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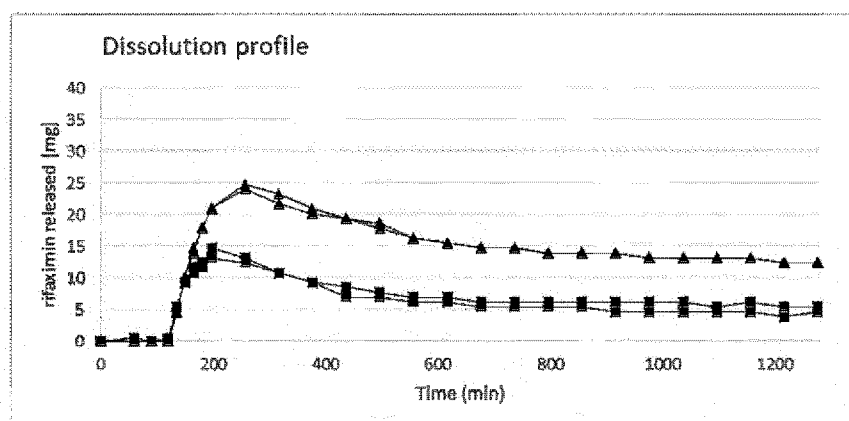
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(54) Title: RIFAXIMIN-CONTAINING GRANULES

Figure 3



Triangle: present Example 1

Square Reference Example 1

(57) Abstract: The present invention relates to a method for preparing rifaximin-containing granules, the granules obtained by the present method and a dosage form comprising the rifaximin-containing granules.

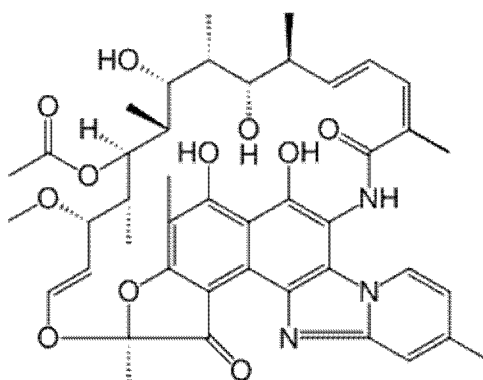


Rifaximin-containing granules

The present invention relates to a method for preparing rifaximin-containing granules, the granules obtained by the present method and a dosage form comprising the rifaximin-containing granules.

Background of the invention

The IUPAC name of rifaximin is (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7-(epoxypentadeca[1,11,13]tri-enimino) benzofuro[4,5-*e*]pyrido[1,2-*a*]-benzimidazole-1,15(2*H*)-dione,25-acetate and the compound is represented by the following Formula (I)



Formula (I)

Rifaximin can be used in the treatment of bacterial infections of the gastrointestinal tract, for example in the treatment of traveler's diarrhea. Further, the active pharmaceutical agent can be used in the treatment or prevention of hepatic encephalopathy and in addition, the active pharmaceutical agent is said to be efficacious in relieving chronic functional symptoms of bloating and flatulence that are common in irritable bowel syndrome (IBS) and Crohn's disease. Crohn's disease, which is also referred to as Morbus Crohn, is a type of inflammatory disease that may affect the whole gastrointestinal tract. In particular, Morbus Crohn (Crohn's disease) is regarded as belonging to the group of inflammatory

bowel diseases, wherein these diseases are reported to be inter alia caused by bacterial infections.

Rifaximin is reported to show its efficiency almost exclusively locally, i.e. rifaximin exerts its effects at the site of application, i.e. in the gastrointestinal tract.

Several polymorphic forms of rifaximin are described, wherein these polymorphic forms can convert into each other. Viscomi G. C. et al., "Crystal forms of rifaximin and their effect on pharmaceutical properties", Royal Society of Chemistry, CrystEngComm, 10 (2008), pages 1074-1081, describe in Figure 4 the relationship of the various polymorphic forms of rifaximin. As can be seen from Table 7, the bioavailabilities of the various forms differ from each other (in dogs).

Form	C _{max} [ng/ml]	AUC [ng/ml x h]
Alpha	2.6	17
Beta	1.1	12
Gamma	1,085.1	4,894
Delta	308.3	830
Epsilon	6.9	77

Taking into account the above-mentioned local effectiveness of rifaximin, US 8,568,782 B2 describes a method for the preparation of rifaximin-containing gastro-resistant microgranules, wherein rifaximin and Aerosil are fluidized bed coated with an aqueous suspension inter alia containing methacrylic acid ethylacrylate copolymer (also known as KOLLICOAT[®] MAE 100P) as enteric material. Said granules are reported not to be dissolved in the stomach and, thus, the release of the active pharmaceutical agent is said to be only in the intestinal tract.

However, the method for the preparation of the above-described rifaximin-containing gastro-resistant microgranules seems to be improvable with regard to its processability, in particular the fluidizability of the starting materials and the homogeneity/uniformity of the obtained gastro-resistant microgranules.

Further, the microgranules should be improved with regard to their dissolution properties, for example the release of the active pharmaceutical ingredient, within the intestinal tract.

5 WO 2014/091432 A1, EP 2 011 486 A1 and WO 2018/175414 A1, AU 2016 203 925 B2 and WO 2015/173697 A1 are related to blends, pharmaceutical compositions comprising rifaximin, respectively, and the use thereof. Further, also processes for the preparation of said blends, pharmaceutical compositions and dosage forms are described.

10

Thus, there is still a need for an effective method for the preparation of gastro-resistant rifaximin-containing granules having an advantageous homogenous dispensation of the enteric material around the active pharmaceutical ingredient and a well-conditioned release in the intestinal tract. Hence, it was an object of the present invention to overcome the drawbacks of the above-mentioned prior art.

15

In particular, it was an object of the present invention to provide a method for the preparation of gastro-resistant rifaximin, wherein the method enables granules having good homogeneity and a well-conditioned release, and which can be used to produce a rifaximin-containing dosage form.

20

The inventors have now unexpectedly found that these objectives can be achieved by granulating a composition comprising rifaximin and glidant and subsequently fluidized bed coating the resulting granules with a coating solution containing an enteric coating material.

25

The subject of the invention is thus a method for preparing rifaximin-containing granules for modified release, wherein the method comprises the step of:

- 30
- (i) granulating a composition comprising rifaximin and glidant; and
 - (ii) fluidized bed coating the granules from step (i) with a coating solution containing an enteric coating material.

The subject of the invention is also rifaximin-containing granules for modified release obtainable by the present method.

5 A further subject of the invention is a dosage form containing rifaximin-containing granules for modified release according to the present invention and one or more pharmaceutical excipient(s).

In addition, the subject of this invention is a method for the preparation of a rifaximin-containing tablet, wherein the method comprises the steps of:

10

- (i) granulating a composition comprising rifaximin and glidant
- (ii) fluidized bed coating the granulates from step (i) with a coating solution containing an enteric coating material
- (iii) mixing the granules from (ii) with further pharmaceutically acceptable excipient(s),
- 15 (iv) compressing the mixture of step (iii) to a tablet, and
- (v) film coating the tablet from step (iv), wherein the coating is substantially free of enteric material.

20 The method of the invention for preparing rifaximin-containing granules for modified release is explained in detail in the following paragraphs.

As used herein, the term “about” means within a statistically meaningful range of a value. Such a range can be within an order of magnitude, typically within 10%,
25 more typically within 5%, even more typically within 1% and most typically within 0.1% of the indicated value or range. Sometimes, such a range can lie within the experimental error typical of standard methods used for the measurement and/or determination of a given value or range.

30 Generally, the term “modified release” can be understood as being a dosage form not showing immediate release (i.e. a release of at least 70% of the active ingredient within one hour). The rifaximin-containing granules for modified

release preferably show a delayed release, i.e. the rifaximin is not released immediately following administration but at a later time when in contact with higher pH (e.g. once entering the stomach). In a preferred embodiment the amount of rifaximin released from the rifaximin-containing granules is less than 5 mg, preferably less than 3 mg and in particular less than 2 mg within 120 minutes. Further, it is preferred that the amount of rifaximin released from the rifaximin-containing granules is more than 20 mg, preferably more than 25 mg, in particular more than 30 mg within 180 minutes.

10 The amount of the released rifaximin from granules containing 400mg of rifaximin is determined according to USP, item 711 Dissolution (Apparatus 2, Method A, 37.5°C ±0.5°C, 100 rpm; 120 minutes in 750ml of 0.1 N HCl and after 2 hours a phosphate buffer solution is added to bring up the solution to 1000ml with a pH to 6.8.

15

In step (i) of the process of the invention, a composition comprising rifaximin and glidant is granulated, i.e. at the end of the granulation step granules comprising rifaximin and glidant are obtained.

20 In a preferred embodiment the rifaximin comprised by the composition of step (i) is rifaximin independently of its polymorphic form, i.e. rifaximin of any of its polymorphic forms and or mixtures thereof. Examples are rifaximin in polymorphic form α , rifaximin in polymorphic form β , rifaximin in polymorphic form γ , rifaximin in polymorphic form δ , rifaximin in polymorphic form ε and/or mixtures thereof. Preferred are rifaximin in polymorphic form α , rifaximin in polymorphic form β , rifaximin in polymorphic form γ and/or mixtures thereof. In a preferred embodiment polymorphic form β is used in step (i).

25 In a preferred embodiment the amount of rifaximin comprised by the composition of step (i) is from 40 to 99.8 wt.%, more preferably from 75 to 99.7 wt.%, in particular about 99.5 wt.% of the total weight of the composition (i).

Glidants are substances that can be used to improve the flowability of a composition containing more substances. Examples of glidants are magnesium stearate, starch, talc, silica and/or mixtures thereof. Silica comprises fumed silica (also known as pyrogenic silica). In a preferred embodiment the glidant is a highly dispersed, hydrophilic fumed silica, preferably having a specific surface area between 50 and 400 m²/g, more preferably between 150 to 250 m²/g measured by gas adsorption according to Ph. Eur., 6.0, Chapter 2.9.26.

In a preferred embodiment the amount of glidant comprised by the composition of step (i) is from 0.02 to 2.5 wt.% more preferably from 0.03 to 1.0 wt.%, in particular about 0.5 wt.% of the total weight of the composition of step (i).

The composition of step (i) can preferably comprise one or more further pharmaceutically acceptable excipient(s).

Generally, suitable pharmaceutical excipients are for example disclosed in “Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete”, published by H.P. Fielder, 4th Edition, and “Handbook of Pharmaceutical Excipients”, 3rd Edition, published by A.H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

In a preferred embodiment the composition of step (i) further comprises a filler.

Fillers can be used to increase the volume and weight of a low-dose drug to a limit at which a pharmaceutical dosage form can be formed. Fillers may fulfil several requirements, such as being chemically inert, non-hygroscopic and biocompatible. Examples of fillers are microcrystalline cellulose, silicified microcrystalline cellulose, dextrose, lactose, sucrose, glucose, mannitol, calcium carbonate, magnesium aluminum silicate and others. Preferably, microcrystalline cellulose (MCC) is used as filler. In particular, the filler is microcrystalline cellulose (MCC).

In case that a filler is comprised by the composition of step (i), the amount of filler comprised by the composition of step (i) is from 6 to 29.5 wt.%, more preferably from 10 to 25 wt.% of the total weight of the composition of step (i).

5 In a preferred embodiment the composition of step (i) can be obtained by mixing and sieving the components comprised by the composition of step (i). In one embodiment, the components can be mixed in a high shear or low shear powder blender, such as a Turbula powder blender, for 2 to 15 minutes. The resulting mixture can preferably be sieved. Sieving can for example be conducted with a 500
10 to 1500 μm , preferably about 1000 μm sieve. Alternatively, the sieving and the mixing step can be carried out in a different order, i.e. one or more of the components can be sieved first and subsequently the components are mixed to obtain the composition of step (i).

15 “Granulating” is generally understood to mean the formation of relatively coarse or granular aggregate material as a powder (granules) by assembling and/or aggregating finer powder particles (agglomerate formation or build-up granulation) and/or the formation of finer granules by breaking up coarser aggregates (disintegration or break-down granulation).

20

In a preferred embodiment the granulating in step (i) is conducted as a dry granulation process comprising compacting the composition from step (i) to a slug and granulating the slug. “Dry” is usually understood to mean that the step is carried out in the absence of a liquid, in particular in the absence of organic
25 solvents and/or water.

In a preferred embodiment in step (i) of the present invention, the composition comprising rifaximin and glidant (and optionally further one or more pharmaceutical excipient(s)) is dry compacted into a slug. This can be performed
30 for example by “slugging”, i.e. by using a large heavy-duty rotary press. Instead of the term “slug”, the expression “compacted material” can be used in the context of

this invention. Subsequently, breaking up the obtained slugs into granulates can be carried out for example with a hammer mill

In step (i) the dry compacting in step (i) of the composition of step (i) is preferably carried out in a roll granulator. Suitable roll granulators are for example BT/WP 200 (Alexanderwerk), BRC25/100 (Bohle), TFC Lab/420 (Freund-Vector), Minipactor, Ultrapactor (Gerteis), preferably a TFC Lab/420 (Freund-Vector).

The roll pressure is preferably from 1×10^5 Pa (1 bar) to 1×10^7 Pa (100 bar), more preferably from 2×10^6 Pa (20 bar) to 7×10^6 Pa (70 bar), in particular about 5×10^6 Pa (50 bar).

The roll control is preferably from 0.1 r/min to 5.0 r/min, more preferably from 0.8 r/min to 3.5 r/min, in particular from 1.5 r/min to 2.5 r/min.

The screw control is preferably from 1 r/min to 50 r/min, more preferably from 10 r/min to 35 r/min, in particular from 15 r/min to 25 r/min.

The compacting apparatus used preferably has a cooling means. In particular, the process is conducted and, where applicable, cooled, such that the temperature of the compacted material does not exceed 55°C.

Further in step (i) of the present method the slug is granulated. The granulating can be performed using processes known in the state of the art.

In a preferred embodiment, the granulation is performed by means of a granulator screen, which may be integrated in the compactor or separate or in a different screen mill. In this case, the mesh width of the screen insert is usually 0.1 to 3.0 mm, preferably 0.5 to 2.0 mm, especially, more preferably 0.8 to 1.5 mm.

In a preferred embodiment of step (i) the compacting step and the granulating step can be repeated if needed, i.e. the granules obtained from a compacting step and

granulating step can be compacted and granulated once more. This procedure can be repeated as often as needed, for example 1 to 5 times, especially 2 to 3 times.

5 In the case of multiple compacting, it is also possible for only parts of the amounts of pharmaceutically acceptable excipients specified within the present application to be added in step (i), with the remaining parts added before the further compacting processes.

10 In a preferred embodiment, the granulation conditions are selected such that the resulting particles (granules) have a mean particle size of 40 to 3000 μm , more preferably 100 to 2000 μm , even more preferably 400 to 1500 μm . For example, the above mean particle size can be obtained via analytical sieving (Amplitude 20%, 15 minutes using an Analysette sieving machine (Type 3010, Fritsch GmbH, Idar-Oberstein, Germany). The median particle size can be obtained via linear
15 extrapolation.

In an alternatively preferred embodiment the granulating in step (i) is conducted as a wet granulation process. "Wet" is usually understood to mean that the step is carried out in the presence of a granulation liquid, in particular in the presence of
20 organic solvents and/or water.

As far as the composition of step (i) to be wet granulated is concerned, the same applies as described above with regard to the composition of step (i) for dry granulation.
25

The composition of step (i) is preferably wetted with a granulation liquid or suspended in a granulation liquid.

The composition of step (i) can preferably comprise one or more further
30 pharmaceutically acceptable excipient(s). Generally, suitable pharmaceutical excipients correspond to the ones as described above.

In a preferred embodiment the granulation liquid preferably comprises a binder.

Binders usually are regarded as substances for ensuring that granules or an oral dosage form, in particular a tablet, can be formed with the required mechanical strength.

The binder can be present in an amount of 0 to 25 wt.%, preferably 1 to 20 wt.%, more preferably 2 to 18 wt.% and still more preferably 4 to 15 wt.% of granules obtained in step (i).

Examples of polymers suitable as binder are polysaccharides such as gum arabic and alginic acid, hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose methyl cellulose, ethyl cellulose hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose (HPC); polyvinyl pyrrolidone, polyvinyl acetate (PVAC), polyvinyl alcohol (PVA), polymers of acrylic acid and their salts, polyacrylamide, poly(meth)acrylates, vinyl pyrrolidone/vinyl acetate copolymers, polyalkylene glycols, such as polypropylene glycol or preferably polyethylene glycol, co-block polymers of polyethylene glycol, especially co-block polymers of polyethylene glycol and polypropylene glycol, and mixtures of the polymers mentioned.

Preferably, the granulation liquid containing binder is a solution or a suspension, preferably a solution. Suitable liquids for preparing the granulation liquid are, for example, water, alcohols and mixtures thereof. A mixture of water and ethanol is preferred.

In a preferred embodiment the composition is wetted and granulated with granulation liquid. The granulates are then dried and optionally screened. A suitable granulating machine is, for example, Diosna® P1/6.

In step (ii) of the process of the invention, the granules from step (i) are subjected to a fluidized bed coating, preferably a fluidized bed spray coating, with a coating solution containing an enteric coating material.

5 Fluidized bed coating is understood as a method step in which the particles to be coated are moved around (kept in elevation) by a gas stream, normally an air stream, in the fluidized bed system, while being sprayed with a coating liquid. Further, said coating liquid is evaporated and the solid that was contained in the coating liquid, forms a coating layer on the particles.

10

Depending on the direction from which the particles are sprayed, the fluidized bed coating step can be carried out in any manner known to skilled person, such as a rotor spray, a tangential spray, a top spray and a bottom spray process. The bottom spray process (also known as Wurster process) is preferred.

15

Fluidized bed coating can generally be performed in common fluidized bed devices such as for example fluidized bed system e.g. Mini-Glatt, GPC 10-30 (Glatt), either top or bottom spray.

20 The coating solution causes primary particles to adhere when the coating solution and the granules obtained from step (i) collide. Sufficient coating solution is sprayed to produce coated granules of the required size. Then the addition of the coating solution is turned off but the fluidizing with the gas stream is continued to dry the coated granules.

25

The duration of the fluidized bed coating step can be from 1 hour to 24 hours, preferably from 2 hours to 5 hours, and in particular about 3 hours.

The inlet temperature, which corresponds to the temperature of the heated gas stream, is between 20°C and 100°C, preferably between 30°C and 80°C, more preferably between 40°C and 70°C in particular about 60°C.

30

The pressure with which the coating solution is sprayed through a nozzle into the container is from 0.1 bar to 2.0 bar, preferably 0.3 bar to 0.6 bar, in particular about 0.5 bar.

- 5 In step (ii) the coating solution contains an enteric coating material.

Suitable liquids for preparing the coating solution are, for example, water and alcohols such methanol, ethanol, propylene glycol and mixtures thereof. Water is preferred. Alternatively, a mixture of water and propylene glycol is preferred.

10

In a preferred embodiment the coating solution contains 60 wt.% to 95 wt.% suitable liquids, preferably 70 wt.% to 90 wt.% suitable liquids, in particular about 80 wt.% suitable liquids, based on the total weight of the coating solution.

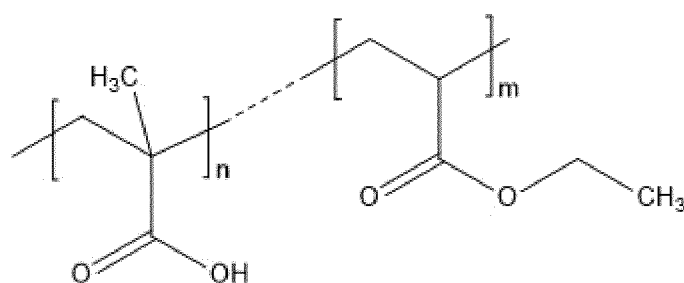
- 15 Generally, an enteric coating material can be regarded as a material which, when coated on or included in a granule or a composition comprising an active pharmaceutical ingredient, ensures the passage of the active pharmaceutical ingredient without substantial dissolution in the stomach such that the release is not before the gastrointestinal tract. In other words, an enteric containing can be
20 regarded as a material which forms a barrier to prevent the dissolution of the active pharmaceutical ingredient already under gastric conditions, i.e. the enteric coating can protect the active pharmaceutical ingredient from the acidity of the stomach.

- Enteric release materials are for example methylcellulose, ethylcellulose,
25 hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, cellulose acetate phthalate, cellulose acetate succinate, cellulose trimellitate, alkyl (meth)acrylate-(meth)acrylate copolymers, carnauba wax, xanthan, gum, gelatin, chitosan, carrageenan, alginates.

- 30 Preferably, an enteric coating material (also referred to an enteric release material) can be regarded as material which is substantially insoluble at a pH value of 5.5 or lower and/or which is substantially soluble at a pH value of 6.5 or higher.

In a preferred embodiment of the invention the enteric coating material is hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, cellulose acetate phthalate, cellulose acetate succinate, cellulose trimellitate, (meth)acrylate-alkyl(meth)acrylate copolymers, wherein alkyl is methyl or ethyl, or mixtures thereof, more preferably (meth)acrylate-alkyl(meth)acrylate copolymers.

A preferred (meth)acrylate-alkyl(meth)acrylate copolymer is methacrylic acid-ethylacrylate copolymer represented by Formula (II)



Formula (II),

wherein $m:n \approx 1:1$

The molecular weight of the above methacrylic acid-ethylacrylate copolymer represented by Formula (II) is from 20000 to 500000 g/mol, more preferred from 50000 to 400000 g/mol, more preferably 100000 to 300000 g/mol, in particular about 250000 g/mol.

In a preferred embodiment the coating solution contains 5 wt.% to 30 wt.% enteric coating material, preferably 10 wt.% to 20 wt.% enteric coating material, in particular about 15 wt.% enteric coating material, based on the total weight of the coating solution.

The coating solution preferably comprises further excipients which are known for example from "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", as described thereof.

In a preferred embodiment the coating solution further comprises coloring agents and glidant.

Suitable coloring agents according to the present invention include, but are not limited to, pigments, inorganic pigments, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel, ferric oxide red, ferric oxide yellow, titanium dioxide and mixtures thereof. Preferred is a mixture of titanium dioxide and ferric oxide red.

In a preferred embodiment the coating solution contains 0.1 wt.% to 3.0 wt.% coloring agents, preferably 0.5 wt.% to 2.0 wt.% coloring agents, in particular about 1 wt.% coloring agents, based on the total weight of the coating solution.

Glidants contained in the coating solution correspond to the ones as described above. Talcum is preferred.

In a preferred embodiment the coating solution contains 1.0 wt.% to 9.0 wt.% glidant, preferably 2.0 wt.% to 6.0 wt.% glidant, in particular about 4 wt.% glidant, based on the total weight of the coating solution.

A further subject of the present invention is rifaximin-containing granules for modified release obtainable by the present method. It turned out that the rifaximin-containing granules for modified release obtainable by the present method substantially do not show any dissolution under acidic conditions (0.1 N HCl, which substantially corresponds to the conditions in the stomach) for 2 hours. After two hours in conditions buffered at a pH value of 6.8 the rifaximin-containing granules show an excellent high dissolution.

A further subject of the present invention is a dosage form containing the granules obtainable by the present method and one or more pharmaceutical excipient(s).

In a preferred embodiment the dosage form contains rifaximin as sole active pharmaceutical ingredient. Alternatively preferably the dosage form contains rifaximin with another active pharmaceutical ingredient(s).

- 5 The present dosage form contains from 30 wt.% to 85 wt.% rifaximin, preferably from 40 wt.% to 80 wt.% rifaximin, in particular from 45 wt.% to 70 wt.%, especially about 50 wt.%.

- 10 The present dosage form contains rifaximin in an amount of 200 to 1000 mg. In a preferred embodiment the dosage contains 400 mg rifaximin. In an especially preferred embodiment the dosage form contains 800 mg rifaximin.

- 15 Again, as described above, suitable pharmaceutical excipients are for example disclosed in “Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete”, published by H.P. Fielder, 4th Edition, and “Handbook of Pharmaceutical Excipients”, 3rd Edition, published by A.H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

- 20 In a preferred embodiment the dosage form comprises one or more pharmaceutically acceptable excipient(s) selected from fillers, glidants, disintegrants and lubricants.

- 25 Fillers correspond to the ones as described above with regard to the composition in step (i) of the present method. In the present invention, the filler can be present in an amount of 0 wt.% to 40 wt%, preferably 5 wt.% to 30 wt.%, more preferably 10 wt.% to 20 wt.%, in particular about 15 wt.%, based on the total weight of the dosage form.

- 30 Glidants correspond to the ones as described above with regard to the composition in step (i) of the present method. The glidant can be present dosage form in an amount of 0 to 8.0 wt.%, preferably in an amount of 1.0 wt.% to 7 wt.%, in particular about 5.0 wt.% based on the total weight of the dosage form.

Disintegrants are compounds which enhance the ability of the dosage form, preferably the ability of the tablet, to break into smaller fragments when in contact with a liquid, preferably water.

- 5 Suitable disintegrants are for example crosslinked sodium carboxymethylcellulose (croscarmellose sodium), sodium carboxymethyl starch, cross-linked polyvinylpyrrolidone (crospovidone), sodium carboxymethylglycolate (= sodium starch glycolate) and sodium bicarbonate, preferably crosslinked sodium carboxymethylcellulose.

10

The disintegrant can be present in an amount of 0 to 20 wt.%, preferably in an amount of 3 wt.% to 15 wt.%, in particular about 9 wt. % based on the total weight of the dosage form.

- 15 Lubricants generally can be regarded as substances which are suitable to reduce friction, such as static friction, sliding friction and rolling friction. In particular, lubricants reduce the shearing forces occurring on the borderline between tablet and mould, especially the sliding friction found during tablet pressing between the punch moving up and down in the die and the die wall on the one hand and
20 between the edge of the tablet and the die wall on the other hand. Alternatively, lubricants can be esters, preferably diesters of glycerol with fatty acids, such as glycerol palmitostearate, or alkaline earth metal salts of fatty acids, such as magnesium stearate. Magnesium stearate is preferred. The lubricant can be present for example in an amount of 0 to 5 wt.%, preferably in an amount of 0.5 wt.% to
25 2.5 wt.%, in particular about 1 wt.%, based on the total weight of the dosage form.

- The skilled person will appreciate that depending on formulation context and concentration a particular excipient can fulfill various and sometimes even different functions. For example, microcrystalline cellulose is a particularly
30 hydrolyzed cellulose which can be used as a filler, binder and/or disintegrating material in tablet production, depending on formulation context and concentration. Reference is made to the literature on pharmaceutical excipients and

pharmaceutical formulation, such as Fiedler - Encyclopedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas, Wissenschaftliche Verlagsgesellschaft Stuttgart, 2013, Bauer, Frömming and Führer, "Lehrbuch der Pharmazeutischen Technologie", Wissenschaftliche Verlagsgesellschaft Stuttgart, 9. Auflage (2012) or, with a particular focus on tablet production, Augsburger and Stephen, Pharmaceutical Dosage Forms: Tablets, Third Edition, Volume 2, Informa Healthcare (2008). The skilled person will therefore appreciate that terms like "disintegrant", "binder", "lubricant", "filler", "plasticizer", "surfactant", "wetting agent", "film-forming agent", "coating material", "sweetener", "flavoring agent" and "coloring agent" are primarily functional definitions and that the structural characterizations provided above are given so as to allow an easier identification of suitable excipients.

Further, the dosage form preferably contains rifaximin in an amount of 30 to 70 wt. %, preferably 40 to 60 wt.%, in particular about 50 wt.%, based on the total weight of the dosage form.

Further, the dosage form preferably contains enteric coating material in an amount of 10 to 30 wt. %, preferably 15 to 25 wt.%, in particular about 18 wt.%, based on the total weight of the dosage form.

The dosage form can be present in any kind of dosage form known to the one skilled in the art. It is preferred that the dosage form is present in form of a capsule or a tablet, in particular a tablet.

Further, the dosage form, preferably the tablet, of the invention preferably has a content uniformity, i.e. a content of active agent(s) which lies within a concentration of 90 to 110%, preferably 95 to 105%, especially preferred from 98 to 102% of the average content of the active agent(s). The "content uniformity" is determined with a test in accordance with Ph. Eur., 6.0, Chapter 2.9.6. According to that test, the content of the active agent of each individual tablet out of 20 tablets must lie between 90 and 110%, preferably between 95 and 105%, especially

between 98 and 102% of the average content of the active agent(s). Therefore, the content of the active agent in each tablet of the invention differs from the average content of the active agent by at most 10%, preferably at most 5% and especially at most 2%.

5

In addition, the resulting tablet preferably has a friability of less than 5%, particularly preferably less than 2%, especially less than 1%. The friability is determined in accordance with Ph. Eur., 6.0, Chapter 2.9.7. The friability of tablets generally refers to tablets without coating.

10

A further subject of the present invention is a method for the preparation of rifaximin-containing tablet, wherein the method comprises the steps of:

- (i) granulating a composition comprising rifaximin and glidant
- (ii) fluidized bed coating the granulates from step (i) with a coating solution containing an enteric coating material
- 15 (iii) mixing the granules from (ii) with further pharmaceutically acceptable excipient(s),
- (iv) compressing the mixture of step (iii) to a tablet, and
- (v) film coating the tablet from step (iv), wherein the coating is
- 20 substantially free of enteric material.

The above statements regarding steps (i) and (ii) apply not only to the preparation of the granules of the invention, but also to the preparation of the tablet of the invention.

25

In step (iii) of the process of the invention, the granules from step (ii) are mixed with further pharmaceutically acceptable excipient(s). These are preferably the pharmaceutically acceptable excipients described in more detail above. The mixing can be performed in conventional mixers, e.g. in a free-fall mixer. The mixing
30 may, for example, be performed in compulsory mixers or free-fall mixers, e.g. using a Turbula T 10B (Bachofen AG, Switzerland).

Mixing (also referred to as blending) can be carried out e.g. for 1 minute to 30 minutes, preferably for 2 minutes to less than 10 minutes

Alternatively, it is possible that in step (i) the composition comprises rifaximin, glidant and just a part of one or more further pharmaceutically acceptable excipient, preferably filler, and that the remaining part of the corresponding excipient(s) is mixed in step (iii) with the granules from step (ii) after the granulation step (c). In the case of multiple compacting, the excipients should preferably be mixed in before the first compacting step, between multiple compacting steps or after the last granulation step.

In step (iv) the mixture of step (iii) and optionally further pharmaceutical excipients, can be compressed to a tablet. As far as the further pharmaceutical excipients in step (iv) are concerned, the same as described above with regard to the pharmaceutical excipient(s) applies. Preferably, the mixture of step (iii) and a lubricant, in particular magnesium stearate, can be compressed to a tablet. The compression may be performed with tableting machines known in the state of the art. Examples of suitable tableting machines are eccentric presses or rotary presses. As an example, a Fette® 102i (Fette GmbH, Germany) can be used. Compressing the mixture of step (iii) into a tablet can preferably be carried out by compressing said formulation on a rotary press. In the case of rotary presses, a main compressive force from 1 to 50 kN, preferably from 2 to 45 kN, more preferably from 2.5 to 40 kN, in particular from 3 to 40 kN is usually applied. With eccentric presses, compressive forces of up to 100 kN are also possible, however.

In addition, the resulting tablets preferably have a breaking strength of 160 to 400 N, particularly preferably 200 to 350 N especially 220 to 270 N. The breaking strength is determined in accordance with Ph. Eur. 6th main edition 2008, section 2.9.8.

The above details regarding breaking strength, friability, and content uniformity preferably relate here to the non-film-coated tablet.

In step (v) of the method of the invention, the tablets from step (iv) are film-coated, wherein the coating is substantially free of enteric substances. As far as enteric substances are concerned, it is referred to the above description with regard to the fluidized bed coating of the compacted material.

5

Methods of film-coating tablets and the liquids for preparing the coating solution/suspension which are both standard in the state of the art may be employed.

- 10 It is preferred that a coating not affecting the release of the active pharmaceutical ingredient is used for the present invention. Preferably a film coating containing polyvinyl alcohol and polyethylene glycol having a molar weight of 3000 to 4000 g/mol, preferably about 3400 g/mol can be used as polymeric substances. Further, the coating preferably comprises titanium oxide, talc and iron oxide red.

15

In particular, the coating comprises the following solid substances:

- 30 – 50 wt.%, preferably about 40 wt.% polyvinyl alcohol,
- 15 – 25 wt.%, preferably about 20 wt.% of polyethylene glycol having a molar weight of 3000 to 4000 g/mol,
- 20 - 20 – 30 wt.%, preferably about 23 wt.% titan oxide,
- 10 – 20 wt.%, preferably about 15 wt. % talc, and
- 1.0 – 5.0 wt.%, preferably about 2 wt.% iron oxide red.

The thickness of the coating is preferably 10 to 100 μm , more preferably 15 to 25 50 μm .

The process of the invention is in particular suitable for the preparation of tablets containing large amounts of rifaximin.

- 30 The invention will now be explained with reference to the following examples.

Preparation of the rifaximin-containing granule for modified release

Dry granulation:

Example 1:

Rifaximin (200 g) and silica (1 g) were weighted and blended in a low shear
5 blender at level 16 for five minutes. Subsequently the blend was sieved over a
hand-held screen with 1000 μm . Subsequently the sieved blend was compacted in
a dry granulator (TFC Lab Micro, Freund Vector) with a roll pressure of 5×10^6 Pa,
a roll control of about 1.8 r/min and a screw control of about 18.5 r/min to obtain a
slug. Said slug was subjected to a treatment by a Frewitt sieve (1000 μm sieve) to
10 obtain granules.

Example 2:

Silica (1 g) and microcrystalline cellulose (64 g) were weighted and blended and
added to rifaximin (200 g). The mixture was sieved over a hand-held screen with
15 1000 μm and blended in an overhead mixer at level 16 for ten minutes.
Subsequently the sieved blend was compacted in a dry granulator (TFC Lab Micro,
Freund Vector) with a roll pressure of 5×10^6 Pa, a roll control of about 1.9 r/min
and a screw control of about 18.8 r/min to obtain a slug. Said slug was subjected to
a treatment by a Frewitt sieve (1000 μm sieve) to obtain granules.
20

Example 3:

Silica (1 g) and microcrystalline cellulose (32 g) were weighted and blended and
added to rifaximin (200 g). The mixture was sieved over a hand-held screen with
1000 μm and blended in an overhead mixer at level 16 for ten minutes.
25 Subsequently the sieved blend was compacted in a dry granulator (TFC Lab Micro,
Freund Vector) with a roll pressure of 5×10^6 Pa, a roll control of about 1.8 r/min
and a screw control of about 20.1 r/min to obtain a slug. Said slug was subjected to
a treatment by a Frewitt sieve (1000 μm sieve) to obtain granules.

30 Example 4:

Silica (1 g), microcrystalline cellulose (34 g) and methacrylic acid-ethylacrylate
copolymer (14.8 g) were weighted and blended and added to rifaximin (200g). The
mixture was sieved over a hand-held screen with 1000 μm and blended in an

overhead mixer at level 16 for ten minutes. Subsequently the sieved blend was compacted in a dry granulator (TFC Lab Micro, Freund Vector) with a roll pressure of 5×10^6 Pa, a roll control of about 1.8 r/min and a screw control of about 20.1 r/min to obtain a slug. Said slug was subjected to a treatment by a Frewitt sieve (1000 μ m sieve) to obtain granules.

Fluidized bed coating:

Preparation of the pigment-containing suspension

- 10 Talcum (5.99 g), titan dioxide (1.35 g) and iron oxide (1.35 g) were weighted and mixed with demineralized water (15.8 g). The mixture was treated in a high speed homogenizer (Ultra Turrax) with a setting of 9600 for 23 minutes.

Preparation of enteric polymer-containing suspension

- 15 To demineralized water (100.91 g) methacrylic acid-ethylacrylate copolymer (22.48 g) was added within one minute under stirring with 400 rpm. Subsequently the suspension was stirred for seven minutes with 700 rpm and propylene glycol (3.35 g) was added. The resulting suspension was stirred for another five minutes while slowly accelerating the stirring to 1000rpm.

20

Preparation of the coating solution

- The pigment-containing suspension was added within two minutes to the of enteric polymer-containing suspension stirred at 1000 rpm. Further, the resulting suspension was stirred at 1000 rpm for another 159 minutes to obtain the coating solution.
- 25

The fluidized bed coating was carried out in a fluid bed dryer (Glatt, adapted for Wurster application) with the following devices:

- peristaltic pump with setting 05 (corresponding to 0.65 g/min)
- 30 - Flocon with an internal tube diameter of 1 mm and an external tube diameter of 5 mm
- product temperature sensor “SDC02-Tempi” with 2 sensors
- humidity sensor TESTO 435

The coating process was conducted as follows:

1. Filling in the product of Example 1, adjusting Wurster tube (20 mm overhang)
- 5 2. Flange-mounting gas and liquid support, mount product temperature sensor
3. Adjust pressure to 0.3 bar (30 kPa) on the side of the product
4. Heating bypass to 60°C
5. Starting filter cleaning with setting 2
6. Adjusting nozzle pressure to 0.5 bar (50 kPa)
- 10 7. Changing from bypass to operating mode
8. Filing tube with demineralized water and plunging it into the coating solution as prepared above
9. Start adding coating
10. Weighting coating solution to determine its consumption (see the following
- 15 Table 1)

Table 1:

Runtime [min]	Consumption [g]
135	91.6
165	107.5
175	112.7

11. Stopping addition of coating after 112.7 g coating solution have been consumed
- 20 12. Drying until the desired parameters are reached in the exhaust air stream
13. Stopping heating and starting cooling
14. Bringing nozzle pressure to 0, pressure on both sides 0
15. Stopping filter cleaning
16. Carefully opening and gathering the coated granules

25

The exact parameters for said procedure are shown in Table 2.

Table 2

Runtime [min]	Pump [rpm]	input temperature [°C]	Product temperature at bottom [°C]	product temperature on top [°C]	Pressure [bar]	Nozzle pressure [bar]	exhaust air temperature [°C]	exhaust air moisture [%]
0	-	60	-	-	-	0.50	-	-
1	5	60	34.0	37.5	0.26	0.50	30.4	7.7
3	5	60	38.4	41.5	0.26	0.50	32.9	7.7
13	5	60	46.3	48.8	0.30	0.50	39.3	6.1
36	5	60	48.9	51.1	0.30	0.50	43.6	5.6
57	5	60	49.6	51.7	0.32	0.50	44.6	5.3
69	5	60	50.3	52.0	0.31	0.50	44.7	5.4
84	5	60	50.7	52.1	0.32	0.50	44.7	5.2
115	5	60	50.1	52.0	0.32	0.50	44.9	5.2
178	0	60	50.4	52.0	0.32	0.50	44.8	5.1
183	0	60 declining to 27	52.4	52.8	0.32	0.50	45.7	3.6
188	0	26	35.8	34.8	0.32	0.50	39.2	4.0

Reference Example 1:

Gastroresistant microgranules according to Example 1 of US 8,568,782 B2 were prepared.

5 Comparison:

1. Imaging pictures of the present granules according to Example 1 and Reference Example 1 were prepared, in which the distribution of rifaximin and enteric material is shown. The corresponding measurement was carried out using
10 ATR on the microtome cut face of the embedded powder. All measurements were performed using a Tensor 27/Hyperion 3000 microscope with a 64x64 Focal-Plane-Array detector. The transmission measurements were done with a x15 Cassegrain objective and the ATR measurements were done with a x20(Gecaystal) objective. Figure 1 shows irregularly agglomerated rifaximin particles with
15 inhomogeneously distributed enteric material in the granules according to the prior art (left side). Contrary, in granules according to the present invention (right side), the enteric material is homogeneously distributed over the surface of the rifaximin.

2. Images were recorded using a Keyence VHX 5000 light microscope. Figure
20 2 shows the overall morphology of particles according to prior art (left side) and according to the present invention (right side). As can be seen from said Figure 2 the particles according to the present invention have a much smoother surface.

3. The dissolution profiles of the present granules containing 400 mg rifaximin
25 as prepared above and the gastroresistant microgranules according to Example 1 of US 8,568,782 B2 were determined according to USP, item 711 Dissolution (Apparatus 2, Method A, 37.5°C $\pm$ 0.5°C, 100 rpm; 120 minutes 0.1 N HCl and after 2 hours a phosphate buffer to bring up the pH to 6.8) twice each and shown in Figure 3. As it can be seen from said Figure 3, after being brought into buffered
30 solution (corresponding to the milieu of the stomach) the present rifaximin-containing granules for modified release show a higher release which is reported to lead to a higher degree of supersaturation such that the corresponding bacteria can be advantageously treated.

4. The granules according to Example 1 were subjected to fluidized bed coating. The mean particle size of the resulting particles (granules) was obtained via analytical sieving (Amplitude 20%, 15 minutes using an Analysette sieving machine (Type 3010, Fritsch GmbH, Idar-Oberstein, Germany) with sieve tower
5 mesh sizes of 250, 300, 500, 800, 1100, 1250 μm and linear extrapolation.

The main particle size of the granules according to Reference Example 1 was obtained via analytical sieving (Amplitude 20%, 15 minutes using an Analysette sieving machine (Type 3010, Fritsch GmbH, Idar-Oberstein, Germany) with sieve
10 tower mesh sizes of 45, 63, 180 and 200 μm and linear extrapolation.

As can be seen from Figure 4 the mean particle size of the granules according to Reference Example 1 is about 30 μm , while the mean particle size of the particles (granules) obtainable according to the present invention is about 500 μm . The
15 large size usually results in improved further processability.

Preparation of a tablet

Granules

20 Rifaximin (297 g) and silica (1.49 g) were sieved over a screen with 800 μm and blended in a mixer (SDC04-TM1) at level 26 for 30 minutes. Subsequently the blend was sieved over a hand-held screen with 1000 μm . Subsequently the sieved blend was compacted in a dry granulator (TFC Lab Micro, Freund Vector) with a
25 roll pressure of 5×10^6 Pa, a roll control of about 1.8 r/min and a screw control of about 18.5 r/min to obtain a slug. Said slug was subjected to a treatment by a Frewitt sieve (1000 μm sieve) to obtain granules.

Pigment-containing suspension

30 Talcum (35.99 g), titan dioxide (8.11 g) and iron oxide (0.90 g) were weighted and mixed with demineralized water (94.69 g). The Suspension as treated in an Ultra Turrax with a setting of 9600 to 25000 for 33 minutes.

Polymer-containing suspension

To demineralized water (605.39 g) methacrylic acid-ethylacrylate copolymer (134.91 g) was added within six minutes under slowly accelerating stirring with
5 400 to 500 rpm. Subsequently the suspension was stirred for five minutes with 700 rpm and propylene glycol (20.04 g) was added. The resulting suspension was stirred for another five minutes with 700 rpm.

Coating solution

10

The pigment-containing suspension was added within five minutes to the polymer-containing suspension stirred at 750 rpm. Further, the resulting suspension was stirred at 600 rpm for another 180 minutes to obtain the coating solution, which was stirred at 280 until the start of the coating.

15

Coating Process

The fluidized bed coating was carried out in a fluid bed dryer (Glatt, adapted for Wurster application) as described above and the coating process was conducted as
20 follows:

1. Filling in the granules (226.8 g) as obtained above, adjusting Wurster tube (10 mm overhang)
2. Flange-mounting gas (below) and liquid (above) support, mount product
25 temperature sensor
3. Adjust pressure to 0.25 bar (25 kPa) on the side of the product
4. Heating bypass to 70°C
5. Starting filter cleaning with setting 2
6. Adjusting nozzle pressure to 0.5 bar (50 kPa)
- 30 7. Changing from bypass to operating mode
8. Spraying demineralized water for 14 minutes at level 10 to humidify the product, further heating to 75°C
9. plunging tube into coating solution
10. Start adding coating (determining amount of coating solution)

11. Constantly determining the amount of sprayed coating solution for 4.2 hours,
12. Stopping coating addition
13. Drying until the desired parameters are reached in the exhaust air stream
- 5 14. Stopping heating and starting cooling
15. Bringing nozzle pressure to 0, pressure on the side of the product to 0
16. Stopping filter cleaning
17. Carefully opening
18. Gathering product ("coated granules")
- 10 19. Cleaning apparatus

The amount of added coating solution was 515.0 g (flow of ca 2.08 g/min).

Preparation of tablets:

- 15 Coated granules as obtained above (250 g, 65.6 wt.% rifaximin), carboxy methyl starch (15.93 g), magnesium stearate (2.69 g) were sieved over a screen with 500 µm and subsequently blended with a mixer (SDC-27-49 Heidolph Reax 20) at level 16 for 20 minutes. From the resulting mixtures tablets were prepared using a
- 20 Flexitab Röntgen with punches of 19.4 x 8.3 mm and a compaction force of 11 kN to obtain tablets of 718 mg and a hardness of 200 kN.

Film-coated tablets

- 25 A. 50 tablets were filmed with a HPMC coating solution, wherein conventional pan coating equipment (Glatt) with the following parameters was applied.

	Supply air temperature:	75°C
	Drum speed:	11 UPM
30	Air flow:	40 m ³ /h
	Nozzle:	1
	Nozzle pressure	1.1 bar (110 kPa)
	Wide jet pressure:	1.1 bar (110 kPa)
	Core temperature:	at least 45°C

	Application rate of film	1.5g/min
	Duration	50 min
	Pump speed	5 to 7
	Exhaust air pressure	100 Pa
5	Exhaust air temperature:	48°C

HPMC coating solution:

- 10 OPADRY OY-S-34907 (30.04 g) was added to demineralized water (170.02 g) under stirring at 500 rpm and stirring was conducted for 130 minutes.

B. 50 tablets were filmed with a PVA coating solution, wherein conventional pan coating equipment (Glatt) with the following parameters was applied.

15	Supply air temperature:	75°C
	Drum speed:	11UPM
	Air flow:	40 m ³ /h
	Nozzle:	1
	Nozzle pressure	1.1 bar (110 kPa)
20	Wide jet pressure:	1.1 bar (110 kPa)
	Core temperature:	55°C
	Application rate of film	4.6g/min
	Duration	18 min
	Pump speed	5 t
25	Exhaust air pressure	100 Pa
	Exhaust air temperature:	47°C

PVA coating solution:

- 30 OPADRY II 85F240191 (30.06 g) was added to demineralized water (169.97 g) under stirring at 500 rpm and stirring was conducted for 120 minutes.

Figures 5 and 6 show cross-sections of the above tablet with an HMPC coating each, wherein the pictures were taken with a 200-fold and 500-fold magnification, respectively.

- 5 Figures 7 and 8 show cross-sections of the above tablet with a PVA coating each, wherein the pictures were taken with a 200-fold and 500-fold magnification, respectively.

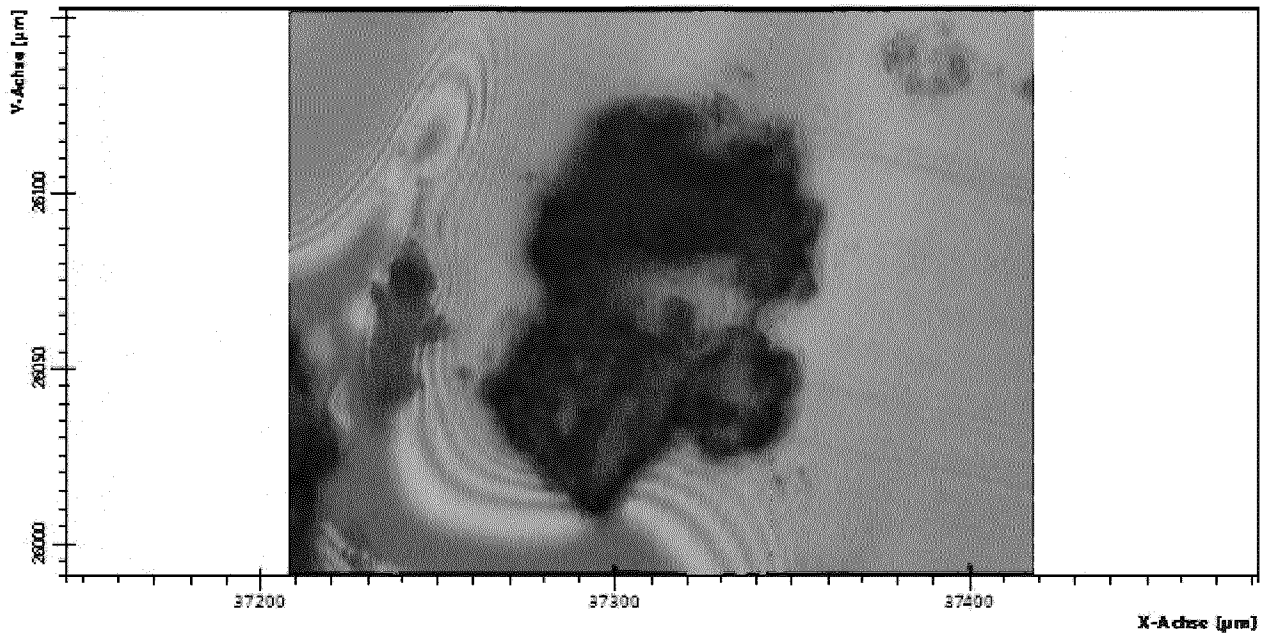
Claims

1. Method for preparing rifaximin-containing granules for modified release, wherein the method comprises the step of:
 - (i) granulating a composition comprising rifaximin and glidant
 - (ii) fluidized bed coating the granules from step (i) with a coating solution containing an enteric coating material.
2. Method according to claim 1, wherein in step (i) the composition comprises a filler and/or binder.
3. Method according claim 1 or 2, wherein the granulating in step (i) is conducted as dry granulation process comprising compacting the composition from step (i) to a slug and granulating the slug.
4. Method according to claim 3, wherein compacting the mixture from step (i) to a slug is carried out in a roll compactor.
5. Method according to claim 4, wherein the roll pressure is from 1×10^5 Pa (1 bar) to 1×10^7 Pa (100 bar).
6. Method according to claim 5 or 6, wherein the roll control is from 0.1 r/min to 5.0 r/min.
7. Method to claim to any one of claim 4 to 6, wherein the screw control is from 1 r/min to 50 r/min.
8. Method according to claim 1 or 2, wherein the granulating in step (i) is conducted as wet granulation process.
9. Method according to any one of claims 1 to 8, wherein in step (ii) the enteric coating material is a methacrylic acid – ethyl acrylate copolymer.

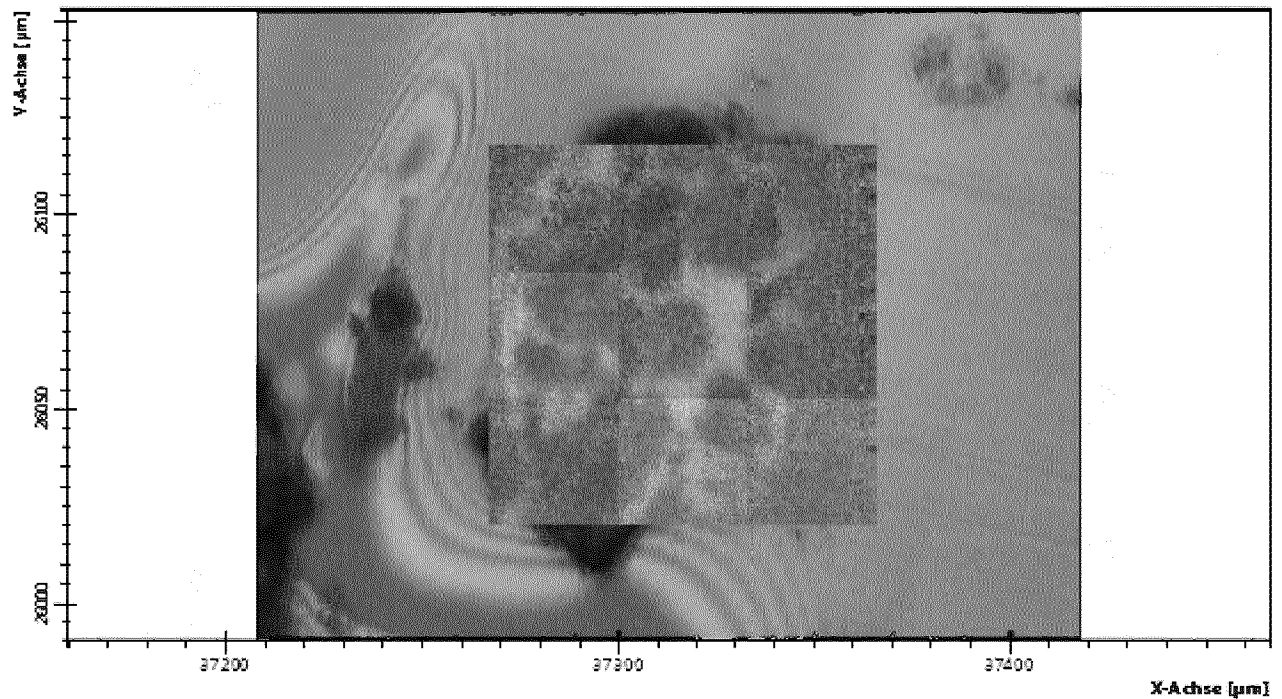
10. Rifaximin-containing granules for modified release obtainable by the method according to any one of claim 1 to 9.
11. Dosage form containing rifaximin-containing granules for modified release according to claim 10 and one or more pharmaceutical excipient(s).
12. Dosage form according to claim 11 being in form of a tablet.
13. Method for the preparation of rifaximin-containing tablet, wherein the method comprises the steps of:
 - (i) granulating a composition comprising rifaximin and glidant
 - (ii) fluidized bed coating the granulates from step (i) with a coating solution containing an enteric coating material
 - (iii) mixing the granules from (ii) with further pharmaceutically acceptable excipient(s),
 - (iv) compressing the mixture of step (iii) to a tablet, and
 - (v) film coating the tablet from step (iv), wherein the coating is substantially free of enteric material.

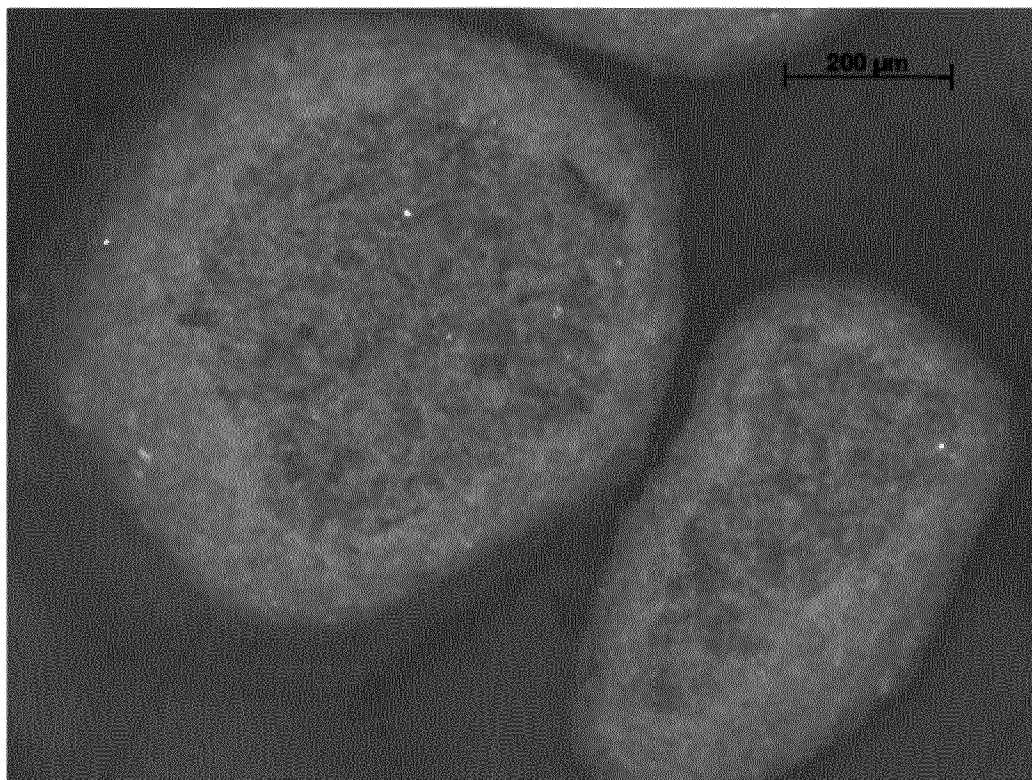
Figure 1

Imaging of enteric coated granules according to the prior art (upper two figures) and according to the present invention (lower two figures).

Results GG1-040-B

Light microscope image of the mapping position in figure below



Results GG2-040-B

Overview light microscope image of the large particles; the mappings were done at the edge of a particle and in the middle of a particle

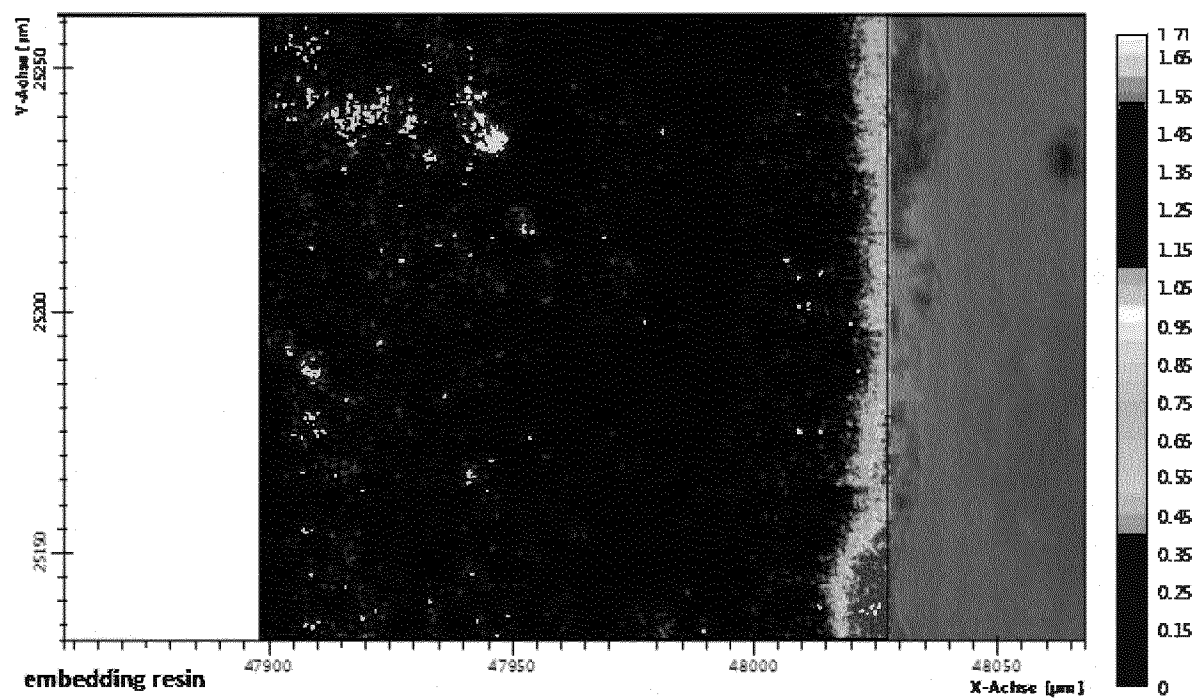


Figure 2

Microscopic images of coated granules according to the prior art (left side) and according to the present invention (right side)

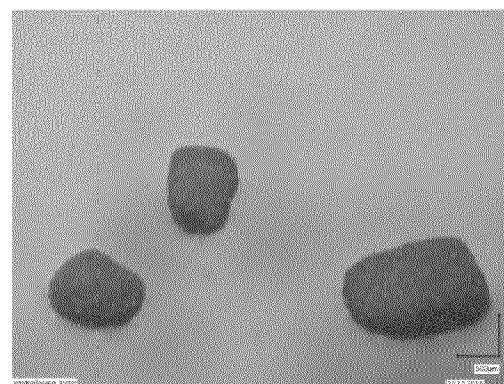
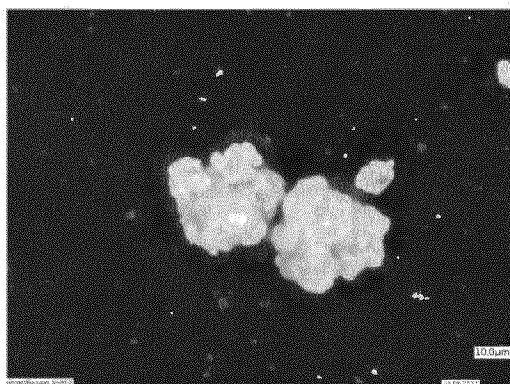
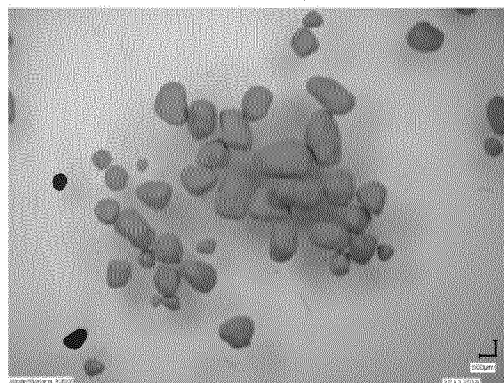
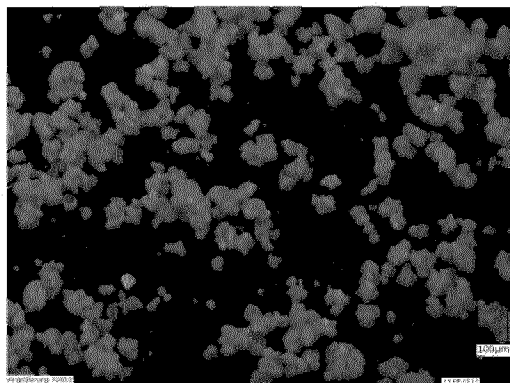
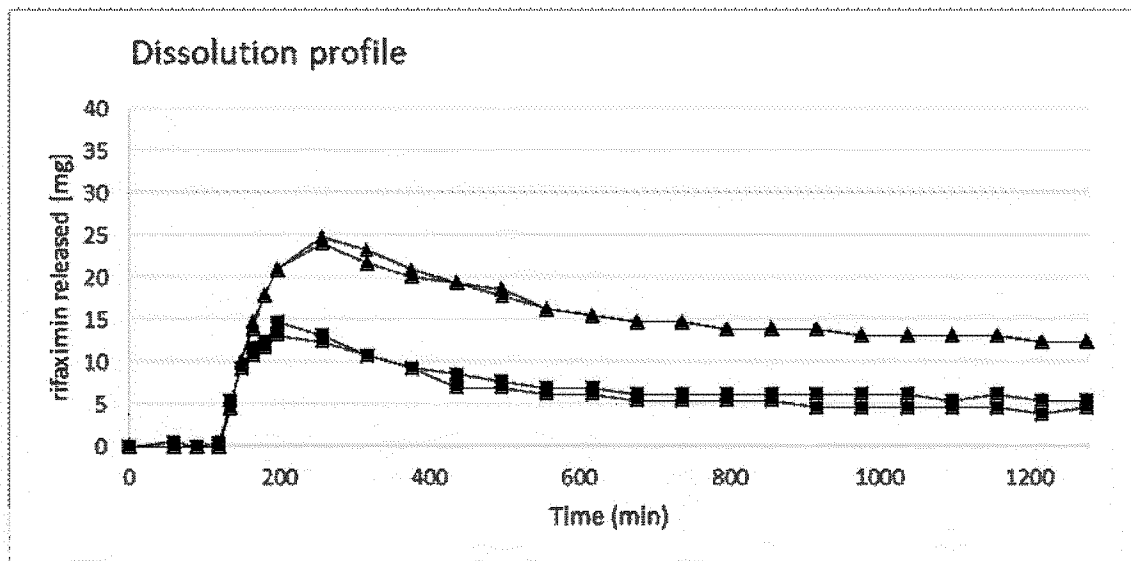


Figure 3



Triangle: present Example 1
Square Reference Example 1

Figure 4

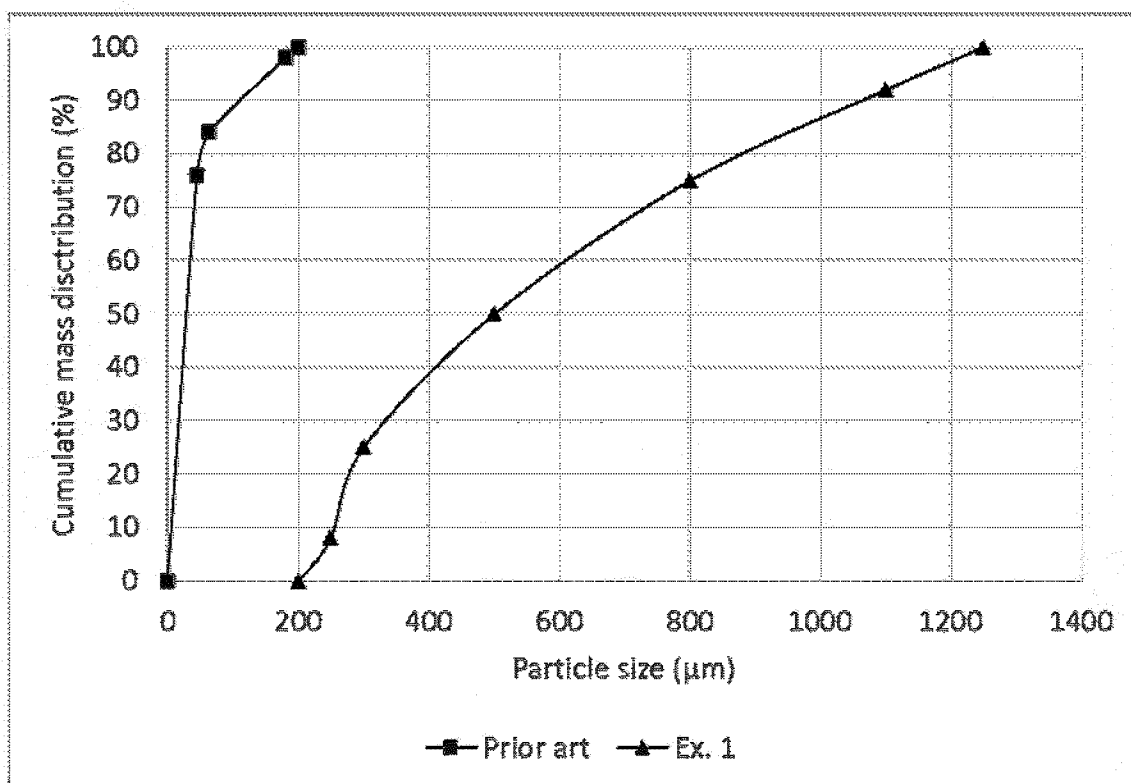


Figure 5

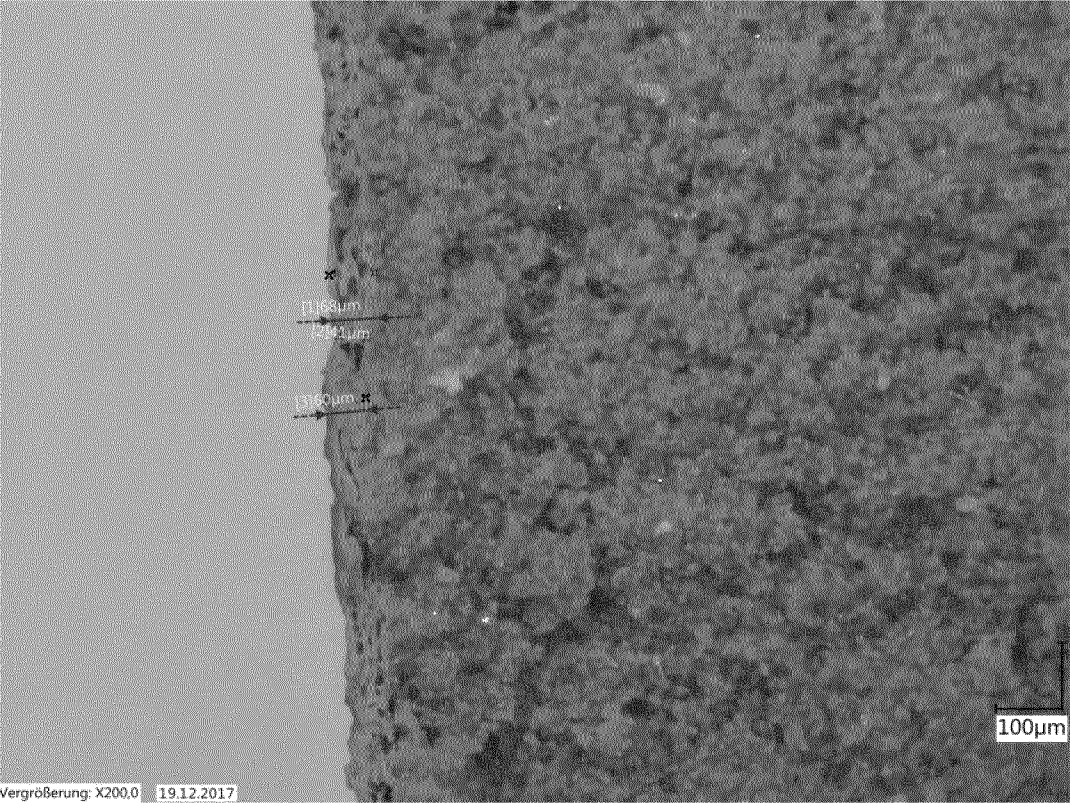


Figure 6

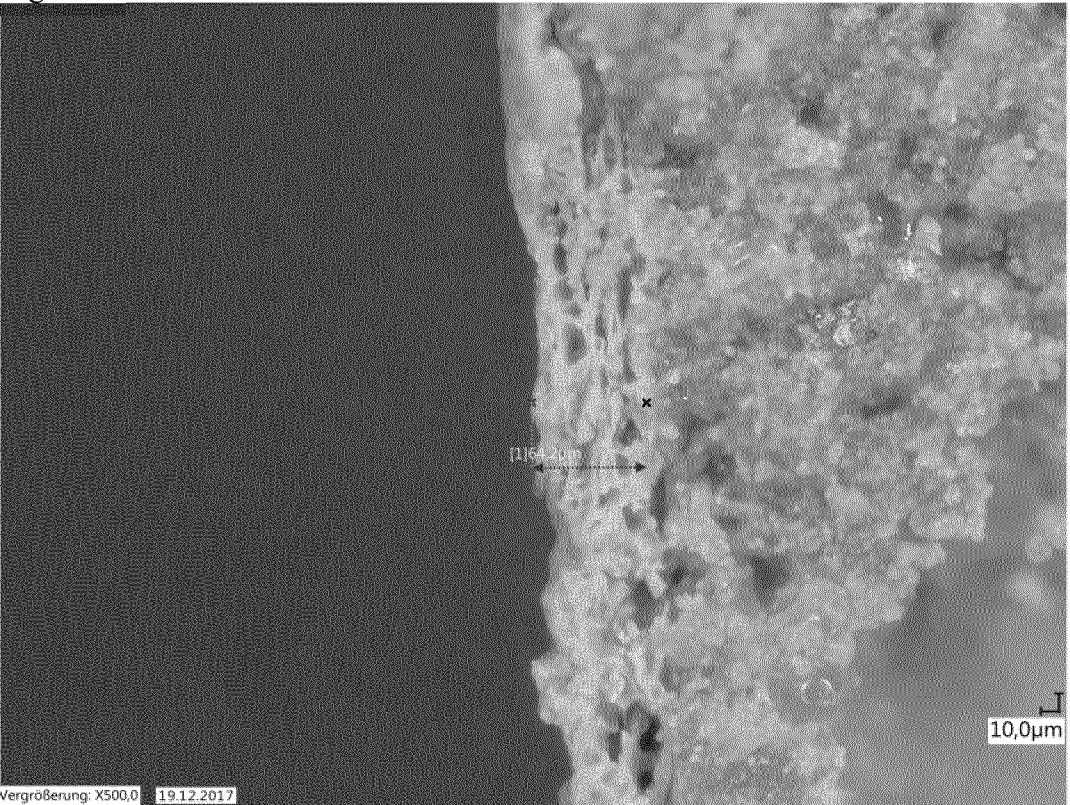


Figure 7

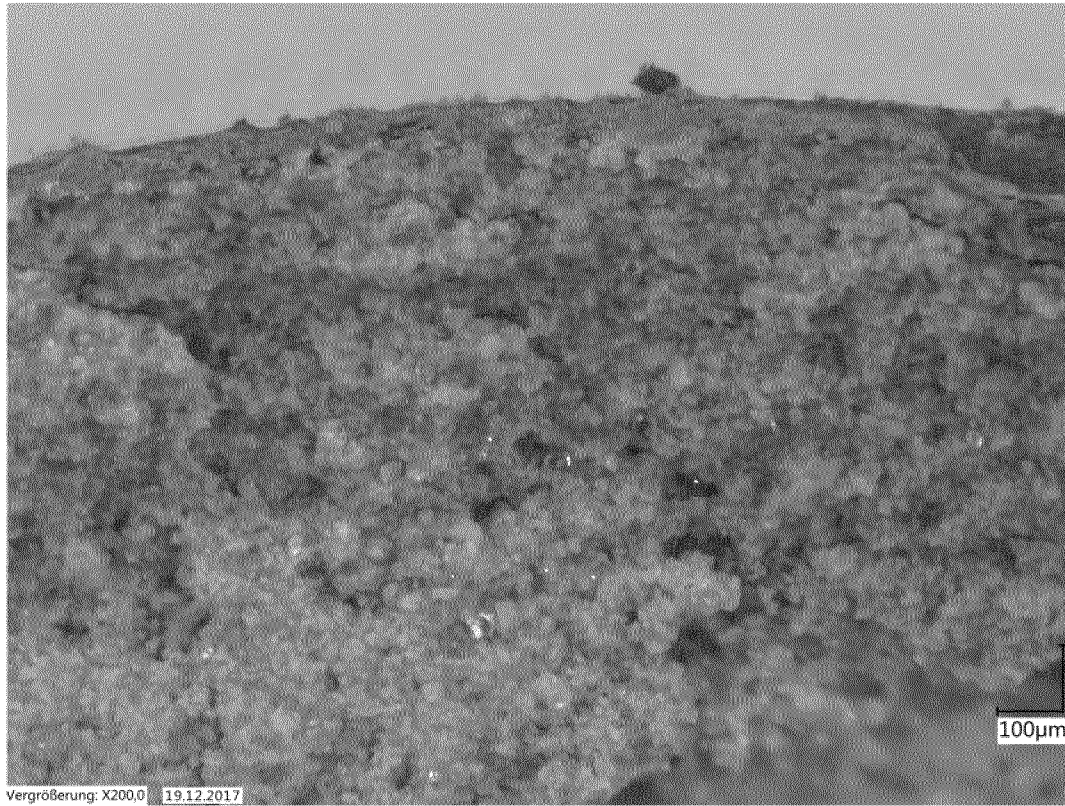
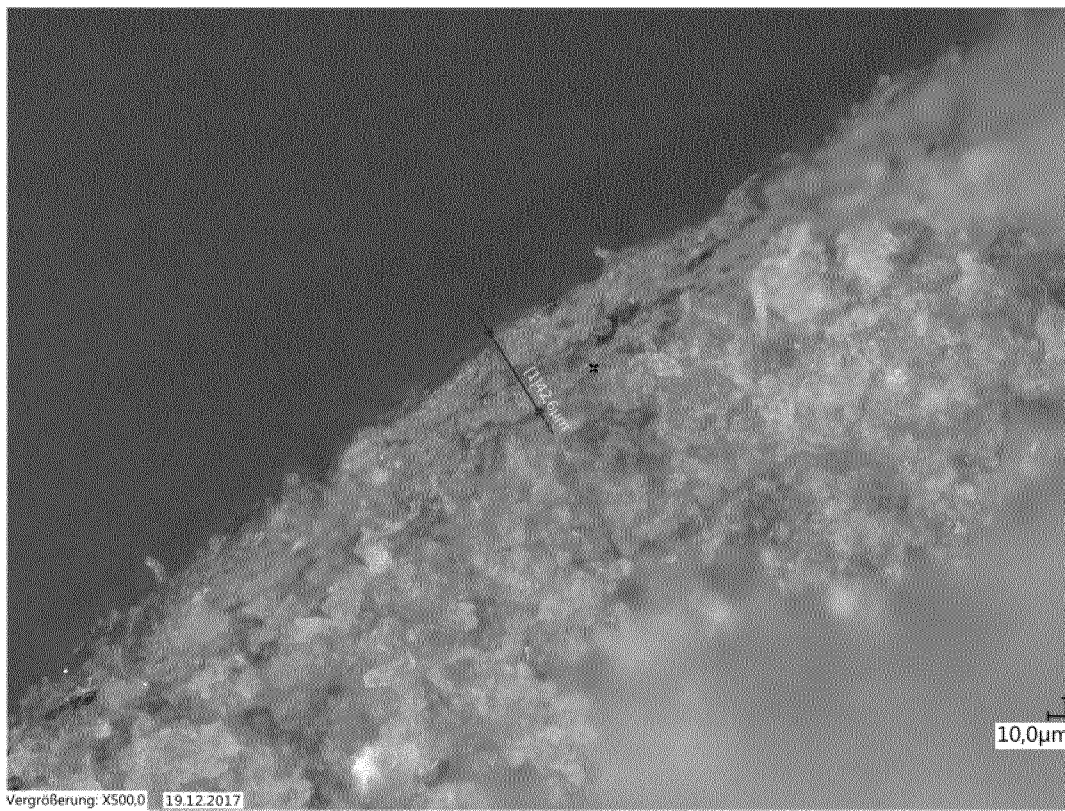


Figure 8



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/060154

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K31/437
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/091432 A1 (RANBAXY LAB LTD [IN]) 19 June 2014 (2014-06-19) the whole document claim 8; example 1 -----	1-13
X	US 8 568 782 B2 (VISCOMI GIUSEPPE CLAUDIO [IT]; PALAZZINI ERNESTO [IT] ET AL.) 29 October 2013 (2013-10-29) cited in the application the whole document example 1 -----	1-13
Y	EP 2 011 486 A1 (LUPIN LTD [IN]) 7 January 2009 (2009-01-07) the whole document paragraph [0103]; examples ----- -/-	1-13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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