >

or ≥55 years who are at increased risk for the development of ischaemic cardiovascular events.

5 In a particular embodiment of the invention, the ACE inhibitor dosage units have an unmodified release profile. In another particular embodiment, said ACE inhibitor is in the form of one or more single separate dosage units selected from the group consisting of tablets, particles, granules, pellets and capsules. In a preferred embodiment, said dosage units are coated dosage units.

10 On average, the daily dose of ramipril in a patient weighing approximately 75 kg is at least 0.001 mg/kg, preferably 0.01 mg/kg, to about 20 mg/kg, preferably 1 mg/kg, of body weight. In a particular embodiment of the invention, the amount of ramipril in said formulation is in the range of 1- 100 mg per dosage unit, more preferably in the range of 2 - 50 mg per dosage unit.

15

EXAMPLES

Film-coated tablets comprising acetylsalicylic acid (ASA), atorvastatin and ramipril were manufactured and encapsulated (AAR capsules).

20 As mentioned above, different film-forming polymers can be used according to the present invention. The term PVA as used herein refers to a partly hydrolyzed polyvinyl alcohol.

Manufacture of atorvastatin coated tablets

25 Atorvastatin tablets were manufactured by wet granulation using a high shear mixer and fluid bed dryer. Granulation solution was prepared dispersing polysorbate 80 and hydroxypropyl cellulose in purified water. The intragranular components (see Table 2) were incorporated to the blend to be granulated. Finally, the extragranular components (see Table 2) were added and blended with the obtained granules.
30 Each blend was compressed in a rotary press machine. After tableting, cores obtained were film coated.

Manufacture of ASA coated tablets

35 Acetylsalicylic acid, sodium starch glycolate and microcrystalline cellulose were sieved in the appropriate proportions (see Table 5) and blended. The talc (lubricant)

20

was sieved and blended with the previously obtained blend and the final blend compressed. The resulting core was coated with the aqueous film-forming solution.

Atorvastatin (10 mg or 20 mg) and ASA (40.5; 50 mg or 100 mg) film coated tablets were manufactured as described above and encapsulated along with ramipril (2.5, 5 or 10 mg) film coated tablets. Ramipril film coated tablets are commercially available.

The composition of the manufactured capsules was as follows:

10

Table 1: Composition of AAR capsules

Component	Example 1 AAR capsules (tablet/capsule)	Example 2 AAR capsules (tablet/capsule)
ASA 100 mg film coated tablets	1	
ASA 50 mg film coated tablets	-	2
Atorvastatin 10/20 mg film coated tablets	2	2
Ramipril 10 mg film coated tablets	1	1

Table 2: atorvastatin 10 mg film-coated tablets composition

Component	(mg/tablet)
Intragranular	
atorvastatin calcium trihydrate ⁽¹⁾	10.845
lactose monohydrate	36.805
pregelatinised starch	21.000
calcium carbonate	29.600
hydroxypropylcellulose	3.000
Polysorbate 80	1.000
purified water ⁽²⁾	22.000
total (mg)	102.25
Extragranular	
crospovidone	6.000
silica colloidal anhydrous	1.000
magnesium stearate	0.750
total (mg)	110.000
Film coating	
Hydroxypropylmethyl cellulose coating	3.300
purified water ⁽²⁾	22.000
Total (mg)	113.300

(1) Equivalent to 10 mg atorvastatin. Atorvastatin calcium trihydrate purity is corrected with lactose monohydrate.

(2) Removed during manufacturing process

Table 3: atorvastatin 20 mg film-coated tablets intragranular composition

Component	(mg/tablet)
Intragranular	
atorvastatin calcium trihydrate ⁽¹⁾	21.690
lactose monohydrate	35.360
pregelatinised starch	21.000
calcium carbonate	49.200
hydroxypropylcellulose	3.000
Polysorbate 80	2.000
purified water ⁽²⁾	27.000
total (mg)	132.250
Extragranular	
Crospovidone	6.000
silica colloidal anhydrous	1.000
magnesium stearate	0.750
total (mg)	140.000
Film coating	
Hydroxypropylmethyl cellulose coating	4.200
purified water ⁽²⁾	28.000
Total (mg)	144.200

5

(1) Equivalent to 20 mg atorvastatin. Atorvastatin calcium trihydrate purity is corrected with lactose monohydrate.

(2) Removed during manufacturing process

Table 4: composition of 100 mg, 50 mg and 40.5 mg ASA film-coated tablets

COMPOSITION	FUNCTION	QUANTITY (mg)	QUANTITY (mg)	QUANTITY (mg)
acetylsalicylic acid	active ingredient	100.0	50.0	40.50
sodium starch glycolate	disintegrant	3.75	7.50	7.10
microcrystalline cellulose	diluent	20.00	41.50	51.00
talc	lubricant	1.25	1.00	1.00
TOTAL:		125.00	100.00	100.00

10

In the finished product film coated tablets of atorvastatin were placed inside a capsule along with film coated tablets of ramipril and film coated tablets of acetylsalicylic acid (ASA).

In order to improve the stability of the formulation, a partly hydrolyzed polyvinyl alcohol, was used as film forming agent for acetylsalicylic acid (ASA) tablets. Different amounts of film coating for ASA tablets were tested: 2.17 mg/cm², 4.3 mg/cm² and 8.7 mg/cm².

Table 5: composition of PVA coating

Component	w/w %
partially hydrolysed polyvinyl alcohol	45.50
titanium dioxide	30.00
Talc	22.00
soy lecithin	2.00
xanthan gum	0.50
Total	100.00

Presence of atorvastatin impurities in capsules comprising ASA film-coated tablets (one tablet of 100 mg ASA or 2x50 mg) under different stress conditions (40 °C, 30 °C, and 25 °C) was tested.

As it is shown in Table 6, in all cases (40 °C, 30 °C, and 25 °C) aspirin tablets with 8.7 mg/cm² coating, yielded lower levels of lactone H than tablets with 4.3 mg/cm² coating (standard level).

Table 6: Atorvastatin impurities when ASA is coated with different thickness of PVA coatings (4.3 mg/cm² and 8.7 mg/cm²):

Example 1 AAR capsules:

ASA 100 mg 4.3 mg/cm²	Initial	40°C 3 months	30°C 3 months	25°C 3 months
ASA Assay	100.2	100.6	98.6	100.1
Impurities				
Salicylic acid	0.05	0.71	0.28	0.12
Total impurities	0.05	0.76	0.35	0.19
ATV Assay	98.7	100.5	99.9	101.9
Impurities				
Impurity D	0.10	0.09	0.09	0.09
Impurity H	0.10	0.57	0.43	0.41
Total impurities	0.20	0.79	0.55	0.53

Example 2 AAR capsules:

ASA 50 mg x2 8.7 mg/cm²	Initial	40°C 3 months	30°C 3 months	25°C 3 months
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23

ASA Assay	97.6	101.3	97.7	98.7
Impurities				
Salicylic acid	0.09	0.19	0.13	0.18
Total impurities	0.19	0.32	0.18	0.33
ATV Assay	99.5	97.4	96.8	98.3
Impurities				
Impurity D	0.05	0.06	0.05	0.06
Impurity H	0.08	0.15	0.05	0.08
Total impurities	0.22	0.58	0.30	0.47

Dissolution profile of ASA tablets

50 mg or 40.5 mg strength formulations of ASA tablets (see Table 4) were prepared in order to check whether the dissolution rate could be improved by reducing the strength of the formulations.

Table 7: Comparative dissolution rate of 100 mg and 50 mg ASA strength formulations

FORMULATION		100 mg		50 mg (x2)	
PARAMETER	UNITS	RESULTS		RESULTS	
Dissolution test (0.05 M Acetate buffer pH 4.5; 50 rpm; 500 ml)	minutes , %	5	Mean = 38 % CV = 23.44 %	5	Mean = 58 % CV = 8.52 %
		15	Mean = 96 % CV = 5.32 %	15	Mean = 103 % CV = 3.21 %
		30	Mean = 99 % CV = 2.84 %	30	Mean = 105 % CV = 3.09 %

Dissolution tests were performed under the following conditions: 0.05 M acetate buffer pH 4.5; 50 rpm US Pharmacopeia type 1 apparatus; 500 ml.

Dissolution data showed (See Figure 1 and Table 7) an improvement in dissolution profile of the ASA tablets when the strength of the formulation is reduced. Dissolution rate of two tablets of acetylsalicylic acid 50 mg is faster than one of acetylsalicylic acid 100 mg.

Next step was to test if similar results are obtained when using film-coated tablets. The effect of PVA coating in the dissolution profile of film-coated tablets of 50 mg ASA compared to 100 mg ASA tablets was tested. Different amounts of film coating agent were tested: 2.17 mg/cm², 4.3 mg/cm² and 8.7 mg/cm².

As it is shown in Table 8 and Figure 2, by increasing the amount of coating by more than 4.3 mg/cm², the dissolution profile of the 100 mg ASA tablets is affected. Mean values of % dissolved at 15 minutes are over 85 % in ASA tablets comprising 2.17 mg/cm² and 4.3 mg/cm² coating. However, said value is below 75% in tablets
5 comprising 8.7 mg/cm² coating.

Dissolution test conditions:

Apparatus: USP 1 (basket)

Stirring speed: 50 rpm

10 Dissolution Volume: 500 mL

Dissolution media: pH 4.5 acetate buffer

Table 8: ASA 100 mg film-coated tablets (PVA coating) dissolution results

Time (min)	ASA 100 mg film-coated tablets 2.17 mg/cm ²	ASA 100 mg film-coated tablets 4.3 mg/cm ²	ASA 100 mg film-coated tablets 8.7 mg/cm ²
0	0	0	0
5	22	33	13
15	88	87	72
30	105	97	101

15 However, as it is shown in Table 9, 50 mg ASA tablets comprising 8.7 mg/cm² coating do not show any negative effect on the dissolution profile, as at 15 minutes mean values of % dissolved are over 85 %.

Table 9: 2x50 mg ASA PVA coated tablets dissolution results

Time (min)	ASA 50 mg film-coated tablets 2.17 mg/cm ²	ASA 50 mg film-coated tablets 4.3 mg/cm ²	ASA 50 mg film-coated tablets 8.7 mg/cm ²
0	0	0	0
5	41	47	33
15	94	96	101
30	101	106	115

20

Dissolution results (see Figure 3; Tables 8 and 9) show that the dissolution rate of 2 tablets of 50 mg ASA is in all cases (2.17 mg/cm², 4.3 mg/cm² and 8.7 mg/cm²) faster than that of one tablet of 100 mg ASA. Also, comparing the dissolution profile of 50 mg tablets and 100 mg tablets with 4.3 mg/cm² and 8.7 mg/cm² coating, it can
25 be observed that 50 mg (2x) tablets with 8.7 mg/cm² coating dissolve faster than 100 mg tablets with 4.3 mg/cm² coating.

Dissolution profiles of AAR capsules containing ASA 50 mg x 2 film-coated tablets with 8.7 mg/cm² were also performed at different conditions:

5 Dissolution test conditions:

Apparatus: USP 1 (basket)

Stirring speed: 100 rpm

Dissolution Volume: 900 mL

Dissolution media: pH 4.5 acetate buffer

10

Results (Table 10 and Figure 4) were as follows:

Table 10: % ASA dissolved in AAR capsules dissolution results

Time (min)	AAR capsule % ASA dissolved
0	0
15	81.3
20	90.7
30	94.4
45	95.5

15 Dissolution test conditions:

Apparatus: USP 1 (basket)

Stirring speed: 100 rpm

Dissolution Volume: 900 mL

Dissolution media: pH 6.8 phosphate buffer

20

Results (Table 11 and Figure 5) were as follows:

Table 11: % ASA dissolved in AAR capsules dissolution results

Time (min)	AAR capsule % ASA dissolved
0	0
15	73.1
20	86.2
30	95.3
45	97.3

25

As shown in Table 10 and Table 11, AAR capsule containing 50 mg ASA film-coated tablets x 2, comprising 8.7 mg/cm^2 of tablet coating, show mean values over 80% at 15 minutes in the case of pH 4.5 and close to 75 % at pH 6.8.

- 5 A formulation comprising ASA tablets with 8.7 mg/cm^2 coating provides more protection and isolation to the acetylsalicylic acid tablet, making more difficult that salicylic acid can sublime and it can trigger the degradation of the other components, in particular, of atorvastatin or rosuvastatin inside the final capsule.

CLAIMS

1. An orally administrable pharmaceutical dosage form for use in the prevention and/or treatment of a cardiovascular disease comprising:

- (a) acetylsalicylic acid as a first active agent; and
- (b) HMG-CoA reductase inhibitor as a second active agent, wherein said HMG- CoA reductase inhibitor is selected from atorvastatin and rosuvastatin and salts thereof, and

wherein

(a) are two or more single separate coated dosage units comprising one or more water-soluble polymer in said coating and being said coating substantially free from a water-insoluble polymer or an enteric polymer which means in an amount ranging between 0 to 5% by weight of the composition of the coating; and wherein the amount of coating is comprised from 8 to 12 mg/cm²; and showing a non-modified release profile; and

(b) is one or more single separate coated dosage units;

the dosage units are in the form of tablets, and

the water soluble polymer is present in an amount by weight above 40% of the total weight of the coating and is selected from the group consisting of  or  or a water-soluble

polyvinyl derivative selected from polyvinyl pyrrolidone, partly hydrolyzed polyvinyl alcohol, polyvinyl alcohol, and mixtures thereof.

2. The pharmaceutical dosage form for use according to claim 1, wherein said dosage form is in the form of a capsule.

3. The pharmaceutical dosage form for use according to any of the preceding claims, wherein the water-soluble polymer is selected from the group consisting of partly hydrolyzed polyvinyl alcohol, polyvinyl alcohol, and mixtures thereof.

4. The pharmaceutical dosage form for use according to any of the preceding claims, wherein acetylsalicylic acid dosage units (a) show a percentage equal to or greater than 65 %, preferably greater than 75 %, more preferably greater than 80% and even more preferably greater than 85% of acetylsalicylic acid dissolved within 60 minutes, preferably within 30 minutes and more preferably within 15 minutes in a US

Pharmacopeia type 1 apparatus in 0.05 M acetate buffer, at pH 4.5, 100 rpm in a volume of 900 ml.

5. The pharmaceutical dosage form for use according to any of the preceding claims, wherein (a) and (b) dosage units are in the form of coated tablets.
6. The pharmaceutical dosage form for use according to any of the preceding claims, wherein the amount of acetylsalicylic acid in said dosage form is in the range of 10 to 400 mg per dosage unit.
7. The pharmaceutical dosage form for use according to any of the preceding claims, wherein the amount of HMG-CoA reductase inhibitor in said dosage form is in the range of 5 to 40 mg per dosage unit.
8. The pharmaceutical dosage form for use according to any of the preceding claims, wherein the HMG-CoA reductase inhibitor is in the form of two or more dosage units.
9. The pharmaceutical dosage form for use according to any of the preceding claims, further comprising one or more single separate dosage units comprising an inhibitor of the rennin-angiotensin system as a third active agent.
10. The pharmaceutical dosage form for use according to the preceding claim, wherein the
inhibitor of the rennin-angiotensin system is an ACE inhibitor selected from the group consisting of ramipril, captopril, cilazapril, delapril, enalapril, fentiapril, fosinopril, indolapril, lisinopril, perindopril, pivopril, quinapril, spirapril,trandolapril, and zofenopril and pharmaceutically acceptable salts or an angiotensin receptor blocker selected from the group consisting of losartan, valsartan, irbesartan, candesartan, telmisartan, eprosartan, tasosartan, zolarsartan, azilsartan, olmesartan, saprisartan, forasartan, E-4177, and ZD-8731, and pharmaceutically acceptable salts.
11. Pharmaceutical dosage form for use according to the preceding claim, wherein said ACE inhibitor is ramipril and pharmaceutically acceptable salts.

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FIGURES

Figure 1

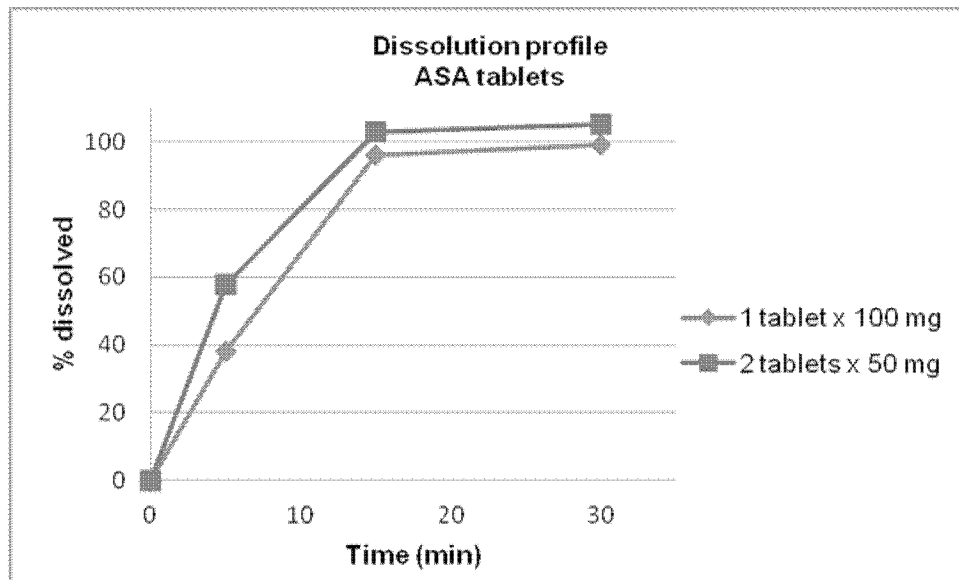
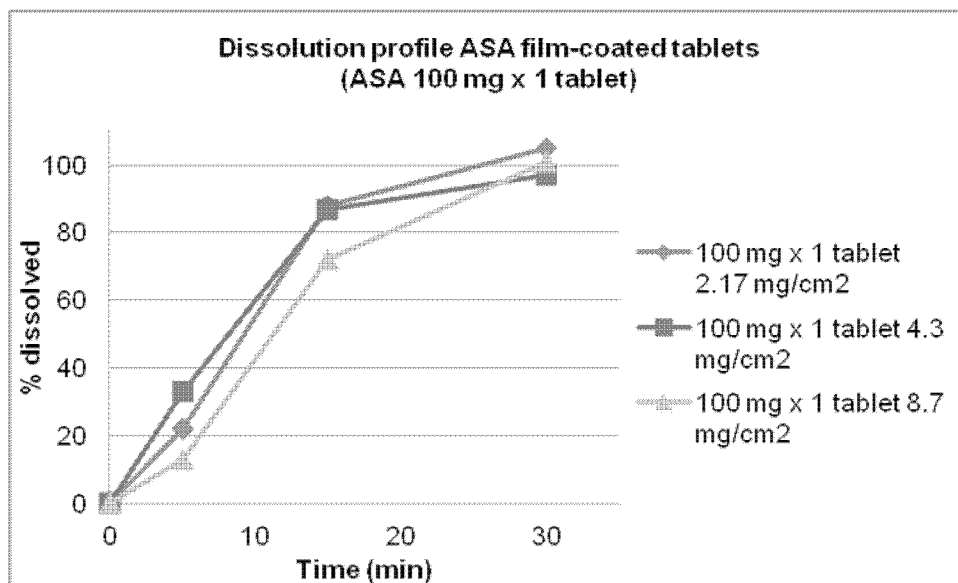


Figure 2



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Figure 3

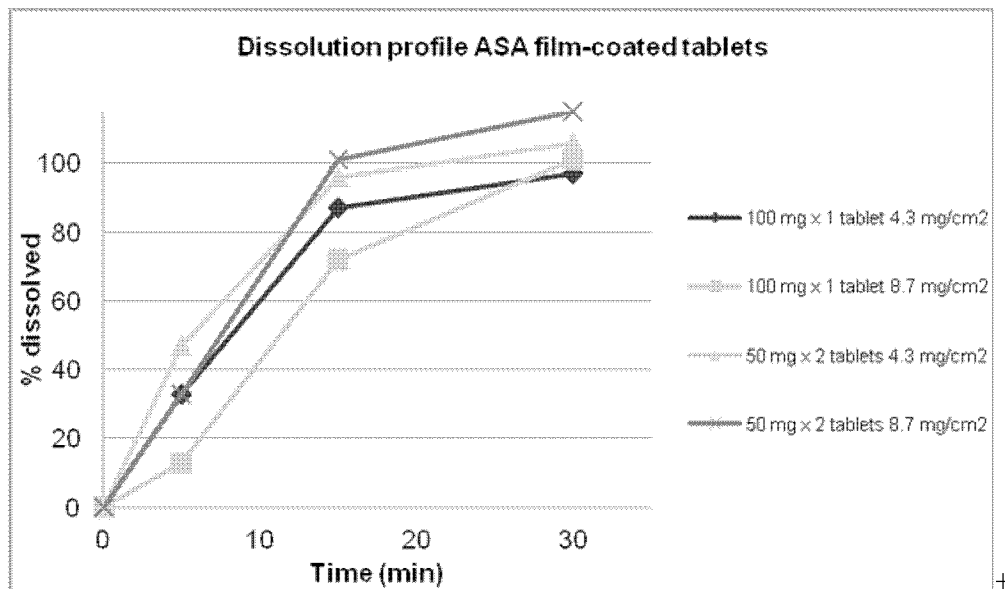
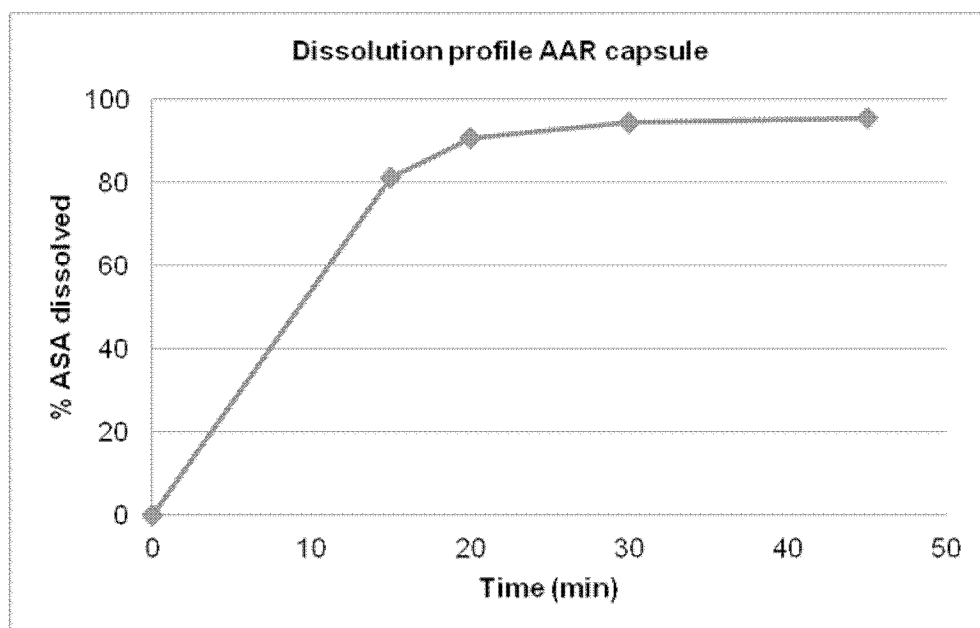


Figure 4



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Figure 5

