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(54) Title: MEDICAL COMPOSITION CONTAINING A CHOLESTEROL ABSORPTION INHIBITOR AND CHOLESTEROL BIOSYNTHESIS INHIBITOR

(57) Abstract: The present invention is related to a pharmaceutical composition containing rosuvastatin and ezetimibe, wherein the interaction of the active ingredient and excipient is minimized, the active ingredients are present in spatially separated or contacting physical phases and wherein the active ingredient release from the two phases takes place in temporarily separated manner rather than occuring at the same time or begins delayed from one phase compared to the other, other. A further aspect of the present invention is method for decreasing an active ingredient- excipient interaction or interaction between active ingredients in combined pharmaceutical composition containing several solid phases produced by compression, which comprises adjusting the disintegration time of the compressed solid phases different from each other.

Medical composition containing a cholesterol absorption inhibitor and cholesterol biosynthesis inhibitor

Technical field of the invention

The present invention relates to an immediate release combined pharmaceutical composition containing a cholesterol biosynthesis inhibitor and a cholesterol absorption inhibitor active ingredient, more specifically, rosuvastatin [((*E*)-(+)-7-[4-(4-fluoro-phenyl)-6-isopropyl-2-(methanesulfonyl-methyl-amino)-pyrimidin-5-yl]-(3*R*,5*S*)-dihydroxi-hept-6-enoic acid] or a pharmaceutically acceptable salt thereof as a HMG-CoA reductase inhibitor and ezetimibe [[((3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxy-phenyl)-2-azetidinon)], wherein the pharmaceutical interaction of the active ingredients is minimized.

The present invention more specifically relates to a pharmaceutical composition, wherein the pharmaceutical interaction of the active ingredients is minimized and which contain the two active ingredients in physical phases which are contacting each other at a small surface area or wherein said physical phases are spatially separated from each other.

Another object of the present invention is immediate release pharmaceutical composition contining rosuvastatin and ezetimibe, wherein the pharmaceutical interaction of the active ingredients is minimized, wherein the two active ingredients are present in physical phases which are contacting each other at a small surface area or wherein said phases are spatially separated from each other and wherein the release of the two active ingredients from the two phases occurs in a manner separated in time or the release of one active ingredient starts with a delay from the first phase compared to the other.

A further object of the present invention is an immediate release pharmaceutical composition containing rosuvastatin and ezetimibe, wherein the interaction of the active ingredients is minimized, wherein the two active ingredients are present in physical phases which are contacting each other at a small surface area or said phases are spatially separated, said phases are produced by compression and wherein the disintegration time of the phases is different

from each other. It is characteristic to such compositions that the release of the active ingredient takes place with a temporary difference.

The state of the art

Ezetimibe is a selective cholesterol inhibitor, which, when administered together with a HMG-CoA reductase inhibitor (statin), can be used as adjuvant to diet in the treatment of patients suffering from primary hypercholesterolemia, when the effect of the statin treatment alone is not sufficient.

According to the state of the art, combination of ezetimibe and rosuvastatin could furthermore be used advantageously in the lowering of plasma LDL-C and Apo-B concentration in lipid metabolism disorders.

As far as physical-chemical properties are concerned, ezetimibe is a white crystalline powder having poor solubility in water and gastrointestinal fluids but soluble in organic solvents. According to the Biopharmaceutical Classification System (BCS), ezetimibe belongs to Class II. In case of such active ingredients, the bioavailability is determined by the solubility of the active ingredient.

Rosuvastatin is selective and competitve inhibitor of the enzyme 3-hydroxy-3-methyl-glutaryl coenzym-A reductase and by inhibiting the same enzyme, decreases the rate of cholesterol biosynthesis in the liver. Rosuvastatin is used in therapeutical applications as pharmaceutically acceptable salt, such as calcium or zinc salt. Rosuvastatin belongs to Class III of the Biopharmaceutical Classification System (BCS) having good solubility in water and in body fluids.

During the formulation of a composition containing ezetimibe having poor solubility and rosuvastatin or a pharmaceutically acceptable salt thereof, the compliance with the regulatory requirement during in vitro dissolutions test shall be ensured, according to which the dissolved amount of the active ingredient shall be at least 80% within 30 minutes of testing

time. The composition of the dissolution medium has been specified by the guidelines of the regulatory authorities.

During the formulation of combined pharmaceutical compositions, pharmaceutical interactions between the individual active ingredients and between an active ingredient and anexcipient should be considered. The expression „pharmaceutical interaction" (abbreviated hereinbelow as „interaction") is meant in the sense of an interaction which influence the stability of the active ingredient, capable of causing the decomposition of the active ingredient during manufacturing, storage or use or which influences the suitability of the pharmaceutical composition for use, such as influencing the dissolution of or reproducibility of the dissolution of an active ingredient.

In cases of preparing a combined pharmaceutical formulation wherein several active ingredients exhibit significantly different properties from the pharmaceutical technology point of view or when some active ingredients are incompatible with each other, such actives should be formulated with a separate excipient system. In such cases, however, possibility of the interaction with an active ingredient and an excipient used in the excipient system for the formulation of a second active ingredient should also be taken into account..

There are several methods known from the state of the art for the improvement of solubility of ezetimibe, which are based on ezetimibe's amorphization, transformation thereof into a polymer dispersion, hydrophilization thereof by co-milling with a hydrophilic excipient, addition of a surfactant or micronization. In addition to the above, dissolution rate of ezetimibe can be influenced by the choice of the crystalline form thereof.

The disadvantage of the utilization of an amorphized active ingredient resides in that due to the high free energy of the amorphous state, the active ingredient may transform into a crystalline form which may be accompanied by the change of the solubility and bioavailability. Furthermore, the stability of an active ingredient in amorphous state is usually low. Consequently, in order to preserve the amorphous morphology, usually special excipients and methods are required.

According to one of such methods disclosed in European Patent No. 1799648, ezetimibe is adsorbed in amorphous state to a polymer substrate or manufactured in such a polymer as a solid amorphous dispersion. Similar methods have been disclosed in International Patent Applications WO2008063766, WO2008101723 and WO2010037728.

In European Patent No. EP1531805, a pharmaceutical composition free from ascorbic acid has been disclosed which comprises as active ingredients ezetimibe and simvastatin and furthermore an antioxidant excipient, e.g. butylhydroxyanisole or propylgallate. During the formulation, solubility of ezetimibe is enhanced by granulation in the presence of a hydrophilic polymer, povidone.

According to a further method disclosed in International Patent ApplicationWO 2007/011349, bioavailability of poorly water-soluble active ingredients such as ezetimibe is improved by formulating the actibe ingredient with a pharmaceutically acceptable sugar.

During micronization, the free energy of the active ingredient is similarly increased to amorphization. In addition, micronization usually results in significant loss of material. Furthermore, due to electrostatic charges building up in a micronized substance and resulting in repulsive forces between the particles, a substance having disadvantageously low density and less suitable for further manipulation is formed.

In US Patent Application No. 2007/027052, a pharmaceutical composition is disclosed wherein the suitable solubility of ezetimibe is obtained by an active ingredient having a particle size d(90) less than 25 μm.

In European Patent Application No. 1849459, a pharmaceutical composition is disclosed wherein ezetimibe is co-milled with at least one hydrophilic excipient, such as a saccharide or polysaccharide, starch or pregelatinized starch. The particle size of ezetimibe d(50) after milling is less than 25 μm. Thus, according to the method disclosed in this application, micronization is combined with the use of a hydrophilic excipient.

According to the composition disclosed in International Patent Application No. 2009/074286, suitable solubility of ezetimibe is achieved by using a solubility-increasing component, such

as sodium laurylsulfate or a hydrophilic excipient having basic character such as N-methyl-D-glucamine and by decreasing the particle size of ezetimibe.

In International Patent Application No. 2009/077573, a suspension has been disclosed wherein ezetimibe is present as precipitated microparticles. During the preparation of the suspension, ezetimibe is dissolved, precipitated by an antisolvent, isolated, dried and resuspended. The thus obtained suspension is subsequently homogenized. The disadvantage of the method disclosed in this application is that the complex, multistep method is not suitable for preparing a suspension containing ezetimibe particles with suitably narrow particle size distribution on an industrial scale.

The disadvantages of the method disclosed in International Patent Application No. 2009/077573 are largely eliminated by the method disclosed in International Patent Application No. 2011012912. The method is essentially based on precipitating ezetimibe from solution thereof by an antisolvent, optionally containing a surfactant such as a lauryl sulfate derivative or other excipients and preparing ezetimibe-containing granules by using the thus obtained ezetimibe suspension comprising micro-sized crystalline ezetimibe particles. In this case, the micro-sized ezetimibe particles are directly used during formulation and besides eliminating the above-mentioned disadvantages, neither the aggregation of ezetimibe microparticles nor decomposition of ezetimibe occurs at a significant degree.

In a known commercially available pharmaceutical composition, solubility of ezetimibe is increased by using sodium laurylsulfate. The advantage of this method resides in that it does not require the use of high-energy micronized ezetimibe or amorphous ezetimibe susceptible to crystallization.

In International Patent Application No. 2009/024889, a pharmaceutical composition in capsule form is disclosed, which comprises an HMG-CoA reductase inhibitor ingredient and ezetimibe in granulated form, wherein the HMG-CoA reductase inhibitor containing component also contains an alkaline earth metal salt. The alkaline earth metal salt in this formulation plays the role of stabilizing the HMG-CoA reductase inhibitor. No data has been disclosed with respect the dissolution of the tablet or the pharmacokinetics of the composition.

In International Patent Application No. 2011/019326, a pharmaceutical composition comprising ezetimibe and rosuvastatin calcium salt and a method of preparation thereof has been disclosed. According to the method, rosuvastatin is formulated by wet granulation and tabletted after homogenization with ezetimibe. The disadvantage of the method is that during wet granulation, rosuvastatin lactone impurity may be formed from rosuvastatin. The application is silent about the dissolution of active ingredients from the tablet or pharmacokinetics of the active constituents.

International Patent Application No. 2013/066279 discloses an ezetimibe-containing pharmaceutical composition wherein the particle size of the active ingredient is between 10 and 50 μm and the composition contains at least 1 weight % disintegrant. According to the application, the composition having the above-mentioned ingredients can also be used as a phase in a bilayer tablet. The application furthermore discloses a bilayer tablet containing rosuvastatin and ezetimibe active ingredients. However, no disclosure is provided in respect of the dissolution, stability and pharmacokinetics data neither the compositions are disclosed sufficiently to be prepared by a person skilled in the art.

International Patent Application No. 2008/095263 is related to a pharmaceutical composition containing different active ingredients in two different physical phase, wherein the pharmaceutical interaction between the active ingredients and between the active ingredient and the excipients is prevented by formulating the different active ingredients into separate physical phases and capsulating them.

Short description of the invention

The objective of our research-development work was to prepare a stabstablele pharmaceutical composition containing ezetimibe and a pharmaceutically acceptable salt of rosuvastatin preferably rosuvastatin zinc (2:1) salt, which satisfies regulatory requirements and which could be produced by a simple process on an industrial scale.

During this work aimed at the preparation of a stable, immediate release pharmaceutical composition containing ezetimibe and a pharmaceutically acceptable salt of rosuvastatin which can satisfy the therapeutical needs and which is amenable to industrial manufacturing by a simple process, ezetimibe-containing granules produced according to International Patent Application No. 2011/012912 were homogenized with and tabletted together with a pharmaceutically acceptable salt of rosuvastatin. During the testing of the pharmaceutical compositions obtained in this way, we have surprisingly recognized that the rosuvastatin salt decreases the dissolution of ezetimibe from the tablet in such an extent that the thus obtained combined composition fails to satisfy therapeutical criteria. Furthermore, during the formulation of a bilayer tablet containing ezetimibe and rosuvastatin in separate layers, we have also found that during the formulating of the active ingredients according to the state of the art as bilayer tablet, the effect of rosuvastatin resulting in decreased dissolution of ezetimibe can also observed.

This recognition is surprising since documents belonging to the state of the art disclosing pharmaceutical compositions containing ezetimibe and rosuvastatin fail to disclose any information about a pharmaceutical interaction occuring between the active ingredients rosuvastatin and ezetimibe resulting in disadvantageous dissolution of ezetimibe. The state of the art is even completely silent to provide guidance to the solution of the technical problem resulting from the above-mentioned observation.

The above-mentioned recognition is further surprising for the reason that rosuvastatin and ezetimibe are chemically compatible active ingredients. During the compatibility testing carried out during pharmaceutical development phase, no chemical change was observed in rosuvastatin or ezetimibe when the active ingredients were challenged in mixed form.

Consequently the technical problem to be solved during our research-development work was to provide a stable pharmaceutical composition containing ezetimibe and a pharmaceutically acceptable salt of rosuvastatin, preferably rosuvastatin zinc (2:1) salt, which complies with regulatory requirements and which can be produced by a simple process on an industrial scale and wherein at the same time the dissolution-decreasing effect of a pharmaceutically acceptable rosuvastatin salt to the dissolution of ezetimibe is absent or decreased to a minimal extent.

The above-mentioned objective is solved by the present invention.

An object of the present invention is a pharmaceutical composition containing ezetimibe, rosuvastatin and a surfactant, preferably sodium lauryl sulfate, wherein the pharmaceutical interaction of the active ingredients is minimized.

A further object of the present invention is a pharmaceutical composition containing rosuvastatin and ezetimibe, wherein the interaction between active ingredient and excipient is minimized and which contains the active ingredients in separate physical phases which are separated spatially or contacting each other at a minimal surface area.

In the present specification, „minimal" or „small" contacting surface area is meant as equal or smaller area than the cross-sectional area of the pharmaceutical formulation. In this way, according to the present specification, a contacting surface area can be regarded as small for example when such an area is equal or smaller than the cross-sectional area of a tablet. Preferably, the small contacting surface area is manifested as the mutual contacting surface area of two convex pharmaceutical dosage form, for example, two biconvex tablets when these are placed in close proximity, e.g. by touching each other.

According to a preferable embodiment of the present invention, there is provided an immediate release pharmaceutical composition containing rosuvastatin and ezetimibe, wherein the interaction of the active ingredient and excipient is minimized, said composition contains the two active ingredients in individual physical phases which are physically separated or contacting each other at a small surface area and wherein the release of the two active ingredients from the two phases takes place separatedly in time or begins delayed from one of the phases as compared with the another.

The release of the two active ingredients can be controlled by, among others, methods known from the state of the art, e.g. by coating one or both phases. Alternatively, when the two active ingredients are formulated as a compressed dosage form such as tablets, one can proceed according to the present invention by choosing a different disintegration time for each of the phases in order to achieve active ingredient release separated in time.

According to a further aspect of the present invention, there is provided an immediate release pharmaceutical composition containing rosuvastatin and ezetimibe, wherein the interaction of the active ingredients is minimized, wherein said composition contains each of the two active ingredients in individual phases which are spatially separated or contacting each other at a small area, optionally formulated in a capsule, wherein the phases are produced by compression and wherein the disintegration time of the phases is different from each other. It is characteristic for such formulations that the release of the two active ingredients takes place with delay from the second phase.

It is characteristic for the immediate release pharmaceutical compositions according to the present invention that at least 80 weight% of each active ingredients is dissolved from the formulation within 30 minutes.

The above observation is especially surprising for the reason because on the basis of experience obtained with single- or bilayer tablets wherein the two active ingredients are formulated in a common layer or into two layers contacting one active ingredient each, pharmaceutical interaction with rosuvastatin resulting in the decreased dissolution of ezetimibe would be expected even when the two active ingredients are formulated separately as tablets and two such formulated tablets with each of the active ingredients are filled into a capsule. The basis of this assumption is that the release of the active ingredients takes place in a limited common space compared to the volume of the tablets and according to the state of the art, difference in disintegration time does not have any technical effect in this respect. However, according to our experiments, this assumption was not justified and we experienced that by filling a rosuvastatin- and ezetimibe-containing small-size tablet having different disintegration time into capsules, the disadvantageous effect of rosuvastatin for the dissolution of ezetimibe could be essentially eliminated.

The state of the art is silent about a method suitable for decreasing interaction between active ingredients or between an active ingredient and an excipient of an immediate release pharmaceutical composition, which is based on the release of the two active ingredients shifted in time from different physical phases having different disintegration time.

A preferable embodiment of the present invention is an immediate release pharmaceutical composition, wherein one tablet containing ezetimibe and one tablet containing rosuvastatin are filled into a capsule, wherein the interaction of the ingredients of the two tablets is minimized and the release of the active ingredients from the corresponding tablets is separated spatially and if desired, adjusted to occur separatedly in time.

A further object of the present invention is a method for decreasing the interaction of the ingredients of combined pharmaceutical composition, which comprises formulating the combined pharmaceutical in a manner that the two or more active ingredients contact each other at a small surface area or are present in a spatially separated physical phases and if desired, in a manner suitable for providing the release of the active ingredients from each of the physical phases separately in time or or starting with a delay from certain phases.

In order to delay the release of the ezetimibe active ingredient from the corresponding phase, it is possible to provide one of the physical phases with a coating suitable for delaying the active ingredient release. Such coatings are known in the state of the art.

According to one of the preferable embodiments of the present invention, two or more phases present in the combined composition contacting each other at a small surface area are produced by a compression method such as tabletting and adjusting the disintegration time of the tablets in different phases to a different length.

We have found that according to the present invention, the distance of the phases separated spatially and containing different pharmacaeutically active ingredients each, by which the distance between the most closely arranged surfaces of the respective phases is meant, can range from contacting to a distance practically achieveable in a pharmaceutical composition, which is determined by the physical dimensions of the composition. Thus, the characteristic distance of spatially separate phases is smaller than about 35 mm, usually between 1 and 30 mm.

The release of the active ingredients from the respective physical phases can be characterized by the disintegration or dissolution time, which can be determined for the phases according to

methods known in the art, such as by pharmacopoeial methods defined for determination of disintegration time or by methods of dissolution testing.

According to the present invention, the difference between the disintegration time or the dissolution time measured in the phases is between 5 and 1800 seconds, preferably between 10 and 300 seconds, the most advantageously between 20 and 240 seconds.

In the pharmaceutical composition containing ezetimibe and rosuvastatin according to the present invention, preferably rosuvastatin zinc (2:1) salt is used, although other pharmaceutically acceptable rosuvastatin salts, such as rosuvastatin calcium salt, rosuvastatin sodium salt, rosuvastatin iron salt, rosuvastatin copper salt, rosuvastatin manganese salt or rosuvastatin magnesium salt could also be formulated according to the method of the present invention.

The ezetimibe-containing phase of the pharmaceutical composition according to the present invention is preferably produced by tabletting ezetimibe granules containing ezetimibe microparticles and sodium lauryl sulfate as solubility increasing component prepared according to International Patent Application No. 2011/012912 itself or an admixture thereof with further pharmaceutically acceptable excipients. Nevertheless, the ezetimibe active ingredient containing phase of the pharmaceutical composition according to the present invention can also be produced by alternative methods, such as by using an amorphized ezetimibe dispersion, a micronized active ingredient or by using a solubility-increasing component different from sodium lauryl sulfate.

We have found generally desirable that among the physical phases each characterized by different disintegration time, the phase having the shortest disintegration time contains the pharmaceutically active ingredient having the best solubility and that a phase having longer disintegration time contains a less soluble pharmaceutically active ingredient. Consequently in the pharmaceutical composition according to the present invention, the pharmaceutically acceptable salt of rosuvastatin is formulated in a phase having shorter disintegration time, while ezetimibe is formulated in a phase having longer disintegration time.

Thus a further problem to be solved during the accomplishment of the present invention was providing a phase containing a rosuvastatin pharmaceutically acceptable salt, preferably rosuvastatin zinc (2:1) salt wherein said phase is characterized by short disintegration time. At the same time, however, it was required that the comprimate, preferably a tablet should exhibit sufficient strength and hardness and low abrasion and friability and providing at the same time that the dissolution of the active ingredient corresponds to the expected therapeutical objectives.

There are several methods known from the state of the art for influencing the disintegration time of pharmaceutical dosage forms produced by compression. For exampe, it is known that the binder, filler and disintegrant components of the dosage form affect the disintegration time significantly. It is furthermore known that besides the viscosity of the intruding liquid, the internal pore structure, average pore size and internal binding forces present in tablets also influence the disintegration time of tablets. It was furthermore assumed that the disintegration time is also influenced by the relationship between the internal adhesive force within a tablet and the interactions between the particles of the disintegrating liquid phase and tablet ingredients (Sofia Mattsson: Pharmaceutical Binders and Their Function in Directly Compressed Tablets. Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy, 238, Acta Universitatis Upsaliensis, Uppsala Sweden 2000). However, there is no known method in the state of the art suitable for predicting disintegration time as a function of composition or for quantitative characterization of the effect of individual excipients to the disintegration time. Furthermore, there is no known method for exploiting the difference between disintegration time values for decreasing or eliminating the interaction between active ingredients despite of the fact that it is known and accepted for a person skilled in the art that disintegration is a prerequisite for dissolution. At the same time, however, the person skilled in the art is also aware that disintegration of a pharmaceutical composition is a step having the greatest uncertainty during the process of active ingredient release.

Furthermore, in case of phases delimited spatially or contacting each other at a small surface area and having different composition and different active ingredients, it can not be predicted that how much difference should be provided between the respective disintegration time values of the individual phases in order to achieve the decrease or elimination of the interaction.

We have surprisingly found that when using rosuvastatin zinc (2:1) salt active ingredient, a rapidly disintegrating, stable compressed pharmaceutical composition having suitable strength, hardness and friability as well as low abrasion could be prepared by using microcrystalline cellulose, colloidal silica and a lubricant, such as magnesium stearate in a composition of 5-40 weight% rosuvastatin zinc (2:1) salt, 60-95 weight% microcrystalline cellulose, 0.05-2.0 weight% colloidal silica and 0.1-2.0 weight% lubricant even though no stabilizing compound for HMG-CoA reductase inhibitor compounds including rosuvastatin, such as an antioxidant, an alkaline earth metal salt or alkaline earth metal phosphate is used. An especially advantageous composition consists of 14 weight% rosuvastatin zinc (2:1) salt, 85 weight% microcrystalline cellulose, 0.15 weight% colloidal silica and 1.2 weight% magnesium stearate lubricant. For the preparation of the pharmaceutical composition, the ingredients are homogenized and the homogenate is directly used for manufacturing e.g. a monocomponent small tablet suitable for filling into capsules. If desired, the disintegration time of the pharmaceutical composition dan be adjusted by adding a binder and optionally a disintegrant known from the state of the art. In the case when the tablet contains a binder, a disintegrant is required for improving the speed of disintegration.
It has been surprisingly found that in case of a tablet containing rosuvastatin zinc (2:) salt having the composition described above, no film coating is required, especially in case of tablets filled into capsules. Omitting the film coating operation is advantageous since during film coating, the decomposition of the active ingredient may occur.

However, in those cases when the delimination of the release of the active ingredients in time is especially desirable from the individual solid phases, besides the different disintegration time of the two phase, one or both phases may be provided with an active ingredient release controlling coating. Such solutions may be required if it is not possible to achieve the difference in the disintegration time values of the chosen excipient systems for the two active ingredient necessary for preventing the pharmaceutical interaction.

A preferable embodiment of the present invention is a capsule containing small tablets having different disintegration time each individually containing the above-mentioned ezetimibe and rosuvastatin zinc (2:1) salt pharmaceutical compositions. Such a formulation could be prepared by using the method disclosed in International Patent Application No. 2011/012912

for the preparation of granules containing ezetimibe microparticles and sodium lauryl sulfate, which are, after optional admixing of further excipients known from the state of the art, such a a binder or disintegrant, transformed into small tablets and from the the above-mentioned rosuvastatin-containing composition containing rosuvastatin zinc (2:1) salt, microcrystalline cellulose, colloidal silica and a lubricant, preferable magnesium stearate optionally after addition of further excipients. Both compositions are transformed into small sized tablets individually and one ezetimibe as well as onerosuvastatin zinc (2:1) salt containing tablet is filled into a capsule. As a capsule, a suitably sized hard gelatine capsule known from the state of the art is used.

In principle, there is no limitation regarding the strength of the formulation or the concentration of the active ingredients in each of the phases. Considering that the composition according to the present invention is used in the medicine according to the indications of monocomponent rosuvastatin and monocomponent ezetimibe formulations, it is convenient to choose the dose of the individual active ingredients present in a dosage unit accordingly. Thus, it is advantageous if the rosuvastatin tablet residing in the composition contains, for example an amount of a pharmaceutically acceptable salt of rosuvastatin corresponding to 10, 20 or 40 mg rosuvastatin. It is furthermore advantageous that the small sized tablet present in the composition contains 10 mg of ezetimibe.

The dissolution of ezetimibe and rosuvastatin is almost quantitative from the immediate release capsule according to the present invention containing ezetimibe and rosuvastatin zinc (2:1) salt, thus the composition fully complies with the regulatory requirement prescribing the dissolution of at least 80% amount of the active ingredient during 30 minutes testing. Furthermore, the stability of the formulation satisfies the requirements of the pharmaceutical industry.

The pharmaceutical composition according to Example 1 of the present application containing 10 mg of ezetimibe and rosuvastatin zinc salt corresponding to 40 mg of rosuvastatin has been compared to the commercially available EZETROL ® tablets (containing 10 mg of ezetimibe) and CRESTOR ® 40 mg tablets (containing rosuvastatin calcium salt corresponding to 40 mg of rosuvastatin) known from the state of the art in a single dose, crossover, two-period pharmacokinetic study in 56 healthy white male volunteers. The reference products were

administered simultaneously. It has been concluded that after the administration of the pharmaceutical composition according to Example 1 of the present application, for the active ingredient rosuvastatin, the C_{max} value was 22.971 ng/ml, (CV 78.3%), the AUC_{0-T} value was 215.857 ng.h/ml (CV 62.9%) and the T_{max} value was 4.50 hours. In case of unconjugated ezetimibe, the C_{max} value was 3326.2 pg/ml (CV 53.7%), the AUC_{0-72} value was 74761.2 pg.h/ml (CV 53.3 %) and the T_{max} value was 6.00 hours. In the case of the pharmaceutical composition according to the present invention and the products EZETROL® 10 mg and CRESTOR® 40 mg administered simultaneously, the 90% confidence interval of the ratio of the measured and logarithmically transformed C_{max} and AUC_{0-T} or AUC_{0-72} values fell within the required (80-125%) bioequivalence range when the reference products were administered simultaneously, thus the bioequivalence has been proven.

The pharmacokinetics of the pharmaceutical composition prepared according to the method of Example 1 with the only difference that the composition contained the amount of rosuvastatin zinc salt corresponding to 20 mg of rosuvastatin but otherwise identical to the composition of Example 1 according to the present invention, has been tested similarly to the above study in 66 healthy white male subjects. During the reference treatment, volunteers were administered one EZETROL® 10 mg and one CRESTOR® 20 mg (containing an equivalent amount of rosuvastatin calcium salt to 20 mg rosuvastatin) simultaneously. During the treatment of the composition according to the present invention, the pharmacokinetic parameters for rosuvastatin were as follows: C_{max} value was 10.951 ng/ml (CV 48.5%), AUC_{0-T} value was 111.521 ng.h/ml (CV 46.5%), the T_{max} value was 4.50 hours. In case of unconjugate ezetimibe, the C_{max} value was 3646.5 pg/ml (CV 53.1%), the AUC_{0-72} value was 85863.5 pg.h/ml (CV 42.0%) and the T_{max} value was 5.50 hours. In the case of the pharmaceutical composition according to the present invention and the products EZETROL® 10 mg and CRESTOR® 40 mg known from the state of the art, in case of simultaneous administration of the reference products, the 90% confidence interval of the ratio of the measured and logarithmically transformed C_{max} and AUC_{0-T} or AUC_{0-72} values fell within the required (80-125%) bioequivalence range, thus the bioequivalence has been proven.

According to a further aspect of the present invention, there is provided a method for decreasing or eliminating interaction between an active ingredient and excipient or between active ingredients in immediate release combined pharmaceutical compositions, which comprises formulating the active ingredients in individual physical phases which are

separated spatially from each other or which are contacting each other at a small surface area and adjusting the release of the active ingredients from the individual phases, preferably from physical phases produced by compression in such a way, for example by adjusting the disintegration time of tablets such that the release of the active ingredients from the two phases takes place separatedly in time or begins delayed or shifted from one phase compared to the second phase.

The method according to the present invention can be used for immediate release combined pharmaceutical composition wherein the active ingredient combination is different from the combination of rosuvastatin and ezetimibe and irrespectibly whether an interaction is present between the active ingredients or between an excipient and an active ingredient. In this way, fixed-dose pharmaceutical compositions containing at least two different active ingredients could be obtained, wherein the individual active ingredients reside either in spatially separated physical phases or in physical phases contacting each other at a small surface area and wherein the disintegration time of the phases containing the individual active ingredients is different or alternatively the active ingredients are released from the phases in a manner separated in time. In the formulations according to the present invention, the characteristic distance of the spatially separated or separating phases ranges from the contacting (<1mm) up to 35 mm and the difference of the disintegration times measured in the individual physical phases or the difference of the active ingredient release is between 5 and 1800 seconds, preferably 10 to 300 seconds, more preferably 20 to 240 seconds, the most preferably 60 to 222 seconds.

The invention is demonstrated by the following examples without limiting the invention in any way to the examples.

Examples:

Comparative example 1

Ezetimibe tablets containing 10 mg of ezetimibe

Composition (one tablet):

ezetimibe	10 mg
sodium lauryl-sulfate	4.4 mg
microcrystalline cellulose (Vivapur 102)	30.3 mg
D-mannitol (Pearlitol 160 C)	30.3 mg
Croscarmellose sodium (Ac-Di-Sol DS 711)	19 mg
Low-substituted hydroxypropyl cellulose (L-HPC B1)	10 mg
polyvinyl-pyrrollidone (Povidone K-25)	5 mg
magnesium stearate	1 mg
Weight of a tablet	110 mg

Method:

Polyvinylpyrrollidone and sodium lauryl sulfate are dissolved in purified water at room temperature in a way that the concentration of polyvinyl pyrrollidone in water is 6.5-7.0 weight%. Ezetimibe is dissolved at a temperature of 45-50 °C in double-weight 96 % ethanol. A suspension is prepared by mixing the two solutions in a FrymaKoruma kolloidal mill.
Components of the internal phase, which are two-third of the weight of microcrystalline cellulose, mannitol, low substituted hydroxypropyl cellulose and croscarmellose sodium, respectively, are homogenized in a fluid granulating apparatus. The homogenate is granulated by spraying the previously prepared ezetimibe suspension thereon and subsequently dried until the prescribed loss of drying.
Granules having suitable loss of drying are sieved with the aim of regranulation. Granules are first mixed with the remaining part of croscarmellose sodium and subsequently with magnesium stearate, homogenized and the homogenate is compressed into tablets.

From the thus prepared tablets, about 95-98% of ezetimibe is dissolved within 15 minutes. The weight of the tablets is 110 mg, the disintegration time thereof is 240 to 300 seconds.

Comparative Example 2

Rosuvastatin zinc (2:1) film coated tablets (40 mg strength)

Composition:

rosuvastatin zinc (2:1) salt	42.72 mg
Lactose monohydrate	484.8 mg
Povidone K30	18.2 mg
Crospovidone	48.2 mg
Magnesium stearate	6 mg

Coating:

Polyvinyl-alcohol	6 mg
titanium dioxide	3.8 mg
PEG3350	3 mg
Talc	2.2 mg

Rosuvastatin zinc is weighed and mixed with a part of lactose, povidone and crospovidon and sieved using a vibrating sieve. After sieving, the mixture together with the remaining part of crospovidone, povidone and lactose monohydrate are homogenized in a drum homogenizer for 10 minutes. Magnesium stearate is sieved using a 0.5 mm mesh manual sieve, mixed with part of the homogenized mixture containing the active ingredient and homogenized with the remaining part of the mixture containing the active ingredient in a drum homogenizer for 2 minutes. The final mixture is compressed into tablets. Tablets are film-coated according to methods known in the art by using a dispersion of the ingredients of the coating in purified water in approximately 20% excess at a temperature of 55-60 °C using an air volumetric flow rate of 10 m^3/min and the coated tablets are dried.

The weight of the tablets obtained in this way is approximately 615 mg, disintegration time thereof is between 157 and 716 seconds.

Comparative Example 3

Ezetimibe (10 mg/tablet) and rosuvastatin calcium salt (10 mg/tablet) containing monolayer tablet

Composition:

rosuvastatin calcium salt	10.42 mg
crospovidone (Polyplasdone XL-10)	7.5 mg
Ludipress (Lactose monohydrate, povidone, crospovidone)	130.58 mg
Magnesium stearate	1.5 mg
ezetimibe	10.0 mg
polyvinyl-pyrrolidone (PVP K-25)	5.0 mg
Croscarmellose sodium (AcDiSol)	19.0 mg
microcrystalline cellulose (Vivapur 102)	30.3. mg
mannitol (Pearlitol 160 C)	30.3 mg
sodium lauryl sulfate	4.4 mg
Low substituted hydroxypropyl cellulose (L-HPC B1)	10.0 mg
magnesium stearate	1.00 mg

Coat:

Opadry white 85F18422	6.40 mg

Method:

Rosuvastatin calcium salt homogenate:

The weighed amount of rosuvastatin salt is mixed with part of Ludipress and sieved using a 0.8 mm mesh manual sieve. The sieved active ingredient mixture, the remaining part of Ludipress and the AcDiSol are homogenized in a 25-l or 30-l Pharmatech MB 30 drum mixer at 17 rpm for 10 minutes. The sieved magnesium stearate is added to the homogenized powder mixture and a final homogenization is carried out in a Pharmatech MB 30 drum mixer at 17 rpm for 2 minutes.

Ezetimibe granules:

The ezetimibe-containing granules are prepared according to Example 2 of International Patent Application No. 2011/012912 with the modification that instead of hydroxypropyl

methyl cellulose, hydroxypropyl cellulose (L-HPC B1) is used and AcDiSol is omitted from the external phase.

Preparation of monolayer tablets:

The weighed rosuvastatin homogenate, the ezetimibe granules and the AcDiSol are homogenized for 10 minutes. The weighed magnesium stearate is sieved using a 0.5 mm mesh manual sieve, added to the mixture obtained in previously, homogenized for 2 minutes and tabletted.

The dissolution of ezetimibe from the tablets is lower than 25% in 30 minutes.

Comparative Example 4

Bilayer tablets containing 10 mg of ezetimibe and 10 mg rosuvastatin (as rosuvastatin calcium salt)

Rosuvastatin-containing layer:	
rosuvastatin calcium salt	10.42 mg
crospovidone (Polyplasdone XL-10)	7.5 mg
Ludipress (Lactose monohydrate, povidone, crospovidone)	130.58 mg
Magnesium stearate	1.5 mg
Ezetimibe-containing layer:	
ezetimibe	10.0 mg
polyvinyl-pyrrolidone (PVP K-25)	5.0 mg
croscarmellose sodium (AcDiSol)	19.0 mg
microcrystalline cellulose (Vivapur 102)	30.3. mg
mannitol (Pearlitol 160 C)	30.3 mg
sodium lauryl sulfate	4.4 mg
Low substituted hydroxypropyl cellulose (L-HPC B1)	10.0 mg
magnesium stearate	1.00 mg

Coat:

Opadry White 85F18422	6.40 mg

Rosuvastatin calcium salt homogenate:

The weighed amount of rosuvastatin salt (d90=89 μm) is mixed with a part of Ludipress and sieved using a manual sieve having 0.8 mm mesh size. The sieved mixture containing the active ingredient, the remaining part of Ludipress and the AcDiSol are homogenized for 10 minutes in a 25-l or 30-l Pharmatech MB 30 drum mixer at 17rpm. The sieved magnesium stearate is added to the homogenized powder mixture and a final homogenization is carried out in a Pharmatech MB 30 drum mixer at 17 rpm for 2 minutes.

Ezetimibe granules:

The ezetimibe-containing granules are prepared according to Example 2 of International Patent Application No. 2011/012912 with the modification that instead of hydroxypropyl-methyl cellulose, low substituted hydroxypropyl cellulose (L-HPC B1) is used and AcDiSol is omitted from the external phase.

Preparation of bilayer tablets:

The rosuvastatin homogenate and ezetimibe granules are filled into the two hoppers of the tabletting machine separately and pressed into bilayer tablets.

The dissolution of ezetimibe from the tablets produced according to the method described above is lower than 45% in 30 minutes.

Example 1

Capsules containing rosuvastatin zinc (2:1) salt (40 mg) tablet and ezetimibe (10 mg) tablet

Composition:

Rosuvastatin zinc (2:1) salt containing tablet:

rosuvastatin zinc (2:1) salt	42.72 mg
Prosolv HD90 (microcrystalline cellulose, colloidal silica)	253.33 mg
colloidal silica (Aerosil 200)	0.45 mg
magnesium stearate	3.5 mg
Tablet weight:	300 mg

ezetimibe-containing tablet:

ezetimibe	10 mg
Povidone PVP K-25	5.0 mg
croscarmellose sodium (AcDiSol)	19.00 mg
microcrystalline cellulose (Vivapur 102)	30.3 mg
mannitol (Pearlitol 160 C)	30.3 mg
sodium lauryl sulfate	4.4 mg
Low substituted hydroxypropyl cellulose (L-HPC B1)	10.00 mg
magnesium stearate	1.00 mg
Tablet weight:	110 mg

Preparation of rosuvastatin zinc (2:1) salt containing tablets

The Prosolv HD 90 is weighed into an acid-proof drum. Aerosil 200 and magnesium stearate are weighed into an acid-proof container and mixed with an acid-resistant spoon.

The mixture is sieved using a manual sieve to the Prosolv HD 90 in the acid-proof drum and mixed.

The amount of rosuvastatin zinc (2:1) salt is corrected with its moisture content and weighed, transferred into the drum, mixed and after closing the drum, homogenized. Subsequently the pre-homogenate is mixed in an apparatus equipped with mesh inlay and sieved. Until further use, is is kept in the closed drum and granulated by compaction.

A magnesium stearate is sieved using a manual sieve and mixed with an approximately 0.5 kg amount of the pre-homogenate. The pre-homogenate thus obtained is transferred into the drum containing the remaining part of the same and a final homogenization is carried out. The final homogenate is pressed into tablets.

The average disintegration time of tablets obtained in this way is 22 seconds (minimum 6 seconds, maximum 83 seconds).

Ezetimibe-containing tablets

Ezetimibe is dissolved in 96 % ethanol at a temperature of 30-40 °C, povidone and sodium lauryl sulfate are dissolved in water. During intense mechanical stirring, the two solutions are mixed in 30-60 seconds with each other and if necessary, the precipitated suspension is filtered using a 0.4-0.6 mm mesh sieve. The suspension is continously stirred until further use. The Glatt GPCG 3.1 fluid granulating apparatus is charged with the microcrystalline cellulose, D-mannitol, the low-substituted hydroxypropyl cellulose and the croscarmellose sodium and using a suitable air flow at the temperature of 75 °C is preheated and homogenized for five minutes.

The aggregate-free suspension is sprayed onto the fluidized powder mixture in the fluid granulating apparatus while is is stirred continously with a laboratory stirrer.

Feed rate: 30-50 g/min, spray pressure: 2.5 bar.

The granules thus obtained are subsequently dried in sufficient flow of air having the temperature of 75-85 °C. The dry granules are regranulated using a perforated plate having 0.63 mm openings.

Granules are mixed in a drum mixer with AcDiSol (5 minutes homogenization) and finally the magnesium stearate (2 minutes homogenization).

The homogenate thus prepared is pressed into tablets having 110 mg weight using a 7-mm plain tool.

The average disintegration time of tablets thus obtained is 187 seconds (minimum: 143 seconds, maximum 228 seconds). Dissolution of ezetimibe from the composition is 95-98% in 30 minutes.

Tablets containing rosuvastatin zinc (2:1) salt and tablets containing ezetimibe are filled into capsules in a way that each capsula contains one rosuvastatin zinc containing tablet and one ezetimibe containing tablet.

During the testing of the dissolution of capsules obtained in this way according to the pharmacopoeial procedure, it has been found that while the dissolution of rosuvastatin commences instantly after the capsule is dissolved, the dissolution of ezetimibe is delayed by approximately 300 seconds. More than 90% amount of both active ingredients are dissolved in 1200 seconds.

We claim:

1. Fixed dose, immediate release pharmaceutical composition containing ezetimibe and rosuvastatin or pharmaceutically acceptable salt thereof, characterized by that the active ingredients each reside in physical phases which are spatially separated or contacting each other in small surface area and the release and dissolution of the active ingredient from the two phases takes place separatedly in time.
2. Pharmaceutical composition according to claim 1, characterized by that the phases being spatially separated or contacting each other in small surface area are produced by compression.
3. Composition according to claim 1 or claim 2, wherein the phases containing the active ingredients are tablets.
4. Composition according to any of claims 1 to 3, characterized by that the ezetimibe-containing phase comprises sodium lauryl sulfate.
5. Composition according to any of claims 1 to 4, which comprises two phases in form of tablets physically separated or contacting each other at a small surface area, filled into a capsule.
6. Pharmaceutical composition according to any of claims 2 to 5 wherein the disintegration time of the phases is different.
7. Pharmaceutical composition according to claim 6, characterized by that the difference in the disintegration time of the physical phases spatially separated or contacting each other at a small surface area is between 5 and 1800 seconds, preferably 10 to 300 seconds, the most preferably 20 to 240 seconds.
8. Pharmaceutical composition according to any of claims 1 to 6, characterized by that it contains as active ingredient rosuvastatin in free acid form or a pharmaceutically acceptable rosuvastatin salt, preferably rosuvastatin calcium salt or rosuvastatin zinc (2:1) salt.
9. Pharmaceutical composition according to any of claims 1 to 8, characterized by that it contains ezetimibe in form of microparticles.
10. Pharmaceutical composition according to any of claims 1 to 8, characterized by that the characteristic distance of the spatially separated physical phases is 1 to 35 mm.

11. Tablet containing rosuvastatin zinc (2:1) salt as active ingredient having decreased disintegration time, which comprises 5 to 40 weight% rosuvastatin zinc (2:1) salt, 60-95 weight% microcrystalline cellulose, 0.05 to 2.0 weight% colloidal silica and 0.1 to 2.0 weight% lubricant.
12. Tablet according to claim 11, which comprise 14 weight% rosuvastatin zinc (2:1) salt, 85 weight% microcrystalline cellulose, 0.15 weight% colloidal silica and 1.2 weight% magnesium stearate lubricant.
13. A tablet according to claim 11 or claim 12, characterized by that the disintegration time is between 6 and 83 seconds.
14. Pharmaceutical composition containing ezetimibe and rosuvastatin zinc (2:1) salt which comprises in capsulated form a small tablet containing ezetimibe and a small tablet containing a pharmaceutically acceptable salt of rosuvastatin in an arrangement wherein the tablets contact each other at a small surface area, wherein the difference in the disintegration time of the ezetimibe containing tablet and the tablet containing rosuvastatin or a salt thereof is between 60 and 222 seconds, wherein the small tablet containing ezetimibe contains ezetimibe microparticles and sodium lauryl sulfate and wherein the small tablet containing rosuvastatin exhibits decreased disintegration time and said tablets consists of 5 to 40 weight% rosuvastatin zinc (2:1) salt, 60 to 95 weight% microcrystalline cellulose, 0.05 to 2.0 weight% colloidal silica and 0.1 to 2.0 weight% lubricant.
15. Method for decreasing or eliminating interaction between an active ingredient and an excipient or between active ingredients in combination pharmaceutical composition, which comprises formulating the active ingredients in individual physical phases which are separated spatially or contacting each other at a small surface area and adjusting the disintegration time of such phases, preferably tablets in a way that the release of the active ingredient takes place separatedly in time from the two phases or begins delayed from the first phase compared to the other.