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(54) Title: ENCAPSULATED PARTICLES COMPRISING A PHARMACEUTICALLY ACTIVE INGREDIENT

Dissolution profile of examples 1-6 and comparative examples 1 and 2 in 0.1 N HCl

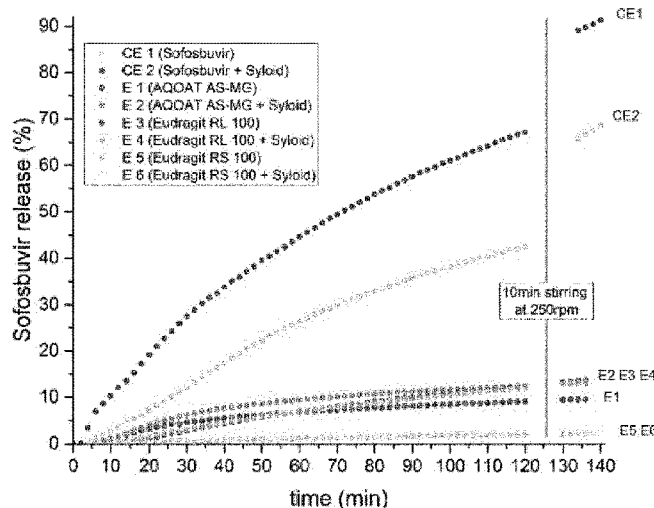


Figure 8

(57) Abstract: The present invention relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein the particles are encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymer. The present invention further relates to a process for preparing the encapsulated particles and the use of the encapsulated particles in particular in the treatment of HCV and in anti-coagulation therapy.



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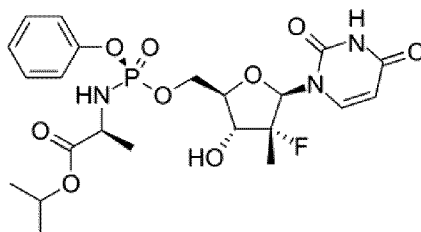
— *with international search report (Art. 21(3))*

Encapsulated particles comprising a pharmaceutically active ingredient

The present invention relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein the particles are encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymer. The present invention further relates to a process for preparing the encapsulated particles and the use of the encapsulated particles in particular in the treatment of HCV and in anti-coagulation therapy.

Background section

Sofosbuvir according to formula (I)

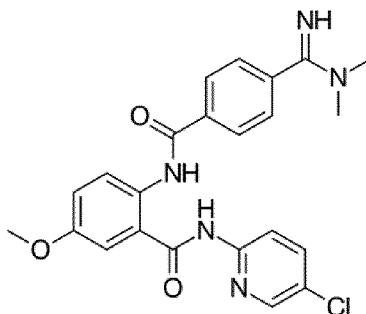


(I)

with IUPAC name (S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-amino)propanoate is a drug which inhibits the RNA polymerase used by the hepatitis C virus to replicate its RNA.

In WO 2010/135569 A, sofosbuvir is described as a moisture sensitive compound. In particular, it is disclosed that under stress conditions at 40 °C and a relative humidity (RH) of 75 %, sofosbuvir deliquesces after a few hours. Amorphous sofosbuvir, compared to its crystalline forms, is even more moisture sensitive and deliquesces at a relative humidity above about 50 %.

Betrixaban (INN) is a compound according to formula (II)



with IUPAC name N-(5-chloropyridin-2-yl)-2-[[4-(N,N-dimethylcarbamimidoyl)benzoyl]amino]-5-methoxybenzamide and codenamed PRT-054,021 is an anticoagulant drug which acts as a direct factor Xa inhibitor.

5

Difference in drug release through the use of different coating materials is known in the pharmaceutical industry. In principle, a distinction is made between single and multiple dosage units. The single dosage units are generally tablets, to which a suitable coating material is applied after completion of the tableting. In the presence of multiple dosage units, the original shaped
10 body (e.g., hard gelatin capsule or tablet) usually decays into many subunits in the stomach. The subunits are coated pellets (e.g., Antra MUPS® tablet, Kapanol retard capsule), microtablets (e.g., cholspasminase® microcapsule, capsule) or microparticles. In the preparation of single and multiple dosage units mentioned above, the preparation of the coated particles requires two steps: the formation of the particles and subsequent coating step.

15

It is hence an object of the present invention to provide a simplified process wherein a shell surrounding each of the particles can be directly formed during the production of the particles. It is further advantageous for the purpose of improving bioavailability and at the same time the patient compliance to tailor the release of the active ingredient from the particles so as to
20 modulate the dissolution and hence the bioavailability of the active ingredient. For example, it is desirable to tailor the dissolution of the active ingredient so that the bioavailability of the active ingredient is not affected by the fed/fasted status of the patient. It is further advantageous to provide an amorphous form of the active ingredient that is stable and does not need to be immediately processed to the dosage form.

25

The above mentioned advantages are achieved by the present invention.

It has been surprisingly found that encapsulated particles preferably prepared via spray drying can be obtained in one step process and provide the means to easily modulate the release profile
30 of the drug compound.

When a polymer is added to an active ingredient solution for spray drying, it is possible for the polymer to accumulate on the surface of the particles during the drying of the droplets and form a polymer sheath (shell). Without being bound to any theory, it is explained that an important
5 property of the polymer is a migration rate of the polymer in the drying droplet that is different to the migration rate of the active ingredient or of other excipients that may be present in starting solution for spray drying. In this way, the polymer can enrich at the surface of the drying droplet and forms a shell (Figure 1). It has been further found that the polymer may preferably be dissolved in the mixture to be spray dried. In the case of an undissolved state of the polymer, a
10 temperature above the glass transition temperature would be necessary for the encapsulation formation. This would entail an additional thermal stress. There is no thermal stress in the case of a polymer dissolved since the shell is formed below the glass transition temperature. In addition, it has been found that the polymer must not increase the viscosity of the solution to an extent where the atomization of the solution is not possible.

15 It has been found that by spray drying a mixture wherein the drug and the polymer are dissolved in a solution, encapsulated particles are obtained wherein the active pharmaceutical ingredient (API) is in the form of particles each being encapsulated with said polymer. Furthermore, it has been found that excipients may be added. In this case, the starting mixture to be spray dried can
20 be a suspension comprising the one or more excipients. It is however preferred that in the suspension the drug and the polymer are dissolved.

It has been further advantageously found that the presence of the polymer during the spray drying process allows obtaining the pharmaceutically active ingredient in the amorphous form. Hence,
25 the present invention advantageously provides a method for preparing an amorphous pharmaceutical active ingredient in the form of encapsulated particles.

Therefore, the present invention is directed to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more
30 pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers. The polymer is forming a shell. The encapsulated particles are hence in a single-particle single-shell configuration. Each single particle of the encapsulated particles is encapsulated in the shell formed by the pharmaceutically acceptable polymer or the mixture of pharmaceutically
35 acceptable polymers as depicted in Figure 1.

The present invention is further directed to a process for preparing the encapsulated particles, the process comprising

- i) preparing a mixture comprising one or more pharmaceutically active ingredients, a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers, one or more solvents and optionally one or more pharmaceutically acceptable excipients;
- ii) spray encapsulating the mixture of i).

The present invention is further directed to encapsulated particles obtained or obtainable by a process according to the invention.

The present invention is further directed to encapsulated particles for use as a medicament.

The present invention is further directed to encapsulated particles for use in the treatment of HCV.

The present invention is further directed to encapsulated particles for use in anticoagulant therapy.

The present invention is further directed to a mixture comprising the encapsulated particles of the invention and non-encapsulated particles.

The present invention is further directed to a pharmaceutical dosage form comprising the encapsulated particles of the invention or a mixture comprising the encapsulated particles of the invention and non-encapsulated particles wherein the pharmaceutical dosage form is preferably an oral dosage form.

Therefore, the present invention is directed to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers. The pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers forms a shell surrounding each particle.

As explained above, encapsulated particles are preferably formed via spray-drying from a mixture comprising the one or more pharmaceutically active ingredients, a pharmaceutically

acceptable polymer or a mixture of pharmaceutically acceptable polymers, one or more solvents and optionally one or more pharmaceutically acceptable excipients. During the drying step the polymer migrates toward the surface of the forming particle to form a shell surrounding the particle. Therefore, in the present context “encapsulated particle” means a particle encapsulated with the shell formed by the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers. Each encapsulated particle of the encapsulated particles is encapsulated with the pharmaceutically acceptable polymer or by the mixture of pharmaceutically acceptable polymers forming a shell as depicted in Figure 1.

In the present context, „encapsulated particles” refers to encapsulated particles comprising a core and a shell. In the context of the present invention, the term “particle” or “particles” without the antecedent term “encapsulated” refers to the inner part of the encapsulated particles i.e., the “core”.

The core and the shell are characterized by having different compositions with respect to each other (i.e. the core with respect to the shell) with regard to the identity and/or quantity of the chemical components forming the encapsulated particles. In the “encapsulated particles” of the present context, the API and the acceptable excipients are enriched in the core, whereas the concentration of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers is increased in the shell, thereby forming a functional shell. Preferably in the present context, the above defined „encapsulated particles” are in a single-particle (i.e., wherein the core is formed by one particle) single-shell configuration wherein each particle is surrounded by a shell formed or mainly formed by the pharmaceutically acceptable polymer or by the mixture of pharmaceutically acceptable polymers. The single-particle single-shell configuration is different from a multiple-particles (wherein the core is formed by a multiplicity of particles) single-shell configuration wherein a multiplicity of particles is surrounded by the same shell. In the context of the single-particle single-shell configuration, the term “particles” without the antecedent term “encapsulated” refers to the inner part of the encapsulated particles i.e., the particles wherein the above-mentioned core is formed by one particle. In the context of the multiple-particle single-shell configuration, the term “particles” without the antecedent term “encapsulated” refers to the inner part of the encapsulated particles i.e., the particles wherein the above mentioned core is formed by a multiplicity of particles.

In the present context, the composition (in terms of components) of the encapsulated particles reflects the composition of each encapsulated particle. The one or more active ingredients and the optional one or more acceptable excipients are comprised or mainly comprised in the particles

moiety of the encapsulated particles and the polymer is comprised or mainly comprised in the shell moiety of the particles.

According to the present invention “mainly comprised” referred to the one or more active ingredients means that at least 90 weight-%, preferably at least 95 weight-%, more preferably in the range of from 95 to 99 weight-% of the one or more active ingredients is comprised in the particles moiety of the encapsulated particles. The weight-% values are based on the total weight of the one or more active ingredients comprised in the encapsulated particles. It is preferred that from 99 weight-% to 99.9 or to 100 weight-% of the one or more active ingredients is comprised in the particles.

According to the present invention “mainly comprised” referred to the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers means that at least 90 weight-%, preferably at least 95 weight-%, more preferably in the range of from 95 to 99 weight-% of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers is comprised in the shell of the encapsulated particles. The weight-% values are based on the total weight of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers comprised in the encapsulated particles. It is preferred that from 99 weight-% to 99.9 or to 100 weight-% of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers is comprised in the shell of the encapsulated particles.

Pharmaceutically active ingredients

Generally, there is no specific restriction as to the one or more pharmaceutically active ingredients. Any pharmaceutically active ingredient that can be subjected to a spray drying process is suitable for the purpose of the present invention. Preferably, the one or more pharmaceutically active ingredients is one or more anti-HCV agents or anticoagulant agents or antihypertension agents or anti-inflammatory agents or antibiotics or anti-cancer agents or hormonal therapy agents or weight loss agents or anti-insomnia agents or combinations thereof, more preferably the one or more pharmaceutically active ingredients is one or more of anti-HCV agents or anticoagulant agents.

An antihypertension agent is for example Selexipag (ATC B01AC27), which has vasodilating, antifibrotic and antiproliferative properties. These effects are due to selective agonism at the IP receptor (prostacycline receptor) on the smooth vascular muscle. In pulmonary arterial hypertension, the expression of the IP receptors and the synthesis of prostacyclin is reduced, which contributes to the development of the disease.

A weight-loss agent is for example Lorcaserin, which acts as an appetite inhibitor and saturating agent by selectively activating the 5-HT_{2C} receptor on certain nerve cells in the hypothalamus.

- 5 An anti-insomnia agent is for example suvorexant, which is a selective and dual antagonist at the Orexin Receptors OX_{1R} and OX_{2R}.

An anticancer agent is for example Idelalisib (ATC L01XX47) which has antiproliferative, selective cytotoxic and antitumoral properties. The effects of Idelalisib are due to the inhibition of
10 phosphatidylinositol-3-kinase p110 δ . A further example of an anticancer agent is Ibrutinib (ATC L01XE27), which is a non-competitive (irreversible) inhibitor of the Bruton tyrosine kinase (BTK), whereby this signal molecule is involved in the pathogenesis of the sheath cell lymphoma.

- 15 Generally, there is no specific restriction as to the one or more anti-HCV agents. Preferably, the one or more anti-HCV agents is one or more of sofosbuvir, daclatasvir, ledipasvir, ravidasvir, pibrentasvir, glecaprevir, paritaprevir, ombitasvir, dasabuvir, velpatasvir, grazoprevir, elbasvir, interferon, more preferably the one or more anti-HCV agents comprises, more preferably is sofosbuvir. These active ingredients are known in the art.

20 Generally, there is no specific restriction as to the one or more anticoagulant agents. Preferably, the one or more anticoagulant agents is Betrixaban or a pharmaceutically acceptable salt thereof wherein the pharmaceutically acceptable salt is preferably one or more of maleate, hydrochloride, sulfate, acetate, phosphate, diphosphate or chloride, more preferably the pharmaceutically
25 acceptable salt is maleate.

Generally, there is no specific restriction as to the one or more anti-inflammatory agents. Generally, there is no specific restriction as to the one or more antibiotics. Generally, there is no specific restriction as to the one or more anti-cancer agents. Generally, there is no specific
30 restriction as to the one or more hormonal therapy agents. In all cases provided that the encapsulated particles of the invention are formed

It is further contemplated that the one or more pharmaceutically active ingredients comprised in the encapsulated particles is crystalline or amorphous, preferably amorphous. It has been found
35 that the amorphous form of a pharmaceutically active ingredient in the encapsulated particles is

particularly stable. In this context, “stable” means that the amorphous form does not undergo polymorphic transformations or does not deliquesce under humidity conditions.

Therefore, the present invention is further directed to the encapsulated particles as disclosed herein above, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-% of the one or more pharmaceutically active ingredients comprised in the encapsulated particles is in amorphous form, based on the total amount of the one or more pharmaceutically active ingredients. The one or more pharmaceutically active ingredients is comprised in the particles moiety of the encapsulated particles.

Therefore, the present invention is further directed to the encapsulated particles as disclosed herein above wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-% of the one or more anti-HCV agents is in amorphous form based on the total amount of the one or more anti-HCV agents, wherein preferably the one or more anti-HCV agents comprises, more preferably is sofosbuvir.

As to the composition of the encapsulated particles, as already disclosed above, the particles comprise the one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers. Preferably, at least 95 weight-%, more preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles (particles plus shell) consists of the one or more pharmaceutically active ingredients, of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers and optionally of one or more pharmaceutically acceptable excipients. The weight-% values are based on the total weight of the encapsulated particles. The one or more pharmaceutically active ingredients and the optional pharmaceutically acceptable excipients are comprised in the particles moiety of the encapsulated particles. The pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers forms the shell that encapsulates each of the particles.

Preferably at least 95 weight-%, more preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles consists of the one or more anti-HCV agents, of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers and optionally of one or more pharmaceutically acceptable excipients, wherein preferably the anti-HCV agent is sofosbuvir, based on the total weight of the encapsulated particles.

It is contemplated that the encapsulated particles further comprise one or more pharmaceutically acceptable excipients. In this case, preferably the one or more pharmaceutically acceptable excipients is not the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers forming the shell of the encapsulated particles.

Hence, the present invention is further directed to encapsulated particles wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles (i.e. particle and shell) consists of the one or more pharmaceutically active ingredients, of the one or more pharmaceutically acceptable excipients and of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers. As mentioned above, the particles moiety of the encapsulated particles comprises or mainly comprises the one or more pharmaceutically active ingredients and of the one or more pharmaceutically acceptable excipients and the shell of the encapsulated particles comprises or mainly comprises the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers. The weight-% values are based on the total weight of the encapsulated particles.

Hence, the present invention is further directed to encapsulated particles, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles consists of one or more anti-HCV agents, of one or more pharmaceutically acceptable excipients and of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers, wherein preferably the anti-HCV agent is sofosbuvir. The weight-% values are based on the total weight of the encapsulated particles.

The one or more pharmaceutically acceptable excipients are preferably comprised in the particles: therefore, it is preferred that during the formation of the encapsulated particles, the one or more pharmaceutically acceptable excipients do not migrate to the surface of the particles to form the shell.

The present invention is further directed to encapsulated particles, wherein at least 50 weight-%, preferably from 50 to 99.5 weight-%, more preferably from 55 to 70 weight-% of the encapsulated particles consists of the pharmaceutical active ingredients and wherein 0.5 to 50 weight-%, or from 0.5 to 15 weight-%, or from 25 to 35 weight-%, or from 28 to 33 weight-% of

the encapsulated particles consists in the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles.

Hence, the present invention is further directed to encapsulated particles, wherein at least 50 weight-%, preferably from 50 to 99.5 weight-%, more preferably from 55 to 70 weight-% of the encapsulated particles consists of the pharmaceutical active ingredients and wherein 0.5 to 50 weight-%, more preferably from 30 to 45 weight-% of the encapsulated particles consists in the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles.

Hence, the present invention is preferably directed to encapsulated particles, wherein at least 85 weight-%, more preferably from 90 to 99.5 weight-% of the encapsulated particles consists of the one or more pharmaceutical active ingredients and wherein the weight-% is based on the total weight of the encapsulated particles.

Hence, the present invention is more preferably directed to encapsulated particles wherein the encapsulated particles consist of the one or more pharmaceutical active ingredients and of the pharmaceutically acceptable polymer or of a mixture of pharmaceutically acceptable polymers, wherein at least 85 weight-%, preferably from 90 to 99.5 weight-% of the encapsulated particles consists of the said one or more pharmaceutical active ingredients wherein the weight-% is based on the total weight of the encapsulated particles and preferably wherein pharmaceutically acceptable polymer is as defined herein below in the "*Pharmaceutically acceptable polymers*" paragraph.

With regard to the encapsulation of the particles, it is contemplated that the particles are completely or partially encapsulated with the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers. Within the context of the present invention, the term "partially encapsulated" means that part of the surface of the particles is not encapsulated with the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers. In other words, a particle is only partially surrounded by a shell. Without being bound to any theory, it has been found that the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers during the process of formation of the particles may migrate non-uniformly towards the surface of the particles. Thereby only part of the surface of the particles is encapsulated. Generally, it is preferred that at least the 50%, more preferably from 60 to 90%, more preferably from 70 to 80% of the surface area of the partially encapsulated

particles is encapsulated with the pharmaceutically acceptable polymer or in the mixture of pharmaceutically acceptable polymers.

Therefore, the present invention is directed to encapsulated particles wherein the encapsulated particles comprise, preferably consist of completely and partially encapsulated particles, wherein at least 50%, preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90% of the encapsulated particles are completely encapsulated, based on the total amount of encapsulated particles. The % values are based on the total amount of the (completely and partially) encapsulated particles

Therefore, the present invention is further directed to encapsulated particles wherein at least the 50% preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90% of the particles are partially encapsulated based on the total amount of the (completely and partially) encapsulated particles.

Generally, there is no specific restriction as to the size of the encapsulated particles. Preferably, the median particle size distribution value D50 of the encapsulated particles is of at least 1 μm , more preferably, the D50 value is in the range of from 10 to 300 μm or in the range of from 10 to 200 μm , more preferably, in the range of from 15 to 100 μm or in the range of 15 to 35 μm , wherein the D50 value is measured according to the method disclosed in Reference Example 1.1.

Generally, there is no specific restriction as to the bulk distribution of encapsulated particles as disclosed above. Preferably, the encapsulated particles have a bulk density in the range of 0.15 to 1.00 g/ml, more preferably in the range of 0.20 to 0.25 g/ml, wherein the bulk density is measured according to the method disclosed in Reference Example 1.3.

Advantageously, the encapsulated particles as disclosed herein do not comprise or adsorb water. Hence, preferably less than 5 weight-% or from 0.00 to 4.9 weight-% or from 0.2 to 3.5 weight-% of the encapsulated particles consists of water, based on the total weight of the encapsulated particles. More preferably, the encapsulated particles as disclosed herein do not comprise water. The water amount of the encapsulated particles is measured according to the Karl-Fischer titration method. The Karl-Fischer titration is the standard titration method in chemistry to determine the water amount in a sample and is known in the art.

Pharmaceutically acceptable polymers

Generally, there is no specific restriction as to the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers provided that the encapsulated particles as disclosed above are formed. The choice of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers may also depend on the type of release desired for the one or more active ingredients, and on the polymer solubility in the solvents used for the encapsulating spray drying process. Further excipients may be added to the composition to change, adapt and/or modify its properties, e.g. to ensure the elasticity and stability of the film (e.g. through the addition of plasticizers, pigments and the like). The addition of such further excipients is known to the skilled person and belongs to his or her common general knowledge.

Preferably, the pharmaceutically acceptable polymers are pH-dependent release polymers (enteric polymers) or time-dependent release polymers (diffusion-controlled release polymer). The term “enteric polymer” or the term “pH-dependent polymer” in the context of the present invention refers to those polymers that provide a release of the pharmaceutically active ingredient which is pH-dependent. Enteric polymers are known in the art. An enteric polymer is for example hypromellose acetate succinate (HPMCAS) such as AQOAT®. For example the polymer AQOAT® AS-MG dissolves at a pH=6. Preferably, enteric polymers according to the present invention are:

- natural film former such as Shellac,
- cellulose acetate phthalate such as Aquacoat® CPD;
- polyvinyl acetate phthalate (CAP) such as Coateric® and Sureteric®;
- hydroxypropyl methylcellulose phthalate (HPMCP) such as Mantrocel® HP 55;
- hydroxyl-propyl-methylcellulose-acetate-succinate (HPMCAS) such as Aquoat® and AQOAT® AS-MG and
- methacrylic acid copolymers wherein the methacrylic acid copolymers preferably are diethylaminoethyl-methacrylate-methyl-methacrylate-copolymers (DEAEMA-MMA 3:7) such as Eudragit® E100, Eudragit® E P0 and Eudragit® E12,5 or methylacrylacid-methylmethacrylate-copolymer 1:1 (MA-MM 1:1) such as Eudragit® L100 and Eudragit® L12,5, methacrylacid-methylmethacrylate-copolymer 1:2 (MA-MM 1:2=PMMA 1:2) such as Eudragit® S100, and Eudragit® S12,5).

Preferably, the one or more pharmaceutically acceptable enteric polymers is one or more of hydroxyl-propyl-methylcellulose-acetate-succinate or methacrylic acid copolymers.

The term “time-dependent release polymer” in the contest of the invention means a polymer which provides a release of the pharmaceutically active ingredient in the gastrointestinal tract that it is time-dependent and is preferably pH independent. “Time-dependent release polymers” are for examples methacrylic ester polymers such as of Eudragit type such as Eudragit RL100 (high permeability) and Eudragit RS 100 (low permeability). The “time release dependent polymer” may also be indicated as “diffusion-controlled release polymer”. Preferably time-dependent release polymers according to the present invention are:

- polyvinylacetate (PVA) such as Kollicoat® SR 30 D;
- ethyl cellulose (EC) such as Aqualon® EC, Ethocel®, Surelease®);
- cellulose acetate-butyrate;
- cellulose acetate;
- type A and type B ammonio-methacrylate copolymers such as Trimethylammoniummethylemethacrylate-chlorid-Ethylacrylate-Methylmethacrylate (TAMCL-EA-MMA) such as Eudragit® RL 100 and Eudragit® RS 100;
- Ethylacrylate-methylmethacrylate-copolymers 2:1 (EA-MMA 2:1), such as Eudragit® NE 30 D, Eudragit® NE 40 D and Kollicoat® EMM 30 D;
- Hydroxyethylcellulose (HEC) such as Natrosol® and Tylose® H.

Some polymers such as methacrylic ester can be either or both enteric polymer (pH-dependent) or time-dependent release polymers. It is within the skilled person knowledge which polymer e.g amongst the methacrylic esters is an enteric polymer and which is a time-dependent release polymer. For example, Eudragit E12.5 is soluble in the gastric fluid at pH 5.5, Eudragit L100-55 is soluble in intestinal fluid from pH 5.5. Eudragit® L and S are used as enteric polymer which are insoluble at pH below 5 and thus are resistant to the gastrointestinal fluid.

The enteric polymers and the time-dependent release polymers may be used in combination to further modulate the release of the pharmaceutically active ingredient.

Therefore, the present invention relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients, wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically acceptable polymer is one or more enteric polymers (pH-dependent polymers) or one or more time-dependent release polymers (diffusion controlled release polymers) or a combination thereof.

Therefore, the present invention relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically acceptable polymer is one or more enteric polymers (pH-dependent polymers).

Therefore, the present invention relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically acceptable polymer is one or more time-dependent release polymers (diffusion controlled release polymers).

Therefore, the present invention relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in one or more pharmaceutically acceptable enteric polymers, wherein the one or more pharmaceutically acceptable enteric polymers is one or more of

- natural film former such as Shellac;
- cellulose acetate phthalate such as Aquacoat® CPD;
- polyvinyl acetate phthalate (CAP) such as Coateric® and Sureteric®;
- hydroxypropyl methylcellulose phthalate (HPMCP) such as Mantrocel® HP 55;
- hydroxyl-propyl-methylcellulose-acetate-succinate (HPMCAS) such as Aquoat® and AQOAT® AS-MG and
- methacrylic acid copolymers

wherein the methacrylic acid copolymers are preferably diethylaminoethyl-methacrylate-methyl-methacrylate-copolymers (DEAEMA-MMA 3:7) such as Eudragit® E100, Eudragit® E P0 and Eudragit® E12,5 or methylacrylacid-methylmethacrylate-copolymer 1:1 (MA-MM 1:1) such as Eudragit® L100 and Eudragit® L12,5 methacrylacid-methylmethacrylate-copolymer 1:2 (MA-MM 1:2=PMMA 1:2) such as Eudragit® S100, and Eudragit® S12,5).

Preferably, the one or more pharmaceutically acceptable enteric polymers is one or more of hydroxylpropyl-methylcellulose-acetate-succinate or methacrylic acid copolymers.

Therefore, the present invention relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in one or more time-dependent release polymers, wherein the one or more of the time-dependent release polymers is preferably one or more of

- polyvinylacetate (PVA) such as Kollicoat® SR 30 D
- ethyl cellulose (EC) such as Aqualon® EC, Ethocel®, Surelease®)
- cellulose acetate-butyrate
- cellulose acetate
- type A and type B ammonio-methacrylate copolymers such as Trimethylammoniummethylemethacrylate-chlorid-Ethylacrylate-Methylmethacrylate (TAMCL-EA-MMA) such as Eudragit® RL 100 and Eudragit® RS 100
- Ethylacrylate-methylmethacrylate-copolymers 2:1 (EA-MMA 2:1), such as Eudragit® NE 30 D, Eudragit® NE 40 D and Kollicoat® EMM 30 D
- Hydroxyethylcellulose (HEC) such as Natrosol® and Tylose® H.

There is no specific restriction with regard to the weight ratio of the one or more pharmaceutically active ingredients relative to the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers in the encapsulated particles, provided that the encapsulated particles as disclosed herein are obtained. Preferably, the weight ratio of the one or more pharmaceutically active ingredients relative to the pharmaceutically acceptable polymer or to the mixture of pharmaceutically acceptable polymers is in the range of from 1 : 1 to 200 : 1, more preferably in the range of from 1.5 : 1 to 50 : 1, more preferably in the range of from 1.5 : 1 to 20 : 1, more preferably in the range of from 1.6 : 1 to 2.5 : 1. As shown in the dissolution examples provided below advantageously the dissolution of the one or more pharmaceutically acceptable ingredients can be tailored by lowering the ratio and the amount of polymers of the encapsulated particles, relative to the amount of the one or more pharmaceutically active ingredients.

Hence, the present invention is further directed to encapsulated particles

- wherein the weight ratio of the one or more pharmaceutically active ingredients relative to the pharmaceutically acceptable polymer or to the mixture of pharmaceutically acceptable polymers is in the range of from 1 : 1 to 200 : 1, more preferably in the range of from 1.5 : 1 to 50 : 1, more preferably in the range of from 1.5 : 1 to 20 : 1, more preferably in the range of from 1.6 : 1 to 2.5 : 1,

-wherein the pharmaceutically acceptable ingredients is an anti-HCV agent, wherein preferably the anti-HCV agent is sofosbuvir and

-wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is an enteric polymer or a time-dependent polymer, wherein the enteric polymer is preferably one or more of hydroxy-propyl-methyl-cellulose-acetate-succinate or a methacrylate copolymer.

Hence, the present invention is further directed to encapsulated particles

-wherein the weight ratio of the one or more pharmaceutically active ingredients relative to the pharmaceutically acceptable polymer or to the mixture of pharmaceutically acceptable polymers is in the range of from 1 : 1 to 200 : 1, more preferably in the range of from 1.5 : 1 to 50 : 1, more preferably in the range of from 1.5 : 1 to 20 : 1, more preferably in the range of from 1.6 : 1 to 2.5 : 1,

-wherein the pharmaceutically acceptable ingredients is an anti-coagulant agent wherein preferably the anticoagulant agent is Betrixaban or a pharmaceutically acceptable salt thereof as disclosed herein above, wherein the salt is preferably Betrixaban maleate and

-wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is an enteric polymer or a time-dependent polymer, wherein the enteric polymer is preferably one or more of hydroxy-propyl-methyl-cellulose-acetate-succinate or a methacrylate copolymer.

Hence, the present invention is further directed to encapsulated particles

-wherein at least 50 weight-%, preferably from 50 to 99.5 weight-%, more preferably from 55 to 70 weight-% of the encapsulated particles consists of the pharmaceutical active ingredients and wherein 0.5 to 50 weight-%, or from 0.5 to 15 weight-%, or from 25 to 35 weight-%, or from 28 to 33 weight-% of the encapsulated particles consists in the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles,

-wherein the pharmaceutically acceptable ingredients is an anti-HCV agent wherein preferably the anti-HCV agent is sofosbuvir and

-wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is an enteric polymer or a time-dependent polymer, wherein the enteric polymer is preferably one or more of hydroxy-propyl-methyl-cellulose-acetate-succinate or a methacrylate copolymer.

Hence, the present invention is further directed to encapsulated particles

-wherein at least 50 weight-%, preferably from 50 to 99.5 weight-%, more preferably from 55 to 70 weight-% of the encapsulated particles consists of the pharmaceutical active ingredients and wherein 0.5 to 50 weight-%, or from 0.5 to 15 weight-%, or from 25 to 35 weight-%, or from 28 to 33 weight-% of the encapsulated particles consists in the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles,

-wherein the pharmaceutically acceptable ingredients is an anti-coagulant agent wherein preferably the anticoagulant agent is Betrixaban or a pharmaceutically acceptable salt thereof as disclosed herein above, wherein the salt is preferably Betrixaban maleate and

wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is an enteric polymer or a time-dependent polymer, wherein the enteric polymer is preferably one or more of hydroxy-propyl-methyl-cellulose-acetate-succinate or a methacrylate copolymer.

Pharmaceutically acceptable excipients

As mentioned above, the encapsulated particles of the invention may further comprise one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients are not the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers forming the shell. The one or more pharmaceutically acceptable excipients do not migrate to the surface of the particles to form the encapsulation. Rather they form the particles together with the one or more pharmaceutically active ingredients.

Therefore, the present invention further relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and one or more pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers.

Generally, there is no specific restriction as to the one or more pharmaceutically acceptable excipients, provided that it is not the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers forming the shell. Preferably the one or more pharmaceutically acceptable excipients comprises, more preferably consists of a silicon-based inorganic adsorbent.

Regarding the silicon-based inorganic adsorbents they include, preferably are, one or more of silica and silicates. Preferably, the one or more silicon-based inorganic adsorbent is one or more of silica, silicates, and a combination of two or more thereof, wherein the silica is preferably one

or more of fumed silica, precipitated silica, gel silica, colloidal silica, and a combination of two or more thereof, and wherein the silicates are preferably aluminosilicates preferably comprising at least one alkali metal element and/or at least one alkaline earth metal element, more preferably at least one alkaline earth metal element, more preferably magnesium, wherein more preferably, at least 90 weight-%, more preferably at least 95 weight-%, more preferably at least 99 weight-% of the at least one silicon-based inorganic adsorbent are present in amorphous form. The weight-% values are based on the total weight of the silicon-based inorganic adsorbent.

Examples of silicon-based inorganic adsorbents include, but are not restricted to, silica, silicates, and a combination of two or more thereof. For example, the silicon-based inorganic adsorbent is selected from the group consisting of silicas and combinations of two or more thereof; or from the group consisting of silicates and combinations of two or more thereof; or from the group consisting of at least one silica and at least one silicate. The term "silicate" as used in this context of the present invention refers to naturally occurring or synthesized compounds containing an anionic silicon compound, preferably an oxide. Examples of such silicates include, but are not restricted to, nesosilicates comprising the structure unit $[\text{SiO}_4]^{4-}$, sorosilicates comprising the structure unit $[\text{Si}_2\text{O}_7]^{6-}$, cyclosilicates comprising the structure unit $[\text{Si}_n\text{O}_{3n}]^{2n-}$, single chain inosilicates comprising the structure unit $[\text{Si}_n\text{O}_{3n}]^{2n-}$, double chain inosilicates comprising the structure unit $[\text{Si}_{4n}\text{O}_{11n}]^{6n-}$, phyllosilicates comprising the structure unit $[\text{Si}_n\text{O}_{5n}]^{2n-}$, or tectosilicates with a 3D framework comprising the structure unit $[\text{Al}_x\text{Si}_y\text{O}_{2(x+y)}]^{x-}$. The term "silica" as used in this context of the present invention refers to naturally occurring or synthesized silica. Examples of such silica include, but are not restricted to fumed silica, precipitated silica, gel silica, colloidal silica, such as Syloid® AL-1 FP and Syloid 72FP silica, Syloid 244 FP silica, Syloid 74FP silica, Syloid 63FP silica or Aerosil. According to the present invention, amorphous silica such as Syloid 72FP silica is more preferred.

It is further contemplated that the particles comprises one or more pharmaceutically acceptable excipients in addition to the one or more silicon-based inorganic adsorbents such as one or more of diluent, a disintegrant, glidant, a lubricant and a binder. However, it is preferred that the particles comprise only the one or more silicon-based inorganic adsorbents as the one or more pharmaceutically acceptable excipients.

Therefore, the present invention further relates to encapsulated particles, wherein the particles comprise

one or more pharmaceutically active ingredients and one or more pharmaceutically acceptable excipients wherein each of the particles is encapsulated in the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers,

wherein the one or more pharmaceutically acceptable excipients is a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises, preferably is silica and wherein preferably the silica is precipitated silica.

Therefore, the present invention further relates to encapsulated particles, wherein the particles comprise

one or more anti-HCV agents and one or more pharmaceutically acceptable excipients wherein each of the particles is encapsulated in the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers,

wherein the one or more pharmaceutically acceptable excipients is a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises, preferably is, silica and wherein preferably the silica is precipitated silica and wherein preferably the one or more anti-HCV agents is sofosbuvir.

Therefore, the present invention further relates to encapsulated particles, wherein the particles comprise

an anticoagulant agent and one or more pharmaceutically acceptable excipients, wherein each of the particles is encapsulated in the pharmaceutically acceptable polymer or in the mixture of pharmaceutically acceptable polymers,

wherein the one or more pharmaceutically acceptable excipients is a silicon-based inorganic adsorbent, wherein preferably, the silicon-based inorganic adsorbent comprises, preferably is, silica and wherein preferably the silica is precipitated silica and wherein preferably the anticoagulant agent is Betrixaban, or Betrixaban maleate.

As disclosed above, the one or more pharmaceutically acceptable excipients do not migrate to the surface of the particles to form the shell. Hence, the one or more pharmaceutically acceptable excipients is comprised or mainly comprised in the particles moiety of the encapsulated particles. It is preferred that from 1 to 20 weight-%, preferably from 10 to 15 weight-% of the encapsulated particles consists of the one or more acceptable excipients based on the total weight of the encapsulated particles, wherein the one or more pharmaceutically acceptable excipients is comprised or mainly comprised in the particles moiety of the encapsulated particles.

According to the present invention “mainly comprised” means that at least 90 weight-%, preferably at least 95 weight-%, more preferably in the range of from 95 to 99 weight-% of the silicon-based inorganic adsorbent is comprised in the particles. The weight-% values are based on the total weight of the silicon-based inorganic adsorbent comprised in the encapsulated particles.

5 It is preferred that from 99 weight-% to 99.9 or to 100 weight-% of the silicon-based inorganic adsorbent is comprised in the particles.

Therefore, the present invention further relates to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and one or more pharmaceutically acceptable excipients wherein each of the particles is encapsulated in the pharmaceutically acceptable polymer or in the mixture of pharmaceutically acceptable polymers.

Hence, the present invention is further directed to encapsulated particles
-wherein at least 50 weight-%, preferably from 50 to 98.5 weight-%, more preferably from 55 to
15 70 weight-% of the encapsulated particles consists of the pharmaceutical active ingredients, -
wherein from 0.5 to 50 weight-%, or from 0.5 to 15 weight-%, or from 25 to 35 weight-%, or
from 28 to 33 weight-% of the encapsulated particles consists in the pharmaceutically acceptable
polymer or the mixture of pharmaceutically acceptable polymers and
-wherein from 1 to 20 weight-%, preferably from 10 to 15 weight-% of the encapsulated particles
20 consists of the one or more acceptable excipients, based on the total weight of the encapsulated
particles,

wherein preferably the one or more excipients comprises, preferably consists of a silicon-based inorganic adsorbent as disclosed herein above.

25 Hence, the present invention is further directed to encapsulated particles
wherein the encapsulated particles consists of one or more the pharmaceutical active ingredients,
of pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable
polymers and of the silicon based inorganic adsorbent, wherein
- from 65 to 85 weight-% of the encapsulated particles, preferably from 70 to 80 weight
30 % of the encapsulated particles consists of the one or more pharmaceutical active
ingredients;
- from 14 to 22 weight % of the encapsulated particles, preferably from 16 to 21 weight
% of the encapsulated particles consists of the silicon based inorganic adsorbents;
- from 0.2 to 21 weight %, preferably from 4 to 10 weight-% of the encapsulated
35 particles, preferably from 16 to 21 weight % of the encapsulated particles consists of

the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers, wherein

preferably the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers is one or more enteric polymers (pH-dependent polymers); wherein preferably the one or more of the enteric polymers is one or more of

-natural film former,

-cellulose acetate phthalate

-polyvinyl acetate phthalate

-hydroxypropyl methylcellulose phthalate

-hydroxyl-propyl-methylcellulose-acetate-succinate

-methacrylic acid copolymers wherein the methacrylic acid copolymers are preferably diethylaminoethyl-methacrylate-methyl-methacrylate-copolymers (DEAEMA-MMA 3:7) or methylacrylacid-methylmethacrylate-copolymer 1:1 (MA-MM 1:1) or methacrylacid-methylmethacrylate-copolymer 1:2 (MA-MM 1:2=PMMA 1:2); more preferably, the one

or more enteric polymers is one or more of hydroxyl-propyl-methylcellulose-acetate-succinate or methacrylic acid copolymers, or

preferably the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is one or more time-dependent release polymers (diffusion controlled release polymers); wherein more preferably the one or more time-dependent release polymers is one or more of

-polyvinylacetate (PVA)

-ethyl cellulose (EC)

-cellulose acetate-butyrate

-cellulose acetate

-type A and type B ammonio-methacrylate copolymers

-Ethylacrylate-methylmethacrylate-copolymers 2:1 (EA-MMA 2:1)

-Hydroxyethylcellulose (HEC); more preferably the one or more time-dependent release polymers is one or more of ethylacrylate-methyl-methacrylate-copolymer 2:1, Trimethylammoniummethylmethacrylate-chlorid-ethylacrylate-methylmethacrylate,

hydroxyethylcellulose, ethylcellulose and polyvinyl acetate; or

preferably the mixture of pharmaceutically acceptable polymers is a combination of one or more enteric polymers (pH-dependent polymers) and one or more time-dependent release polymers (diffusion controlled release polymers) as defined herein above; and

preferably wherein the silicon based inorganic absorbent has a pH in the range of from 6.0 to 9.0,

more preferably in the range of from 6.5 to 8.5, more preferably in the range of from 7.0 to 8.0;

and more preferably wherein the silicon-based inorganic adsorbent comprises, more preferably

consists of silica and wherein preferably the silica comprises, more preferably is, precipitated silica and

wherein the weight % is based on the total weight of the encapsulated particles.

5 It has been further seen that advantageously the dissolution of the one or more pharmaceutically acceptance ingredients can be also tailored by preparing physical mixtures of the encapsulated particles of the invention and non-encapsulated or uncoated particles. Therefore, the present invention is further directed to a mixture, preferably a physical mixture, of the encapsulated particles as described herein and of non-encapsulated particles.

10

Therefore, the present invention is further directed to a mixture comprising

a) encapsulated particles, preferably the encapsulated particle according to the present invention, wherein the particles comprise one or more pharmaceutically active ingredients and optionally the one or more pharmaceutically acceptable excipients as described herein above and wherein each of the particles is encapsulated in the pharmaceutically acceptable polymer or in the mixture of pharmaceutically acceptable polymers according to the present invention as described herein,

15

and

b) particles wherein the particles comprise, preferably consist of,
20 -one or more pharmaceutically active ingredients and optionally
-one or more pharmaceutically acceptable excipients,
wherein said particles are non-encapsulated particles, wherein preferably the one or more pharmaceutically active ingredients are as disclosed above in connection with the encapsulated particles, and the one or more pharmaceutically acceptable
25 excipients are as disclosed above in connection with the encapsulated particle and
preferably wherein the particles comprise, more preferably consist of, one or more pharmaceutically active ingredients.

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Hence, preferably the present invention is directed to said mixture wherein the one or more
30 pharmaceutically active ingredients comprised in the particles of a) and b) is one or more anti-HCV agents, wherein preferably the one or more anti-HCV agents comprises, more preferably is sofosbuvir.

30

Hence, preferably the present invention is directed to said mixture wherein the one or more
35 pharmaceutically active ingredients comprised in the particles of a) and b) is one or more

35

anticoagulant agents, wherein preferably the one or more anticoagulant agents comprises, more preferably is Betrixaban or Betrixaban maleate.

Hence, preferably the present invention is directed to said mixture wherein the one or more pharmaceutically acceptable excipients comprised in the particles of a) and b) is a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises, preferably is silica, wherein the silica is preferably precipitated silica.

Hence, preferably the present invention is directed to said mixture wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers comprised in the encapsulated particles of a) is one or more enteric polymers (pH-dependent polymers) or one or more time-dependent release polymers (diffusion controlled release polymers).

Hence, preferably the present invention is directed to said mixture wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers comprised in the encapsulated particles of a) is one or more of hydroxy-propyl-methyl-cellulose-acetate-succinate or a methacrylate copolymer.

Hence, preferably the present invention is directed to said mixture wherein the weight ratio of the encapsulated particles of a) relative to the particles of b) is in the range of from 9:1 to 1:9, preferably from 5:1 to 2:1.

The particles of b) can be prepared with any suitable method known in the art. For example the particles of b) can be prepared by spray-drying a mixture comprising the one or more pharmaceutically active ingredients and one or more solvents and optionally one or more pharmaceutically acceptable excipients. In this context, the mixture does not comprise the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers according to the invention.

Process for preparing the encapsulated particles

The present invention further relates to a process for preparing the encapsulated particles wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein the particles are encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers according to the present invention as described herein. The process comprises

- i) preparing a mixture comprising the one or more pharmaceutically active ingredients and a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers, one or more solvents and optionally one or more pharmaceutically acceptable excipients;
- 5 ii) spray encapsulating the mixture of i) and obtaining the encapsulated particles.

With regard to the one or more pharmaceutically active ingredients, it is as disclosed above in the paragraph “Pharmaceutically active ingredients”.

10 With regard to the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers, they are as disclosed above in the paragraph “Pharmaceutically acceptable polymers”.

As mentioned above the encapsulated particles may further comprise one or more
15 pharmaceutically acceptable excipients. Therefore, the present invention is further directed to a process as disclosed herein wherein the mixture of i) further comprises one or more pharmaceutically acceptable excipients. With regard to one or more pharmaceutically acceptable excipients it is as disclosed above in the paragraph “Pharmaceutically acceptable excipients”.

20 In general it has been found that by spray-drying a mixture wherein the active ingredient and the polymer are dissolved in solution, encapsulated particles are obtained wherein the active ingredient is in the form of particles encapsulated with said polymer. Hence, in the process as disclosed herein preferably, the one or more pharmaceutically active ingredients and the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers are
25 dissolved in the mixture of i).

In general it has been seen that excipients can be added and are incorporated in the particles. In this case, the starting mixture of i) can be a suspension. It is however preferred that in the suspension the one or more pharmaceutically active ingredients and the pharmaceutically
30 acceptable polymer or the mixture of pharmaceutically acceptable polymers are dissolved.

Generally, there is no specific restriction as to the one or more solvents of i). As explained above it is preferred that both the one or more pharmaceutically active ingredients and the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers are
35 soluble in said solvent so that they are dissolved in said solvent(s). For example, most of the Eudragit polymers are soluble in acetone, some of them are soluble in water or ethanol. For

example, HPMCA is soluble in acetone and water or mixture thereof. Optionally, the one or more excipients may also be soluble or insoluble in said one or more solvents. For example, silica, one of the most preferred excipients according to the invention, is not soluble in the mixture water and acetone, yet the encapsulated particles according to the invention are obtained.

5

The one or more solvents should also be a solvent suitable for spray-drying.

Hence, generally there is no restriction to the one or more solvents of i) provided that the above conditions are met. Preferably, the one or more solvents according to i) is a polar solvent. More preferably the one or more solvents is one or more of a ketone, water, and an alcohol. Preferably the ketone is acetone. Preferably, the alcohol is one or more of methanol, ethanol, isopropyl alcohol, n-butanol. More preferably, the one or more solvents comprises, more preferably is acetone or a mixture of water and acetone.

15 With regard to the viscosity of the mixture of i), there is no specific restriction provided that the encapsulating spray drying can be carried out.

With regard to the amount of the one or more pharmaceutically active ingredients, preferably from 10 to 30 weight-%, more preferably from 15 to 25 weight-% of the mixture of i) consists of the one or more pharmaceutically active ingredients based on the total weight of the mixture based on the total weight of the mixture of i).

Hence, the present invention is further directed to a process as disclosed herein wherein, preferably from 10 to 30 weight-%, more preferably from 15 to 25 weight-% of the mixture of i) consists of one or more anti-HCV agents, wherein preferably the one or more anti-HCV agent comprises, more preferably is sofosbuvir, based on the total weight of the mixture of (i).

Hence, the present invention is further directed to a process, as disclosed herein, wherein, preferably from 10 to 30 weight-%, more preferably from 15 to 25 weight-% of the mixture of i) consists of one or more anticoagulant agents, wherein preferably the one or more anticoagulant agent comprises, more preferably is Betrixaban or Betrixaban maleate, wherein the weight-% values are based on the total weight of the mixture of (i) .

With regard to the amount of the pharmaceutically acceptable polymer or of the mixture of pharmaceutically acceptable polymers preferably from 0.001 to 20 weight-%, preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the

pharmaceutically acceptable polymers or a mixture of pharmaceutically acceptable polymers, based on the total weight of the mixture of (i) .

Hence, the present invention is further directed to a process, as disclosed herein, wherein preferably from 0.001 to 20 weight-%, more preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically acceptable polymer is one or more of an enteric polymer and wherein preferably the enteric polymers is one or more of

-natural film former,

-cellulose acetate phthalate

-polyvinyl acetate phthalate

-hydroxypropyl methylcellulose phthalate

-hydroxyl-propyl-methylcellulose-acetate-succinate

-methacrylic acid copolymers wherein the methacrylic acid copolymers are preferably

wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers.

Preferably, the one or more pharmaceutically acceptable enteric polymers is one or more of hydroxyl-propyl-methylcellulose-acetate-succinate or methacrylic acid copolymers.

Hence, the present invention is further directed to a process, as disclosed herein, wherein preferably from 0.001 to 20 weight-%, more preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically acceptable polymer is one or more of time-dependent release polymers, wherein the one or more time dependent release polymers is preferably one or more of

-polyvinylacetate (PVA)

-ethyl cellulose (EC)

-cellulose acetate-butyrate

-cellulose acetate

-type A and type B ammonio-methacrylate copolymers

-Ethylacrylate-methylmethacrylate-copolymers 2:1 (EA-MMA 2:1)

-Hydroxyethylcellulose (HEC).

The weight-% values are based on the total weight of the mixture of i).

With regard to the amount of the one or more pharmaceutically acceptable excipients in the mixture of i) preferably from 2 to 20 weight-%, more preferably from 3 to 7 weight-% of the mixture of i) consists of the one or more pharmaceutically acceptable excipients, in each case
5 based on the total weight of the mixture of i). Preferably, the one or more pharmaceutically acceptable excipients comprise, more preferably is a silicon-based inorganic adsorbent wherein preferably the silicon-based inorganic adsorbent comprises, more preferably is silica, wherein preferably the silica comprises, more preferably is precipitated silica.

10 Hence, the present invention is further directed to a process as disclosed herein wherein,

from 10 to 30 weight-%, preferably from 15 to 25 weight-% of the mixture of i) consists of one or more anti-HCV agents, wherein preferably the one or more anti-HCV agent comprises, more preferably is sofosbuvir;

15 from 0.001 to 20 weight-%, preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers ; and optionally

20 from 2 to 20 weight-%, preferably from 3 to 7 weight-% of the mixture of i) consists of the one or more pharmaceutically acceptable excipients, wherein preferably, the one or more pharmaceutically acceptable excipients comprise, more preferably is, a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises, more preferably is, silica, wherein preferably the silica comprises, more preferably is,
25 precipitated silica.

In each case, the weight-% values are based on the total weight of the mixture of i).

Hence, the present invention is further directed to a process as disclosed herein wherein,

30 -from 10 to 30 weight-%, preferably from 15 to 25 weight-% of the mixture of i) consists of one or more anti-HCV agents, wherein preferably the one or more anti-HCV agents comprises, more preferably is sofosbuvir;

35 -from 0.001 to 20 weight-%, preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or

of the mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically acceptable polymer is one or more of an enteric polymer and wherein, preferably, the enteric polymers is one or more of

-natural film former,

-cellulose acetate phthalate

-polyvinyl acetate phthalate

-hydroxypropyl methylcellulose phthalate

-hydroxyl-propyl-methylcellulose-acetate-succinate

-methacrylic acid copolymers wherein the methacrylic acid copolymers preferably are diethylaminoethyl-methacrylate-methyl-methacrylate-copolymers (DEAEMA-MMA 3:7) or methylacrylacid-methylmethacrylate-copolymer 1:1 (MA-MM 1:1) or methacrylacid-methylmethacrylate-copolymer 1:2 (MA-MM 1:2=PMMA 1:2)

and optionally

-from 2 to 20 weight-%, preferably from 3 to 7 weight-% of the mixture of i) consists of the one or more pharmaceutically acceptable excipients, wherein preferably, the one or more pharmaceutically acceptable excipients comprise, more preferably is a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises, more preferably is silica, wherein preferably the silica comprises, more preferably is precipitated silica.

Preferably, the one or more pharmaceutically acceptable enteric polymers is one or more of hydroxyl-propyl-methylcellulose-acetate-succinate or methacrylic acid copolymers.

In each case, the weight-% values are based on the total weight of the mixture of i).

Hence, the present invention is further directed to a process, as disclosed herein, wherein,

from 10 to 30 weight-%, preferably from 15 to 25 weight-% of the mixture of i) consists of one or more anti-HCV agents, wherein preferably the one or more anti-HCV agent comprises, more preferably is sofosbuvir and

from 0.001 to 20 weight-%, preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or of the mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically

acceptable polymer is one or more of time-dependent release polymers, wherein the one or more of time-dependent release polymers preferably is one or more of

-ethyl cellulose (EC)

-cellulose acetate-butyrate

-cellulose acetate

-type A and type B ammonio-methacrylate copolymers such as Trimethylammoniummethacrylate-chlorid-Ethylacrylate-Methylmethacrylate (TAMCL-EA-MMA)

-Ethylacrylate-methylmethacrylate-copolymers 2:1 (EA-MMA 2:1)

-Hydroxyethylcellulose (HEC)

and optionally

-from 2 to 20 weight-%, preferably from 3 to 7 weight-% of the mixture of i) consists of the one or more pharmaceutically acceptable excipients, wherein, preferably, the one or more pharmaceutically acceptable excipients comprises, more preferably is, a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises, more preferably is silica, wherein preferably the silica comprises, more preferably is, precipitated silica.

In each case, the weight-% values are based on the total weight of the mixture of i).

Hence, the present invention is further directed to a process as disclosed herein wherein,

-from 10 to 30 weight-%, preferably from 15 to 25 weight-% of the mixture of i) consists of one or more anticoagulant agents, wherein preferably the one or more anticoagulant agents comprises, more preferably is Betrixaban or Betrixaban maleate;

-from 0.001 to 20 weight-%, preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers; and optionally

-from 2 to 20 weight-%, preferably from 3 to 7 weight-% of the mixture of i) consists of the one or more pharmaceutically acceptable excipients, wherein preferably, the one or more pharmaceutically acceptable excipients comprise, more preferably is a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises,

more preferably is silica, wherein preferably the silica comprises, more preferably is, precipitated silica. In each case, the weight-% values are based on the total weight of the mixture of i).

5 Hence, the present invention is further directed to a process as disclosed herein wherein,

-from 10 to 30 weight-%, more preferably from 15 to 25 weight-% of the mixture of i) consists of one or more anticoagulant agents, wherein preferably the one or more anticoagulant agents comprises, more preferably is Betrixaban or Betrixaban maleate;

10 -from 0.001 to 20 weight-%, preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or of the mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically acceptable polymer is one or more of an enteric polymer and wherein preferably the enteric polymers is one or more

15 -natural film former,

-cellulose acetate phthalate

-polyvinyl acetate phthalate

-hydroxypropyl methylcellulose phthalate

20 -hydroxyl-propyl-methylcellulose-acetate-succinate

-methacrylic acid copolymers wherein the methacrylic acid copolymers preferably are diethylaminoethyl-methacrylate-methyl-methacrylate-copolymers (DEAEMA-MMA 3:7) or methylacrylacid-methylmethacrylate-copolymer 1:1 (MA-MM 1:1) or methacrylacid-methylmethacrylate-copolymer 1:2 (MA-MM 1:2=PMMA 1:2).

25 and optionally

-from 2 to 20 weight-%, preferably from 3 to 7 weight-% of the mixture of i) consists of the one or more pharmaceutically acceptable excipients, wherein preferably the one or more pharmaceutically acceptable excipients comprises, more preferably is a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises, more preferably is silica, wherein preferably the silica comprises, more preferably is precipitated silica.

35 Preferably, the one or more pharmaceutically acceptable enteric polymers is one or more of hydroxyl-propyl-methylcellulose-acetate-succinate or methacrylic acid copolymers.

In each case, the weight-% values are based on the total weight of the mixture of i).

Hence, the present invention is further directed to a process as disclosed herein wherein,

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-from 10 to 30 weight-%, preferably from 15 to 25 weight-% of the mixture of i) consists of one or more anticoagulant agents, wherein preferably the one or more anticoagulant agents comprises, more preferably is Betrixaban or Betrixaban maleate; and

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-from 0.001 to 20 weight-%, preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or of the mixture of pharmaceutically acceptable polymers, wherein the pharmaceutically acceptable polymer is one or more of time-dependent release polymers, wherein the one or more of time-dependent release polymers preferably is one or more of

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-polyvinylacetate (PVA)

-ethyl cellulose (EC)

-cellulose acetate-butyrate

-cellulose acetate

-type A and type B ammonio-methacrylate copolymers (TAMCL-EA-MMA)

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-Ethylacrylate-methylmethacrylate-copolymers 2:1 (EA-MMA 2:1)

-Hydroxyethylcellulose (HEC);

and optionally

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-from 2 to 20 weight-%, preferably from 3 to 7 weight-% of the mixture of i) consists of the one or more pharmaceutically acceptable excipients, wherein preferably, the one or more pharmaceutically acceptable excipients comprise, more preferably is a silicon-based inorganic adsorbent, wherein preferably the silicon-based inorganic adsorbent comprises, more preferably is silica, wherein preferably the silica comprises, more preferably is precipitated silica. In each case, the weight-% values are based on the total weight of the mixture of i).

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Step ii)

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The spray-encapsulating of ii) is preferably a spray-drying process. With regard to the conditions of the spray-encapsulating there is no specific restriction provided that the encapsulated particles of the invention are obtained.

Preferably, spray encapsulating comprises, preferably consists of spray-drying. Preferably, the spray drying is carried out with a spray drying nozzle or a rotary atomizer, more preferably with a spray drying nozzle.

5

With regard to the temperature of the spray of ii), there is no specific restriction provided that the components of the mixture of i) can withstand the temperature of the process. Preferably, the spray is carried out at an inlet temperature in the range of from 40 to 200 °C, more preferably in the range of from 50 to 70 °C.

10

With regard to the pressure of the spray of ii), there is no specific restriction provided that the encapsulated particles are obtained. Preferably, the spray is carried out at a pressure in the range of from 0.001 to 0.01 bar(abs), more preferably in the range of from 0.04 to 0.06 bar(abs). The pressure and the nozzle used are interrelated parameters. It is within the knowledge of the skilled person to adjust accordingly these parameters.

15

Therefore, the present invention is directed to encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers as disclosed herein, wherein the encapsulated particles are obtained or are obtainable by a process as disclosed herein.

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Therefore, the present invention is directed to encapsulated particles obtainable or obtained by spray drying.

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Therefore, the present invention is directed to encapsulated particles obtainable or obtained by a process as disclosed herein above

Therefore, the present invention is directed to the encapsulated particles as disclosed herein for use as a medicament.

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Therefore, the present invention is directed to the encapsulated particles as disclosed herein comprising an anti-HCV agent for use in the treatment of Hepatitis C. Preferably, the anti-HCV agent comprises, more preferably is sofosbuvir.

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Therefore, the present invention is directed to the encapsulated particles as disclosed herein comprising an anticoagulant agent for use in an anticoagulant therapy. Preferably, the anticoagulant agent comprises, more preferably is Betrixaban or Betrixaban maleate.

5 *Pharmaceutical dosage form*

The encapsulated particles or the mixture of particles of the invention may be further processed to a pharmaceutical dosage form. Preferably, the pharmaceutical dosage form of the present invention is an oral dosage form, including, but not being restricted to, a granule, a capsule, for example a capsule filled with granules, a sachet, a pellet, a dragee, a lozenge, a troche, a pastille,
10 or a tablet, such as an uncoated tablet, a coated tablet, an effervescent tablet, a soluble tablet, a dispersible tablet, an orodispersible tablet, a tablet for use in the mouth, a chewable tablet or an extrudate. More preferably, the oral dosage form of the present invention is a tablet.

Dosage forms according to the invention comprise the encapsulated particles of the invention or
15 the mixture of encapsulated and non-encapsulated particles as described herein above and one or more pharmaceutically acceptable excipients, wherein the one or more pharmaceutically acceptable excipients are extra-encapsulated-particle and extra-particles excipients. Herein below the term “extra-(encapsulate) particle pharmaceutically acceptable excipients” refers to the excipients of the dosage form that do not form the encapsulated particles or the non-encapsulated
20 particles.

Generally, there is no specific restriction as to the one or more extra-(encapsulated) particle pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients are known in the art. The one or more pharmaceutically acceptable excipients is one or more of diluent, a
25 disintegrant, a glidant, a lubricant and a binder.

a) Diluent

Regarding the diluent, it is preferably one or more of calcium carbonate, dicalcium phosphate, dry starch, calcium sulfate, cellulose, compressible sugars, confectioner's sugar, dextrates,
30 dextrin, dextrose, dibasic calcium phosphate dihydrate, glyceryl palmitostearate, hydrogenated vegetable oil, inositol, kaolin, lactose, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, powdered sugar, pregelatinized starch, sodium chloride, sorbitol, starch, sugar spheres, talc, tribasic calcium phosphate.

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b) Disintegrant

Regarding the disintegrant, it is preferably one or more of agar, alginic acid, bentonite, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, carboxymethylcellulose, cellulose, a cation exchange resin, gums, colloidal silicon dioxide, corn starch, croscarmellose sodium, crospovidone, guar gum, hydrous aluminum silicate, an ion exchange resin such as polacrilin potassium, magnesium aluminum silicate, microcrystalline cellulose, modified cellulose gum, modified corn starch, montmorillonite clay, natural sponge, polacrilin potassium, potato starch, powdered cellulose, povidone, pregelatinized starch, sodium alginate, sodium bicarbonate optionally in admixture with one or more acidulants, sodium starch glycolate, starch, silicates. Silicon dioxide and silica are used interchangeably in the context of the invention.

c) Glidant

Regarding the glidant, it is preferably one or more of colloidal silicon dioxide, talc, starch, starch derivatives. More preferably, the glidant is colloidal silicon dioxide.

d) Lubricant

Regarding the lubricant, it is preferably one or more of calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycerol behenate, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate.

More preferably, the lubricant is magnesium stearate.

e) Binder

Regarding the binder, it is one or more of saccharides such as disaccharides, sugars alcohols, polyvinylpyrrolidone, copovidone and polyethylene glycol.

More preferably, the binder is one or more of polyvinylpyrrolidone, copovidone and polyethylene glycol.

The present invention is further illustrated by the following embodiments and combinations of embodiments as indicated by the respective dependencies and back-references. In particular, it is noted that in each instance where reference is made to more than two embodiments, for example in the context of a term such as "The encapsulated particles of any one of embodiments 1 to 4", every embodiment in this range is meant to be explicitly disclosed, i.e. the wording of this term is to be understood as being synonymous to "The encapsulated particles of any one of embodiments 1, 2, 3, and 4".

The encapsulated particles

1. Encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers.
2. The encapsulated particles of embodiment 1, wherein the one or more pharmaceutically active ingredients is one or more anti-HCV agents or one or more anticoagulant agents or one or more antihypertension agents or one or more anti-inflammatory agents or one or more antibiotics or one or more anti-cancer agents or one or more hormonal therapy agents or one or more weight loss agents or one or more anti-insomnia agents or combination thereof, preferably the one or more pharmaceutically active ingredients is one or more anti-HCV agents or one or more anticoagulant agents.
3. The encapsulated particles of embodiment 1 or 2, wherein the one or more pharmaceutically active ingredients is one or more anti-HCV agents, wherein the one or more anti-HCV agents is one or more of sofosbuvir, daclatasvir, ledipasvir, ravidasvir, pibrentasvir, glecaprevir, paritaprevir, ombitasvir, dasabuvir, velpatasvir, grazoprevir, elbasvir, interferon, more preferably the anti-HCV agent is sofosbuvir.
4. The encapsulated particles of embodiment 1 or 2, wherein the one or more pharmaceutically active ingredients is one or more anticoagulant agents, wherein preferably the one or more anticoagulant agents is Betrixaban or Betrixaban maleate.
5. The encapsulated particles of any one embodiments 1 to 4, wherein the one or more pharmaceutically active ingredients is crystalline or amorphous, preferably amorphous.
6. The encapsulated particles of any one of embodiments 1 to 3 and 5, wherein the one or more anti-HCV agents is sofosbuvir in an amorphous form.
7. The encapsulated particles of any one of embodiments 1 to 6, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-% of the one or more pharmaceutically active ingredients comprised in the particles of the encapsulated particles is in amorphous form.

8. The encapsulated particles of any one of embodiments 1 to 3 and 5 to 7, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-% of the one or more anti-HCV agents comprised in particles of the encapsulated particles is in amorphous form, wherein the one or more anti-HCV agents comprises, preferably is, sofosbuvir.
9. The encapsulated particles of any one of embodiments 1 to 8, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles (particles plus shell) consists of the one or more pharmaceutically active ingredients and of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers, based on the total weight of the encapsulated particles.
10. The encapsulated particles of any one of embodiments 1 to 3 and 5 to 9, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles consists of the one or more anti-HCV agents and of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles and wherein preferably the anti-HCV agent comprises, more preferably is sofosbuvir.
11. The encapsulated particles of any one of embodiments 1, 2, 4, 5, 7 and 9, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles consists of the one or more anticoagulant agents and of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles and wherein preferably the one or more anticoagulant agents comprises, more preferably is Betrixaban or Betrixaban maleate.
12. The encapsulated particles of any one of embodiments 1 to 11, wherein the particles further comprise one or more pharmaceutically acceptable excipients, wherein preferably the one or more pharmaceutically acceptable excipients is not the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers as disclosed in any one of embodiments 27 to 34.

13. The encapsulated particles of any one of embodiments 1 to 12, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles (i.e. particle and shell) consists of the one or more pharmaceutically active ingredients, of the one or more pharmaceutically acceptable excipients and of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles.
14. The encapsulated particles of any one of embodiments 1 to 3 and 5 to 10, 12, 13, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles consists of the one or more anti-HCV agents, of the one or more pharmaceutically acceptable excipients and of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles and wherein preferably the one or more anti-HCV agents comprises, more preferably is sofosbuvir.
15. The encapsulated particles of any one of embodiments 1, 2, 4, 5, 7 and 9, 11, 12, 13, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles consists of the one or more anticoagulant agents, of the one or more pharmaceutically acceptable excipients and of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles and wherein preferably the one or more anticoagulant agents comprises, more preferably is Betrixaban or Betrixaban maleate, wherein in each case the weight-% is based on the total weight of the encapsulated particles.
16. The encapsulated particles of any one of embodiments 1 to 15, wherein at least 50 weight-%, preferably from 55 to 99.5 weight-%, more preferably from 55 to 70 weight-% of the encapsulated particles consists of the one or more pharmaceutical active ingredients based on the total weight of the encapsulated particles wherein in each case the weight-% is based on the total weight of the encapsulated particles.
17. The encapsulated particles of any one of embodiments 1 to 3 and 5 to 10, 12, 13, 14, 16 wherein at least 50 weight-%, preferably from 55 to 99.5 weight-%, more preferably from 55 to 70 weight-% of the encapsulated particles consists of the one or more pharmaceutical active ingredients, wherein the one or more pharmaceutically active ingredients is one or

more anti-HCV agents, wherein preferably the one or more anti-HCV agents comprises, more preferably is sofosbuvir, wherein in each case the weight-% is based on the total weight of the encapsulated particles.

- 5 18. The encapsulated particles of any one of embodiments 1, 2, 4, 5, 7 and 9, 11, 12, 13, 15, 16, wherein at least 50 weight-%, preferably from 55 to 99.5 weight-%, more preferably from 55 to 70 weight-% of the encapsulated particles consists of the pharmaceutical active ingredients, wherein the one or more pharmaceutically active ingredients is one or more anticoagulant agents wherein preferably the one or more anticoagulant agents comprises,
10 more preferably is Betrixaban or Betrixaban maleate, wherein in each case the weight-% is based on the total weight of the encapsulated particles.
- 15 19. The encapsulated particles of any one of embodiments 1 to 18, wherein from 0.5 to 50 weight-%, or from 0.5 to 15 weight-%, or from 25 to 35 weight-%, or from 28 to 33 weight-% of the encapsulated particles consists in the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers.
- 20 20. The encapsulated particles of any one of embodiments 1 to 19, wherein each of the particles is partially encapsulated with the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers.
- 25 21. The encapsulated particles of any one of embodiments 1 to 20, wherein at least the 50%, preferably from 60 to 90%, more preferably from 70 to 80% of the surface area of the partially encapsulated particles is encapsulated in the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers.
- 30 22. The encapsulated particles of any one of embodiments 1 to 21, wherein the encapsulated particles comprise, preferably consist of completely and partially encapsulated particles, wherein at least 50% preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90% of the encapsulated particles are completely encapsulated, wherein the percentage values are based on the total amount of (completely and partially) encapsulated particles.
- 35 23. The encapsulated particles of any one of embodiments 1 to 22, wherein the encapsulated particles comprise, preferably consist of completely and partially encapsulated particles wherein at least 50% preferably at least 60%, more preferably at least 70%, more preferably

at least 80%, more preferably at least 90% of the encapsulated particles are partially encapsulated, wherein the percentage values are based on the total amount of (completely and partially) encapsulated particles.

24. The encapsulated particles of any one of embodiments 1 to 23, wherein the median particle size distribution value (D50) of the encapsulated particles is of at least 1 μm , more preferably the D50 value is in the range of from 10 to 300 μm or in the range of from 10 to 200 μm , more preferably in the range of from 15 to 100 μm or in the range of 15 to 35 μm , wherein the D50 value is measured according to the method disclosed in Reference Example 1.1.

25. The encapsulated particles of any one of embodiments 1 to 24, wherein the encapsulated particles have a bulk density in the range of 0.15 to 1.00 g/ml, preferably in the range of 0.20 to 0.25 g/ml, wherein the bulk density is measured according to the method disclosed in Reference Example 1.3.

26. The encapsulated particles of any one of embodiments 1 to 25, wherein less than 5 weight-% or from 0.00 to 4.9 weight-% or from 0.2 to 3.5 weight-% of the encapsulated particles consists of water, based on the total weight of the encapsulated particles.

Pharmaceutically acceptable polymers

27. The encapsulated particles of any one of embodiments 1 to 26, wherein the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers is one or more enteric polymers (pH-dependent polymers).

28. The encapsulated particles of any one of embodiments 1 to 26, wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is one or more time-dependent release polymers (diffusion controlled release polymers).

29. The encapsulated particles of any one of embodiments 1 to 28, wherein the mixture of pharmaceutically acceptable polymers is a combination of one or more enteric polymers (pH-dependent polymers) and one or more time-dependent release polymers (diffusion controlled release polymers).

30. The encapsulated particles of embodiment 27 or 29, wherein the one or more of the enteric polymers is one or more of
- natural film former,
 - cellulose acetate phthalate
 - 5 -polyvinyl acetate phthalate
 - hydroxypropyl methylcellulose phthalate
 - hydroxyl-propyl-methylcellulose-acetate-succinate
 - methacrylic acid copolymers wherein the methacrylic acid copolymers are preferably diethylaminoethyl-methacrylate-methyl-methacrylate-copolymers (DEAEMA-MMA 3:7) or methylacrylacid-methylmethacrylate-copolymer 1:1 (MA-MM 1:1) or methacrylacid-methylmethacrylate-copolymer 1:2 (MA-MM 1:2=PMMA 1:2).
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31. The encapsulated particles of any embodiment 27 or 29 or 30, wherein the one or more enteric polymers is one or more of hydroxyl-propyl-methylcellulose-acetate-succinate or methacrylic acid copolymers.
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32. The encapsulated particles of embodiment 28, wherein the one or more time-dependent release polymers is one or more of
- 20 -polyvinylacetate (PVA)
 - ethyl cellulose (EC)
 - cellulose acetate-butyrate
 - cellulose acetate
 - type A and type B ammonio-methacrylate copolymers
 - 25 -Ethylacrylate-methylmethacrylate-copolymers 2:1 (EA-MMA 2:1)
 - Hydroxyethylcellulose (HEC).
33. The encapsulated particles of any one of embodiments 28, 29 or 32 , wherein the one or more time-dependent release polymers is one or more of ethylacrylate-methyl-methacrylate-copolymer 2:1, Trimethylammoniummethylmethacrylate-chlorid-ethylacrylate-methylmethacrylate, hydroxyethylcellulose, ethylcellulose and polyvinyl acetate.
- 30
34. The encapsulated particles of any one of embodiments 1 to 33, wherein the weight ratio of the one or more pharmaceutically active ingredients relative to the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is in the range
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of from 1 : 1 to 200 : 1, preferably in the range of from 1.5 : 1 to 50 : 1, more preferably in the range of from 1.5: 1 to 20: 1, more preferably in the range of from 1.6:1 to 2.5 : 1.

Pharmaceutically acceptable excipients

- 5 35. The encapsulated particles of any one of embodiments 1 to 34, wherein the one or more pharmaceutically acceptable excipients comprises one or more silicon-based inorganic adsorbents.
- 10 36. The encapsulated particles of any one of embodiments 1 to 35, wherein the one or more pharmaceutically acceptable excipients consists of at least one silicon-based inorganic adsorbent.
- 15 37. The encapsulated particles of embodiment 35 or 36, wherein the one or more silicon-based inorganic adsorbent is one or more of silica, silicates and a combination of two or more thereof, wherein the silica is preferably one or more of fumed silica, precipitated silica, gel silica, colloidal silica and a combination of two or more thereof, and wherein the silicates are preferably aluminosilicates, preferably comprising at least one alkali metal element and/or at least one alkaline earth metal element, more preferably at least one alkaline earth metal element, more preferably magnesium, wherein more preferably, at least 90 weight-%, more preferably at least 95 weight-%, more preferably at least 99 weight-% of the at least one silicon-based inorganic adsorbent is present in amorphous form.
- 20 38. The encapsulated particles of any one of embodiments 35 to 37, wherein at least one silicon-based inorganic adsorbent has a pH in the range of from 6.0 to 9.0, preferably in the range of from 6.5 to 8.5, more preferably in the range of from 7.0 to 8.0.
- 25 39. The encapsulated particles of any one of embodiments 1 to 38, wherein from 1 to 20 weight-%, preferably from 10 to 15 weight-% of the encapsulated particles consists of the one or more pharmaceutically acceptable excipients wherein the weight-% value are based on the total weight of the encapsulated particles.
- 30 40. The encapsulated particles of any one of embodiments 1 to 39, wherein the one or more pharmaceutically acceptable excipients comprises, more preferably consists of a silicon-based inorganic adsorbent, wherein the silicon-based inorganic adsorbent preferably comprises, more preferably consists of silica, wherein preferably the silica comprises, more preferably is, precipitated silica.
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Process for preparing the encapsulated particles

41. A process for preparing the encapsulated particles of any one of embodiments 1 to 40 or 78 to 85, the process comprising
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- i) preparing a mixture comprising one or more pharmaceutically active ingredients, a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers, one or more solvents and optionally one or more pharmaceutically acceptable excipients;
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- ii) spray-encapsulating the mixture of i) and obtaining the encapsulated particles.
42. The process of embodiment 41, wherein the one or more pharmaceutically active ingredients is as defined in any one embodiments 2 to 4.
43. The process of embodiment 41 or 42, wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is as defined according to any one of embodiments 27 to 34.
- 15
44. The process of any one of embodiments 41 to 43, wherein the one or more solvents of i) is one or more polar solvents.
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45. The process of any one of embodiments 41 to 44, wherein the one or more solvents of i) is one or more of a ketone, water and an alcohol wherein preferably the alcohol is one or more of methanol, ethanol, isopropyl alcohol, n-butanol, wherein preferably the ketone is acetone.
- 25
46. The process of any one of embodiments 41 to 45, wherein the one or more solvents of i) is acetone or a mixture of acetone and water.
47. The process of any one embodiment 41 to 46, wherein the mixture of i) further comprises one or more pharmaceutically acceptable excipients as defined in any one of embodiments 35 to 40.
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48. The process of any one of embodiments 41 to 47, wherein from 10 to 30 weight-%, preferably from 15 to 25 weight-% of the mixture of i) consists of the one or more pharmaceutically active ingredients based on the total weight of the mixture.
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49. The process of any one of embodiments 41 to 48, wherein from 10 to 30 weight-%, preferably from 15 to 25 weight-% of the mixture of i) consists of the one or more pharmaceutically active ingredients, wherein the one or more pharmaceutically active ingredients is one or more anti-HCV agents, wherein the one or more anti-HCV agents comprises, preferably is sofosbuvir, wherein the weight-% value are based on the total weight of the mixture.
50. The process of any one of embodiments 41 to 48 wherein from 10 to 30 weight-%, preferably from 15 to 25 weight-% of the mixture of i) consists of the one or more pharmaceutically active ingredients, wherein the one or more pharmaceutically active ingredients is one or more anticoagulant agents, wherein the one or more anticoagulant agents comprises, preferably is Betrixaban or Betrixaban maleate, wherein the weight-% value are based on the total weight of the mixture.
51. The process of any one of embodiments 41 to 50, wherein from 0.001 to 20 weight-%, preferably from 0.01 to 15 weight-%, more preferably from 7 to 12 weight-% of the mixture of i) consists of the pharmaceutically acceptable polymer or of the mixture of pharmaceutically acceptable polymers, wherein the weight-% values are based on the total weight of the mixture.
52. The process of any one of embodiments 41 to 51, wherein from 2 to 20 weight-%, preferably from 3 to 7 weight-% of the mixture of i) consists of the one or more pharmaceutically acceptable excipients, based on the total weight of the mixture, wherein the one or more pharmaceutically acceptable excipients comprises, preferably consists of one or more silicon-based inorganic adsorbents, wherein preferably the silicon-based inorganic adsorbent comprises, more preferably is silica, wherein preferably the silica comprises, more preferably is precipitated silica.
53. The process of any one embodiment 41 to 52, wherein the mixture of i) is a solution or a suspension.
54. The process of any one of embodiments 41 to 53, wherein the one or more pharmaceutically active ingredients and the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers are dissolved, preferably completely dissolved in the mixture of i).

55. The process of any one of embodiments 41 to 54, wherein the spray-encapsulating preferably comprises, more preferably is spray drying, and wherein the spray-encapsulating is carried out with a spray-drying nozzle or a rotary atomizer, preferably a spray-drying nozzle.

56. The process of any one of embodiments 41 to 55, wherein the spray-encapsulating, preferably the spray drying, is carried out at an inlet temperature in the range of from 40 to 100 °C, preferably in the range of from 50 to 70 °C.

57. The process of any one of embodiment 41 to 56, wherein the spray-encapsulating, preferably the spray drying, is carried out at a pressure in the range of from 0.001 to 0.01 bar(abs), preferably in the range of from 0.04 to 0.06 bar(abs).

58. The encapsulated particles of any one of embodiments 1 to 40, obtained or obtainable by a process according to any one of embodiments 41 to 57.

59. Encapsulated particles according to any one of embodiments 1 to 40 and 58, and for use as a medicament.

60. Encapsulated particles according to any one of embodiments 1 to 3, 5 to 10, 12 to 14, 16 to 17, 19 to 40, 58, 78 to 85 for use in the treatment of Hepatitis C wherein the particles comprise one or more anti-HCV-agents, wherein preferably the one or more anti-HCV-agents comprises, more preferably consists of sofosbuvir.

61. Encapsulated particles according to any one of embodiments 1 to 2, 4 to 5, 7, 9, 11 to 13, 15 to 40, 58, 78 to 85 for use in an anticoagulant therapy, wherein the particles comprise one or more anticoagulant agents, wherein preferably the one or more anticoagulant agents comprises, more preferably is Betrixaban or Betrixaban maleate.

62. A mixture comprising

a) the encapsulated particles according to any one of embodiments 1 to 40, 58 to 61, 74 to 85

and

b) particles wherein the particles comprise, preferably consist of, one or more pharmaceutically active ingredients and optionally

one or more pharmaceutically acceptable excipients,
wherein said particles are non-encapsulated particles, wherein preferably the one
or more pharmaceutically active ingredients are according to any one of
embodiments 2 to 4, and the one or more pharmaceutically acceptable excipients
are according to any one embodiments 35 to 40 and

preferably wherein the particles comprise, more preferably consist of, one
or more pharmaceutically active ingredients.

63. The mixture of embodiment 62, wherein the one or more pharmaceutically active
ingredients is one or more of an anti-HCV agent, wherein preferably the one or more of the
anti-HCV agents comprises, more preferably is sofosbuvir.

64. The mixture of embodiment 62, wherein the one or more pharmaceutically active
ingredients is one or more anticoagulant agents, wherein preferably the one or more of the
anticoagulant agents comprises, more preferably is Betrixaban or Betrixaban maleate.

65. The mixture of any one of embodiments 62 to 64, wherein the one or more
pharmaceutically acceptable excipients of a) and b) is a silicon-based inorganic adsorbent,
wherein preferably the silicon-based inorganic adsorbent comprises, more preferably is
silica, wherein preferably the silica comprises more preferably is colloidal or precipitated
silica.

66. The mixture of any one of embodiments 62 to 65, wherein the pharmaceutically acceptable
polymer or the mixture of pharmaceutically acceptable polymers is one or more of
hydroxy-propyl-methyl-cellulose-acetate-succinate or a methacrylate copolymer.

67. The mixture of any one of embodiments 62 to 66, wherein the weight ratio of the
encapsulated particles of a) relative to the particles of b) is in the range of from 9:1 to 1:9.

68. A pharmaceutical dosage form comprising the encapsulated particles according to of any
one of embodiments 1 to 40 or 58 to 61, 74 to 85 or the mixture according to any one of
embodiments 62 to 67, wherein the pharmaceutical dosage form is preferably an oral
dosage form, wherein preferably the oral dosage form is a granule, a capsule, a sachet, a
pellet, a dragee, a lozenge, a troche, a pastille, or a tablet, such as an uncoated tablet or a
coated tablet, an effervescent tablet, a soluble tablet, a dispersible tablet, an orodispersible

tablet, a tablet for use in the mouth, a chewable tablet or an extrudate, wherein more preferably, the oral dosage form is a tablet.

- 5 69. The pharmaceutical dosage form according to embodiment 68, wherein the pharmaceutical dosage form further comprises one or more extra-(encapsulated) particles pharmaceutically acceptable excipients.
- 10 70. The pharmaceutical dosage form of embodiment 69 wherein the one or more extra-(encapsulated) particles pharmaceutically acceptable excipients is one or more of a diluent, a disintegrant, a glidant, a lubricant, a binder.
- 15 71. The pharmaceutical dosage form of embodiment 69 or 70, wherein the pharmaceutical dosage form is preferably an oral dosage form, wherein preferably the oral dosage form is a granule, a capsule, a sachet, a pellet, a dragee, a lozenge, a troche, a pastille, or a tablet, such as an uncoated tablet or a coated tablet, an effervescent tablet, a soluble tablet, a dispersible tablet, an orodispersible tablet, a tablet for use in the mouth, a chewable tablet or an extrudate, more preferably, the oral dosage form is a tablet.
- 20 72. A pharmaceutical dosage form according to any one of embodiments 68 to 71 for use in the treatment of HCV.
73. A pharmaceutical dosage form according to any one of embodiments 68 to 71 for use in anticoagulant therapy.
- 25 74. The encapsulated particles of any one of embodiments 1 to 40 or 58 to 61, 78 to 85, wherein the encapsulated particles are in single-particle single-shell configuration.
- 30 75. The encapsulated particles of any one of embodiments 1 to 40 or 58 to 61 or 74, 78 to 85, wherein at least 90 weight-%, preferably at least 95 weight-%, more preferably in the range of from 95 to 99 weight-% of the one or more active ingredients is comprised in the particles of the encapsulated particles based on the total weight of the one or more active ingredients.
- 35 76. The encapsulated particles of any one of embodiments 1 to 40 or 58 to 61 or 74 to 75, 78 to 85, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-% of the one or more pharmaceutically acceptable excipients is comprised in the

particles of the encapsulated particles based on the total weight of the one or more pharmaceutically acceptable excipients.

77. The encapsulated particles of any one of embodiments 1 to 40 or 58 to 61 or 74 to 76, 78 to 85 wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-% of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers is comprised in the encapsulating moiety (shell) of the encapsulated particles based on the total weight of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers.

78. The encapsulated particles of any one of embodiments 1 to 40, 58 to 61, 74 to 77, wherein at least 85 weight-%, preferably from 90 to 99.5 weight-% of the encapsulated particles consists of the one or more pharmaceutical active ingredients and wherein the weight-% is based on the total weight of the encapsulated particles.

79. The encapsulated particles of any one of embodiments 1 to 40, 58 to 61 and 74 to 78, wherein the encapsulated particles consist of the one or more pharmaceutical active ingredients and of the pharmaceutically acceptable polymer or of a mixture of pharmaceutically acceptable polymers, wherein at least 85 weight-%, preferably from 90 to 99.5 weight-% of the encapsulated particles consists of said one or more pharmaceutical active ingredients wherein the weight-% is based on the total weight of the encapsulated particles and preferably wherein the pharmaceutically acceptable polymer is as defined in embodiments 27 to 33.

80. The encapsulated particles of any one of embodiments 1 to 40, 58 to 61, 74 to 78, wherein the encapsulated particles consists of one or more the pharmaceutical active ingredients, of pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers and of the silicon based inorganic absorbent, wherein

- from 65 to 85 weight-% of the encapsulated particles, preferably from 70 to 80 weight % of the encapsulated particles consists of the one or more pharmaceutical active ingredients;
- from 14 to 22 weight % of the encapsulated particles, preferably from 16 to 21 weight % of the encapsulated particles consists of the silicon based inorganic absorbents;
- from 0.2 to 21 weight %, preferably from 4 to 10 weight-% of the encapsulated particles, preferably from 16 to 21 weight % of the encapsulated particles consists of

the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers

preferably wherein the pharmaceutically acceptable polymer is as defined in any one of embodiments 27 to 33

preferably wherein the silicon based inorganic absorbent is as defined in any one of embodiments 38 or 40; and

wherein the weight % is based on the total weight of the encapsulated particles.

81. The encapsulated particles of any one of embodiments 78 to 80, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-% of the one or more pharmaceutically active ingredients comprised in the particles of the encapsulated particles is in amorphous form.

82. The encapsulated particles of any one of embodiments 78 to 81, wherein the one or more pharmaceutically active ingredients comprised in the particles of the encapsulated particles is sofosbuvir.

83. The encapsulated particles of any one of embodiments 78 to 81, wherein the one or more pharmaceutically active ingredients comprised in the particles of the encapsulated particles is Betrixaban or Betrixaban maleate.

84. The encapsulated particles of any one of embodiments 78 to 83 obtainable or obtained by spray drying.

85. The encapsulated particles of any one of embodiments 78 to 83 obtainable or obtained by a process as defined in any one of embodiments 41 to 57.

The invention is further illustrated by the following reference examples, examples, and comparative examples

Examples

Reference example 1: Analytical methods

Reference example 1.1: Measurement of the particle size distribution

The particle size distribution D50 is the median diameter or the medium value of the particle size distribution. It is an indication that 50% of the particles in a sample are smaller than the given D50 value.

The particle size distribution D10 is the particle diameter corresponding to 10% cumulative undersized particle size distribution. It is an indication that 10% of the particles in a sample are smaller than the given D10 value.

The particle size distribution D90 is the particle diameter corresponding to 90% cumulative undersized particle size distribution. It is an indication that 90% of the particles in a sample are smaller than the given D90 value.

According to the present invention, the D90, D50 and D10 values of the particles contained in the pharmaceutical composition were determined according to the following method:

The particle size distribution (PSD) was measured by laser diffraction using a Malvern Mastersizer 2000 equipped with a Hydro 2000 μ P cell. The measurements were performed in dodecane with the addition of 0.1% lecithin to facilitate the wetting of the dry powder material. Samples were sonicated (50%) for 30 s prior to measurement. The stirrer speed was adjusted to 2500 rpm. Data were analysed based on Fraunhofer theory (sensitivity: normal; particle shape: irregular; analysis model: general purpose).

Reference Example 1.2 XRPD characterization

XRPD analysis was performed to determine the crystalline or amorphous state of the compositions obtained according to the Examples and Comparative Examples disclosed. The X-ray powder diffraction pattern (XRPD) was obtained with a PANalytical X'Pert PRO diffractometer equipped with a theta/theta coupled goniometer in transmission geometry, programmable XYZ stage with well plate holder, Cu-K α 1.2 radiation (wavelength 0.15419 nm) with a focusing mirror and a solid state PIXcel detector. The patterns were recorded at a tube voltage of 45 kV and a tube current of 40 mA, applying a step size of 0.013 ° 2-theta with 40 s per step (255 channels) in the angular range of 2 ° to 40 ° 2-theta at ambient conditions.

Reference Example 1.3: Determination of the bulk density

Approximately 2-3 g of the powder was poured into a 25 mL measuring cylinder. The bulk density was calculated by dividing the amount of powder (in gram) by the measured volume (in millilitres).

Reference Example 1.4: Determination of stability**a) Determination of the stability (amorphous state)**

25-30 mg of a given composition prepared according to the Examples and Comparative Examples below were sealed in aluminium blisters and exposed to an atmosphere having a relative humidity of 75% and a temperature of 40 °C for a period of time as indicated in Table 1 below. The compositions, if stable and if not liquefied, were analysed via XRPD as described in Reference Example 1.3 with respect to the amorphousness.

b) Determination of the stability (degradation) (Figures 16 and 17)

25-30 mg of a given composition prepared according to the Examples and Comparative Examples below were sealed in aluminium blisters and exposed to an atmosphere having a relative humidity of 75% and a temperature of 40 °C for a period of time as indicated in Figures 16 and 17.

c) Determination of the influence on the moisture stability of different encapsulations (Figures 22 and 23)

The uncovered samples of Examples and Comparative Examples were placed in a climatic chamber at 25°C and 60% RH. SEM images (Figures 22 and 23) were taken at time point zero, after 4-5 hours storage and about 21 hours storage.

Reference Example 1.5: Dissolution test

The dissolution test was carried out on capsule comprising 200 mg of the particles of Examples of the invention or Comparative Examples. The test was performed using a USP 2 apparatus with a stirrer speed of 75 rpm (for 2 hours, followed by 20 min stirring at 250 rpm) and a test temperature of 37 °C. The test were carried out on the following dissolution media:

a) 0.1 N HCl solution (500mL)

b) phosphate buffer at pH 6.8 (500 mL)

The sampling was performed automatically in a 2 minute interval and the drug concentration was measured by UV detection at 230 nm.

Reference Example 1.6: Water determination

The water content was determined by coulometric Karl Fischer titration with a Metrohm 832 KF Thermoprep oven and a Metrohm 831 KF Coulometer using a generator electrode without diaphragm and Hydranal-Coulomat AG Oven analyte solution. The sample was heated to 110°C

in the oven and the released water transferred to the titration cell for analysis, using dry air as a carrier gas.

Comparative Example 1: Preparation of the (non-encapsulated) particles comprising amorphous sofosbuvir (100 weight-%)

119.97 g of sofosbuvir were dissolved in 480.75 g of acetone, then the solution was stirred until it was clear. The solution was spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 20%.

The resulting particles composition had a bulk density of 0.37 g/ml and a water content of 0.25 weight-%. The particles had a D50 value of 6.9 µm, a D10 value of 1.9 µm and a D90 value of 19.4 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 18). Figure 7 shows the SEM images of the obtained particles at different magnitudes.

Comparative Example 2: Preparation of (non-encapsulated) particles comprising amorphous sofosbuvir (80 weight-%) and Syloid 72 FP (20 weight-%)

119.98 g of sofosbuvir were dissolved in 450. g of acetone. The solution was stirred until it was clear, then 30.08 g of Syloid 72 FP were added to the solution. The suspension was stirred vigorously and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 30%.

The resulting particles composition has a bulk density of 0.30 g/ml and a water content of 0.38% weight-%. The particles had a D50 value of 7.2 µm, a D10 value of 2.3 µm and a D90 value of 16.9 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 18). Figure 7 shows the SEM images of the particles at different magnitudes.

Example 1: Preparation of the encapsulated particles comprising amorphous sofosbuvir (67 weight-%) and AQOAT AS-MG (33 weight-%)

A solution comprising 60.25 g of sofosbuvir, 30.20 g of AQOAT® AS-MG and 210 g of acetone was prepared and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert

loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 30%.

The resulting particles composition had a bulk density of 0.21 g/ml and a water content of 0.22 weight-%. The particles had a D50 value of 26.9 µm, a D10 value of 4.4 µm and a D90 value of 65.9 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 18). Figure 2 shows the SEM images of the particles at different magnitudes.

Example 2: Preparation of the encapsulated particles comprising amorphous sofosbuvir (57 weight-%), Syloid 72 FP (14 weight-%) and AQOAT AS-MG (29 weight-%)

A suspension comprising 60 g of sofosbuvir, 15.00 g of Syloid 72 FP, 30.03 g of AQOAT AS-MG and 197 g of acetone was prepared. The suspension was stirred vigorously and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 30%.

The resulting particles composition had a bulk density of 0.24 g/ml and a water content of 0.22 weight-%. The particles had a D50 value of 34.4 µm, a D10 value of 6.3 µm and a D90 value of 86.7 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 18). Figure 2 shows the SEM images of the particles at different magnitudes.

Example 3: Preparation of the encapsulated particles comprising amorphous sofosbuvir (67 weight-%) and Eudragit RL 100 (33 weight-%)

A solution comprising 60.02 g of sofosbuvir, 30.10 g of Eudragit RL 100 and 210.44 g of acetone was prepared and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 30%.

The resulting particles composition had a bulk density of 0.20 g/ml and a water content of 0.30 weight-%. The particles had a D50 value of 17.2 µm, a D10 value of 3.5 µm and a D90 value of 41.0 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 18). Figure 3 shows the SEM images of the particles at different magnitudes.

Example 4: Preparation of the encapsulated particles comprising amorphous sofosbuvir (57 weight-%), Syloid 72 FP (14 weight-%) and Eudragit RL 100 (29 weight-%)

A suspension comprising 60.02 g of sofosbuvir, 15.15 g of Syloid 72 FP, 30.08 g of Eudragit RL 100 and 195 g of acetone was prepared. The suspension was stirred vigorously and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 20%.

The resulting particles composition had a bulk density of 0.22 g/ml and a water content of 0.35 weight-%. The particles had a D50 value of 17.5 µm, a D10 value of 3.4 µm and a D90 value of 43.0 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 18). Figure 3 shows the SEM images of the particles at different magnitudes.

Example 5: Preparation of the encapsulated particles comprising amorphous sofosbuvir (67 weight-%) and Eudragit RS 100 (33 weight-%)

A solution comprising 59.98 g of sofosbuvir, 30.02 g of Eudragit RS 100 and 210 g of acetone was prepared and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 20%.

The resulting particles composition had a bulk density of 0.21 g/ml and a water content of 0.36 weight-%. The particles had a D50 value of 15.2 µm, a D10 value of 2.8 µm and a D90 value of 42.8 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 18). Figure 4 shows the SEM images of the particles at different magnitudes.

Example 6: Preparation of the encapsulated particles comprising amorphous sofosbuvir (57 weight-%), Syloid 72 FP (14 weight-%) and Eudragit RS 100 (29 weight-%)

A suspension comprising 60.09 g of sofosbuvir, 15.01 g of Syloid 72 FP, 29.99 g of Eudragit RS 100 and 195 g of acetone was prepared. The suspension was stirred vigorously and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 20%.

The resulting particles composition had a bulk density of 0.23 g/ml and a water content of 0.43 weight-%. The particles had a D50 value of 14.0 μm , a D10 value of 2.9 μm and a D90 value of 46.6 μm . XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 18). Figure 4 shows the SEM images of the particles at different magnitudes.

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Example 7: Preparation of the encapsulated particles comprising amorphous sofosbuvir (99.5 weight-%) and Eudragit RL 100 (0.5 weight-%)

10 A solution comprising 30.02 g of sofosbuvir, 0.16 g of Eudragit RL 100 and 149.98 g of acetone was prepared and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 20%.

15 The resulting particles composition had a bulk density of 0.28 g/mL and a water content of 0.37 weight-%. The particles had a D50 value of 5.3 μm , a D10 value of 1.8 μm and a D90 value of 12.4 μm . XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 21). Figure 5 shows the SEM images of the particles at different magnitudes.

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Example 8: Preparation of the encapsulated particles comprising amorphous sofosbuvir (95 weight-%) and Eudragit RL 100 (5 weight-%)

A solution comprising 30.01 g of sofosbuvir, 1.53 g of Eudragit RL 100 and 150.01 g of acetone was prepared and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 20%.

25 The resulting particles composition had a bulk density of 0.29 g/mL and a water content of 0.37 weight-%. The particles had a D50 value of 6.6 μm , a D10 value of 1.8 μm and a D90 value of 15.7 μm . XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 21). Figure 5 shows the SEM images of the particles at different magnitudes.

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Example 9: Preparation of the encapsulated particles comprising amorphous sofosbuvir (90 weight-%) and Eudragit RL 100 (10 weight-%)

A solution comprising 30.00 g of sofosbuvir, 3.02 g of Eudragit RL 100 and 151.47 g of acetone was prepared and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert

loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 20%.

The resulting particles composition had a bulk density of 0.28 g/mL and a water content of 0.41 weight-%. The particles had a D50 value of 6.7 µm, a D10 value of 1.9 µm and a D90 value of 15.1 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 21). Figure 5 shows the SEM images of the particles at different magnitudes.

Example 10: Preparation of the encapsulated particles comprising amorphous sofosbuvir (79.6 weight-%), Syloid 72 FP (20 weight-%) and AQOAT AS-MG (0.4 weight-%)

A solution comprising 30.07 g of sofosbuvir, 7.51 g Syloid 72 FP, 0.16 g of AQOAT AS-MG and 149.99 g of acetone was prepared. The suspension was stirred vigorously and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 30%.

The resulting particles composition had a bulk density of 0.27 g/mL and a water content of 0.47 weight-%. The particles had a D50 value of 6.5 µm, a D10 value of 2.2 µm and a D90 value of 13.3 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 21). Figure 6 shows the SEM images of the particles at different magnitudes.

Example 11: Preparation of the encapsulated particles comprising amorphous sofosbuvir (77 weight-%), Syloid 72 FP (19 weight-%) and AQOAT AS-MG (4 weight-%)

A solution comprising 30.07 g of sofosbuvir, 7.50 g Syloid 72 FP, 1.52 g of AQOAT AS-MG and 151.94 g of acetone was prepared. The suspension was stirred vigorously and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 30%.

The resulting particles composition had a bulk density of 0.29 g/mL and a water content of 0.60 weight-%. The particles had a D50 value of 7.2 µm, a D10 value of 2.3 µm and a D90 value of 14.8 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 21). Figure 6 shows the SEM images of the particles at different magnitudes.

Example 12: Preparation of the encapsulated particles comprising amorphous sofosbuvir (74 weight-%), Syloid 72 FP (18.5 weight-%) and AQOAT AS-MG (7.5 weight-%)

- 5 A solution comprising 30.00 g of sofosbuvir, 7.48 g Syloid 72 FP, 3.03 g of AQOAT AS-MG and 150.00 g of acetone was prepared. The suspension was stirred vigorously and spray dried on a Büchi B-290 mini spray dryer equipped with an B-291 inert loop at an inlet temperature of 65 °C, a pressure of 0.053 bar(abs) (40mmHg), under nitrogen at a spray rate of 30%.
- 10 The resulting particles composition had a bulk density of 0.28 g/mL and a water content of 0.65 weight-%. The particles had a D50 value of 7.9 µm, a D10 value of 2.4 µm and a D90 value of 15.9 µm. XRPD analysis showed that the sofosbuvir obtained was amorphous (Figure 21). Figure 6 shows the SEM images of the particles at different magnitudes.

15 **Example 13: Physical mixture of the particle of Example 2 and Comparative example 2**

A physical mixture of 90 weight-% of the particle of Example 2 and 10 weight-% of the particle of Comparative Example 2 was prepared.

- 20 A physical mixture of 10 weight-% of the particle of Example 2 and 90 weight-% of the particle of Comparative Example 2 was prepared.

Example 14: Stability test

- 25 The stability of sofosbuvir was tested as disclosed in the above Reference Example 1.4a) with respect to the amorphousness. The results obtained as shown herein below in tables 1 and 2.

Table 1: without Syloid 72 FP

	Time point	CE.1: No polymer	E.1 AQOAT AS-MG	E.3 Eudragit RL 100	E.5 Eudragit RS 100
XRPD	0	Amorphous			
	1 week				
	2 weeks				
	1 month				
	3 months				

- 30 Table 2: with Syloid 72 FP

	Time point	CE:2 No polymer	E.2 AQOAT AS-MG	E.4 Eudragit RL 100	E.6 Eudragit RS 100
XRPD	0	Amorphous			
	1 week				
	2 weeks				
	1 month				
	3 months				

The results herein above indicate that amorphous sofosbuvir is stable in the compositions of the invention and that no polymorphic transition during storage is observed.

5 The data relative to the stability test disclosed in Reference Example 1.4 b), for Examples 1-6 and Comparative examples 1 and 2, with respect to the decomposition of sofosbuvir are reported in Figures 16 (examples 1, 3, 5 and Comparative Example 1) and 17 (examples 2, 4, 6 and Comparative Example 2). The results indicate no interaction with the polymeric encapsulation and no encapsulation induced degradation in sofosbuvir.

10 The data relative to the influence of different polymer materials and Syloid 72 FP of Examples 1 to 6 and Comparative examples 1 and 2 relative to the stability in humid surrounding measured according to Reference Example 1.4 c) are reported in Figure 22. The data relative to the influence of different polymer materials and Syloid 72 FP of Examples 3, 7 to 9 and Comparative
 15 Example 1 relative to the stability in humid surrounding measured according to Reference Example 1.4 c) are reported in Figure 23. Significant deliquescence can be observed for the comparative sample after 21 hours. As can be seen, based on the 21 hours images, an increasing amount of polymer increases the stability under humid conditions.

20 **Example 14: Dissolution test**

The dissolution tests were carried out as disclosed in Reference Examples 1.5 on the compositions of Examples 1 to 12 and Comparative examples 1 and 2. The results are reported in Figures 8 to 15.

25 In particular, in Figures 8, 10, 12 and 14 it is shown that the dissolution of Sofosbuvir can be reduced by the polymeric encapsulation in acidic conditions (0.1 N HCl medium). The data show that the dissolution of sofosbuvir can be tailored either by preparing physical mixtures of the encapsulated and uncoated/un-capsulated material or by lowering the ratio of polymer in the spray drying solution.

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In Figures 9, 11, 13 and 15 the dissolution profiles in phosphate buffer pH 6.8 are displayed. The Sofosbuvir release for the materials with time-controlled release polymers is reduced in relation to the release given for the Comparative Examples 1 and 2. To the contrary, the dissolution velocity in phosphate buffer pH 6.8 is increased for compositions comprising enteric encapsulation (AQOAT AS-MG).

Short Description of the Figures

Fig. 1 shows a scheme of the spray drying process leading to the encapsulated particles of the invention. The starting mixture comprising the polymer, the API or the API/excipient is spray dried. During the drying of the droplet the polymer accumulates on the surface of the particle and forms a polymer sheath (shell). As can be seen in Fig. 1, a single-particle single-shell configuration is obtained. In the figure the grey colour indicating the API or API/excipient becomes gradually darker to indicate the evaporation of the solvent and the increased concentration of the API or the API/excipient in the particle.

Fig. 2 shows the SEM images of the spray dried batches of examples 1 and 2 at different magnifications.

Fig. 3 shows the SEM images of the spray dried batches of examples 3 and 4 at different magnifications.

Fig. 4 shows the SEM images of the spray dried batches of examples 5 and 6 at different magnifications.

Fig. 5 shows the SEM images of the spray dried batches of examples 7 to 9 at different magnifications.

Fig. 6 shows the SEM images of the spray dried batches of examples 10 to 12 at different magnifications.

Fig. 7 shows the SEM images of the spray dried batches of Comparative examples 1 and 2 at different magnifications.

Fig. 8 shows the dissolution profiles of the batches of Examples 1 to 6, Comparative Examples 1 and 2 in a 0.1 N HCl medium.

Fig. 9 shows the dissolution profiles of the batches of Examples 1 to 6, Comparative Examples 1 and 2 in a phosphate buffer medium.

Fig. 10 shows the dissolution profiles of physical mixtures of the batches of Example 2, Comparative Example 2 and physical mixtures of example 13 in a 0.1 N HCl medium.

Fig. 11 shows the dissolution profiles of physical mixtures of the batches of Example 2, Comparative Example 2 and physical mixtures of example 13 in a phosphate buffer medium.

Fig. 12 shows the dissolution profiles of the batches of Examples 3, 7, 8, and 9, Comparative Examples 1 in a 0.1 N HCl medium.

Fig. 13 shows the dissolution profiles of the batches of Examples 3, 7, 8, and 9, Comparative Examples 1 in a phosphate buffer medium.

5 Fig. 14 shows the dissolution profiles of the batches of Examples 2, 10, 11, and 12, Comparative Examples 2 in a 0.1 N HCl medium.

Fig. 15 shows the dissolution profiles of the batches of Examples 2, 10, 11, and 12, Comparative Examples 2 in a phosphate buffer medium.

10 Fig. 16 shows the result on the stability test with respect to the degradation of sofosbuvir at 40 °C at 75% RH in aluminium blisters of particles without Syloid 72 FP.

Fig. 17 shows the result on the stability test with respect to the degradation of sofosbuvir at 40 °C at 75% RH in aluminium blister of particles with Syloid 72 FP.

15 Fig. 18 shows the XRPD of the compositions according to Examples 1 to 6 and Comparative Examples 1 and 2 (from the top to the bottom) after preparation, prior to the moisture stability test according to Reference Example 1.4.

Fig. 19 shows the XRPD of the compositions according to Examples 1 to 6 and Comparative Examples 1 and 2 (from the top to the bottom) after 1 month storage at 25°C and 54% RH.

20 Fig. 20 shows the XRPD of the compositions according to Examples 1 to 6 and Comparative Examples 1 and 2 (from the top to the bottom) after 3 months in the moisture stability test according to Reference Example 1.4.

Fig. 21 shows the XRPD of the compositions according to Examples 7 to 12 (from the top to the bottom) after preparation.

25 Fig. 22 SEM images of Examples 1-6 and Comparative Examples 1 and 2, taken during a moisture stability test at 25°C 60% RH.

Fig. 23 SEM images of Examples 3, 7, 8 and 9 Comparative Examples 1, taken during a moisture stability test at 25°C 60% RH.

30 **Cited prior art**

WO 2010/135569 A

Claims

1. Encapsulated particles, wherein the particles comprise one or more pharmaceutically active ingredients and optionally one or more pharmaceutically acceptable excipients and wherein each of the particles is encapsulated in a pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers.
2. The encapsulated particles of claim 1, wherein the one or more pharmaceutically active ingredients is one or more anti-HCV agents or one or more anticoagulant agents or one or more antihypertension agents or one or more anti-inflammatory agents or one or more antibiotics or one or more anti-cancer agents or one or more hormonal therapy agents or one or more weight loss agents or one or more anti-insomnia agents or combinations thereof, preferably the one or more pharmaceutically active ingredients is one or more anti-HCV agents or one or more anticoagulant agents.
3. The encapsulated particles of claim 1 or 2, wherein the one or more pharmaceutically active ingredients is one or more anti-HCV agents, wherein the one or more anti-HCV agents is one or more of sofosbuvir, daclatasvir, ledipasvir, ravidasvir, pibrentasvir, glecaprevir, paritaprevir, ombitasvir, dasabuvir, velpatasvir, grazoprevir, elbasvir, interferon, more preferably the one or more anti-HCV agents is sofosbuvir or wherein the one or more pharmaceutically active ingredients is one or more anticoagulant agents, wherein preferably the one or more anticoagulant agents is Betrixaban or Betrixaban maleate.
4. The encapsulated particles of any one of claims 1 to 3, wherein the one or more pharmaceutically active ingredients is crystalline or amorphous, preferably amorphous and wherein preferably at least 95 weight-%, more preferably at least 97 weight-%, more preferably at least 99 weight-% of the one or more pharmaceutically active ingredients comprised in the particles of the encapsulated particles is in amorphous form.
5. The encapsulated particles of any one of claims 1 to 4, wherein the particles comprise one or more pharmaceutically acceptable excipients, wherein preferably the one or more pharmaceutically acceptable excipients is not the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers.

6. The encapsulated particles of any one of claims 1 to 5, wherein at least 95 weight-%, preferably at least 97 weight-%, more preferably at least 99 weight-%, more preferably at least 99.9 weight-% of the encapsulated particles consists of the one or more pharmaceutically active ingredients, of the one or more pharmaceutically acceptable polymers and optionally of the one or more pharmaceutically acceptable excipients.
7. The encapsulated particles of any one of claims 1 to 6, wherein at least 50 weight-%, preferably from 55 to 99.5 weight-%, more preferably from 55 to 70 weight-% of the encapsulated particles consists of the pharmaceutical active ingredients based on the total weight of the encapsulated particles and wherein from 0.5 to 50 weight-%, or from 0.5 to 15 weight-%, or from 25 to 35 weight-%, or from 28 to 33 weight-% of the encapsulated particles consists of the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers based on the total weight of the encapsulated particles.
8. The encapsulated particles of any one of claims 1 to 7, wherein at least 85 weight-%, preferably from 90 to 99.5 weight-% of the encapsulated particles consists of the one or more pharmaceutical active ingredients and wherein the weight-% is based on the total weight of the encapsulated particles.
9. The encapsulated particles of any one of claims 1 to 8, wherein the encapsulated particles consist of the one or more pharmaceutical active ingredients and of the pharmaceutically acceptable polymer or of a mixture of pharmaceutically acceptable polymers, wherein at least 85 weight-%, preferably from 90 to 99.5 weight-% of the encapsulated particles consists of the said one or more pharmaceutical active ingredients wherein the weight-% is based on the total weight of the encapsulated particles.
10. The encapsulated particles of any one of claims 1 to 9, wherein the particles are partially encapsulated with the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers.
11. The encapsulated particles of any one of claims 1 to 10, wherein the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers is one or more enteric polymers or one or more time-dependent release polymers or combinations thereof.

12. The encapsulated particles of claim 11, wherein the one or more enteric polymers is one or more of

-natural film former,
-cellulose acetate phthalate
-polyvinyl acetate phthalate
-hydroxy-propyl methylcellulose phthalate
-hydroxyl-propyl-methylcellulose-acetate-succinate
-methacrylic acid copolymers wherein the methacrylic acid copolymers are preferably diethylaminoethyl-methacrylate-methyl-methacrylate-copolymers or methylacrylid-methylmethacrylate-copolymer 1:1 or methacrylid-methylmethacrylate-copolymer 1:2,
and

and wherein

the one or more time-dependent release polymers is one or more of

-polyvinylacetate
-ethyl cellulose
-cellulose acetate-butyrate
-cellulose acetate
-type A and type B ammonio-methacrylate copolymers
-Ethylacrylate-methylmethacrylate-copolymers 2:1
-Hydroxyethylcellulose.

13. The encapsulated particles of any one of claims 1 to 12, wherein the weight ratio of the one or more pharmaceutically active ingredients relative to the pharmaceutically acceptable polymer or to the mixture of pharmaceutically acceptable polymers is in the range of from 1 : 1 to 200 : 1, preferably in the range of from 1.5 : 1 to 50 : 1, more preferably in the range of from 1.5: 1 to 20: 1, more preferably in the range of from 1.6:1 to 2.5: : 1.

14. The encapsulated particles of any one of claims 1 to 13, wherein the one or more pharmaceutically acceptable excipients is one or more silicon-based inorganic adsorbents, wherein the one or more silicon-based inorganic adsorbents preferably comprises, more preferably is silica, wherein preferably the silica comprises, more preferably is, precipitated silica.

15. The encapsulated particles of claim 14, wherein the encapsulated particles consists of one or more the pharmaceutical active ingredients, of the pharmaceutically acceptable polymer

or a mixture of pharmaceutically acceptable polymers and of the silicon based inorganic absorbent, wherein

- from 65 to 85 weight-% of the encapsulated particles, preferably from 70 to 80 weight % of the encapsulated particles consists of the one or more pharmaceutical active ingredients;
- from 14 to 22 weight % of the encapsulated particles, preferably from 16 to 21 weight % of the encapsulated particles consists of the silicon based inorganic absorbents;
- from 0.2 to 21 weight %, preferably from 4 to 10 weight-% of the encapsulated particles, preferably from 16 to 21 weight % of the encapsulated particles consists of the pharmaceutically acceptable polymer or a mixture of pharmaceutically acceptable polymers

preferably wherein the pharmaceutically acceptable polymer is as defined in claim 11 or 12 preferably wherein the silicon based inorganic absorbent is as defined in claim 14 and wherein the weight % is based on the total weight of the encapsulated particles.

16. A process for preparing the encapsulated particles of any one of claims 1 to 15, the process comprising

- i) preparing a mixture comprising one or more pharmaceutically active ingredients, a pharmaceutically acceptable polymers or a mixture of pharmaceutically acceptable polymers, one or more solvents and optionally one or more pharmaceutically acceptable excipients;
- ii) spray encapsulating the mixture prepared in i) and obtaining the encapsulated particles

wherein preferably the one or more solvents of i) is one or more polar solvents, wherein preferably the one or more polar solvents is one or more of a ketone, water and an alcohol, wherein preferably the alcohol is one or more of methanol, ethanol, isopropyl alcohol, n-butanol and wherein preferably the ketone is acetone.

17. The process of claim 16, wherein the mixture prepared in i) is a solution or a suspension and preferably wherein the one or more pharmaceutically active ingredients and the pharmaceutically acceptable polymer or the mixture of pharmaceutically acceptable polymers are dissolved in the mixture of i).

18. A mixture comprising

- a) the encapsulated particles according to any one of claims 1 to 15 or obtained or obtainable by the process according to claims 16 or 17.

and

- b) particles wherein the particles comprise, preferably consist of,
-one or more pharmaceutically active ingredients and optionally
-one or more pharmaceutically acceptable excipients,

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wherein said particles are non-encapsulated particles,
wherein

the one or more pharmaceutically active ingredients are preferably
according claim 2 or 3, and

10

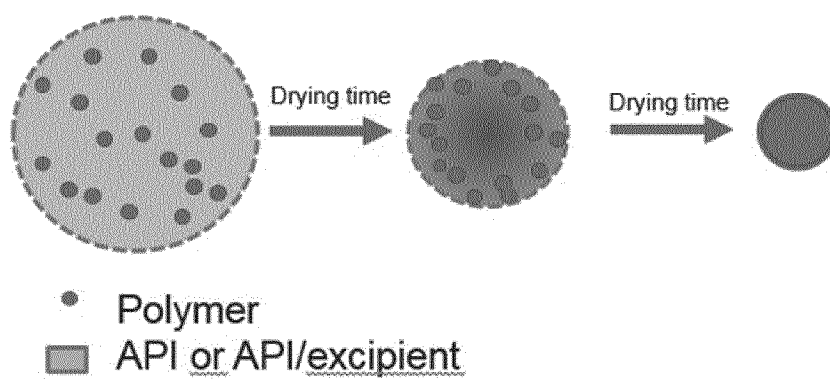
the one or more pharmaceutically acceptable excipients preferably is
according to claim 14 or is the pharmaceutically acceptable polymer or the
mixture of pharmaceutically acceptable polymers according to claim 11 or
12, more preferably the one or more pharmaceutically acceptable
excipients is according to claim 14,

15

preferably wherein the particles comprise, more preferably consist of, one or more
pharmaceutically active ingredients.

19. The encapsulated particles of any one of claims 1 to 15 obtainable or obtained by spray
drying.

20 20. The encapsulated particles of any one of claims 1 to 15 obtainable or obtained by a process
as defined in claims 16 or 17.

**Figure 1**

SEM images of spray dried batches of Examples 1 and 2

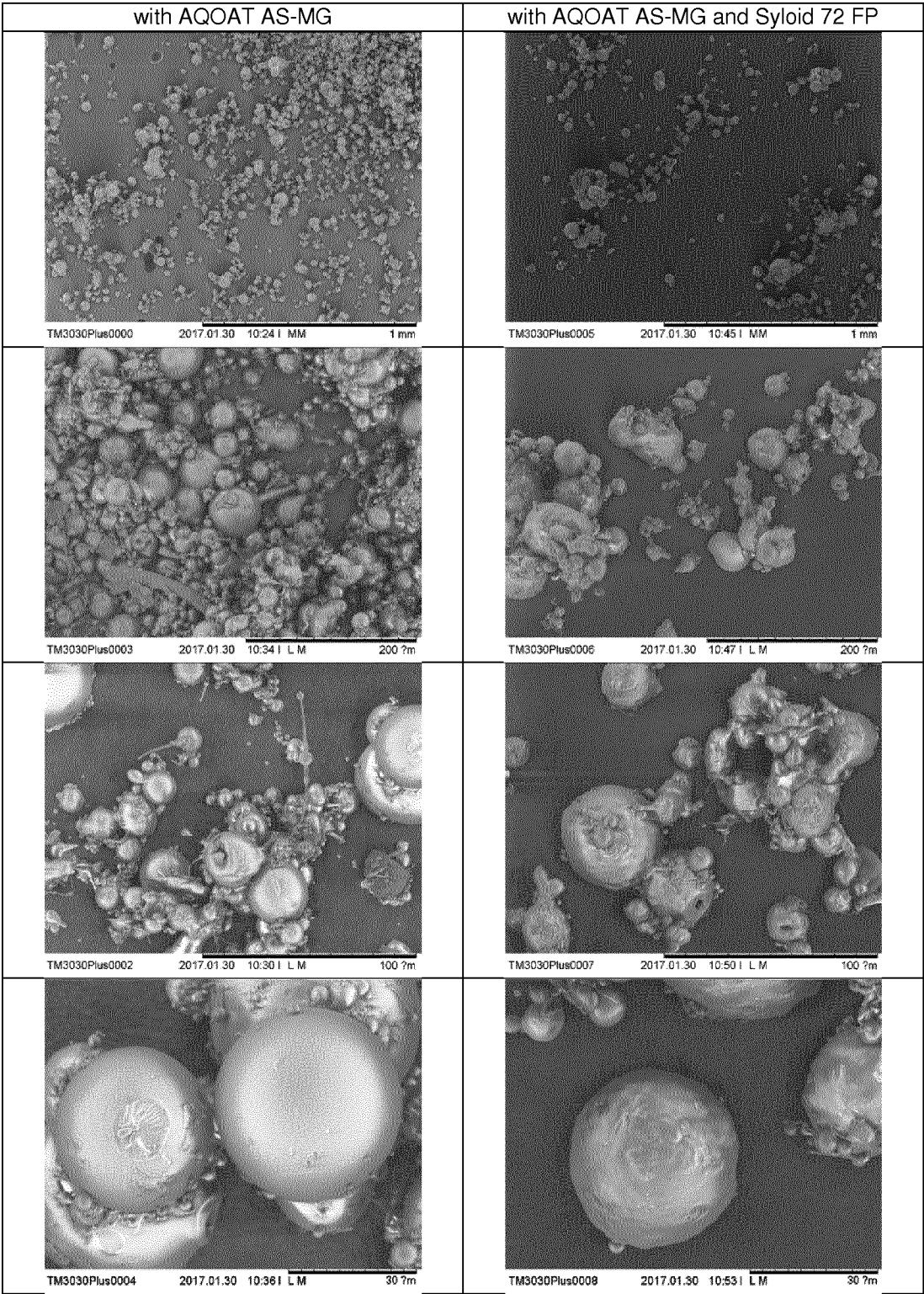


Figure 2

SEM images of spray dried batches of Examples 3 and 4

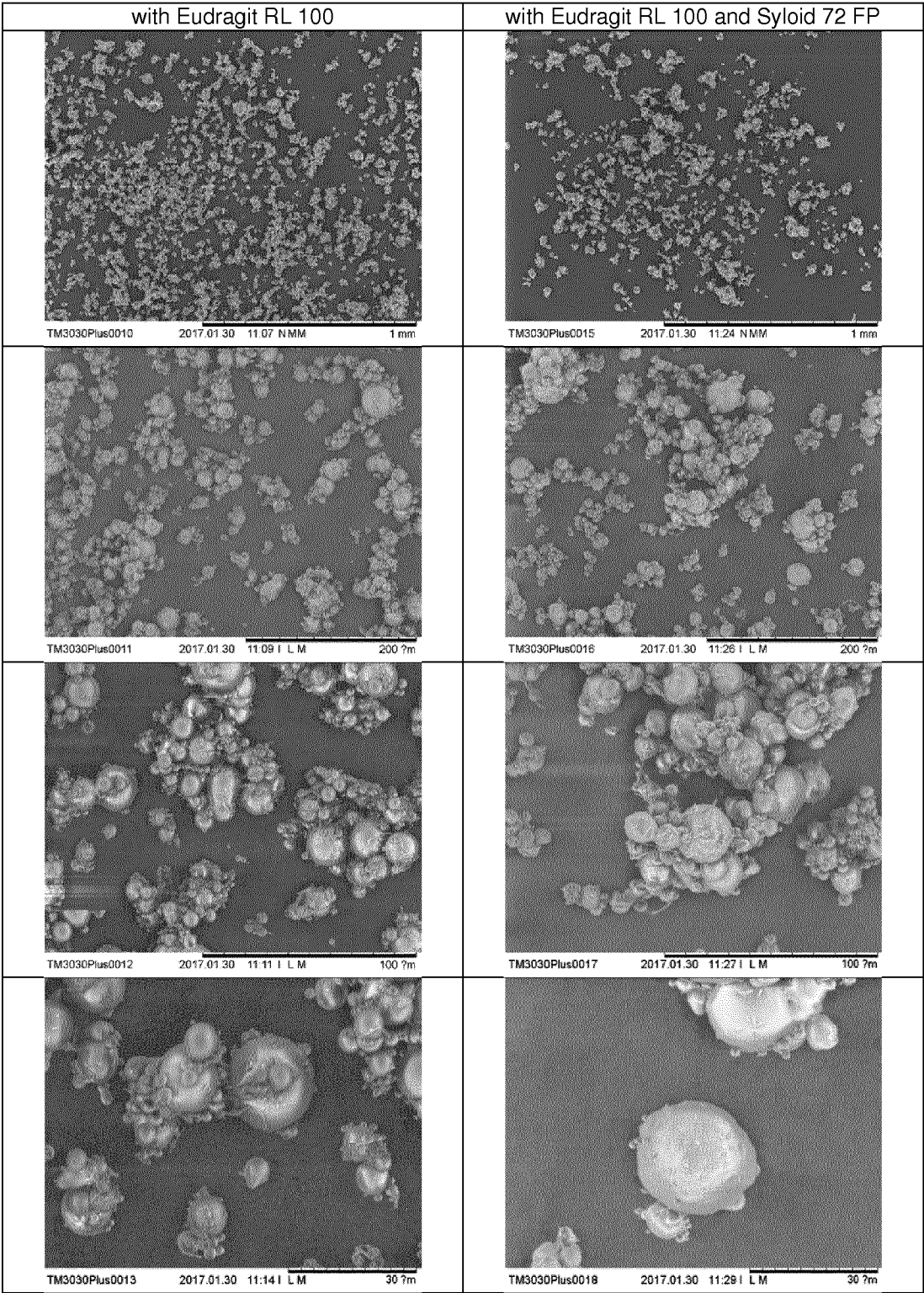


Figure 3

SEM images of spray dried batches of Examples 5 and 6

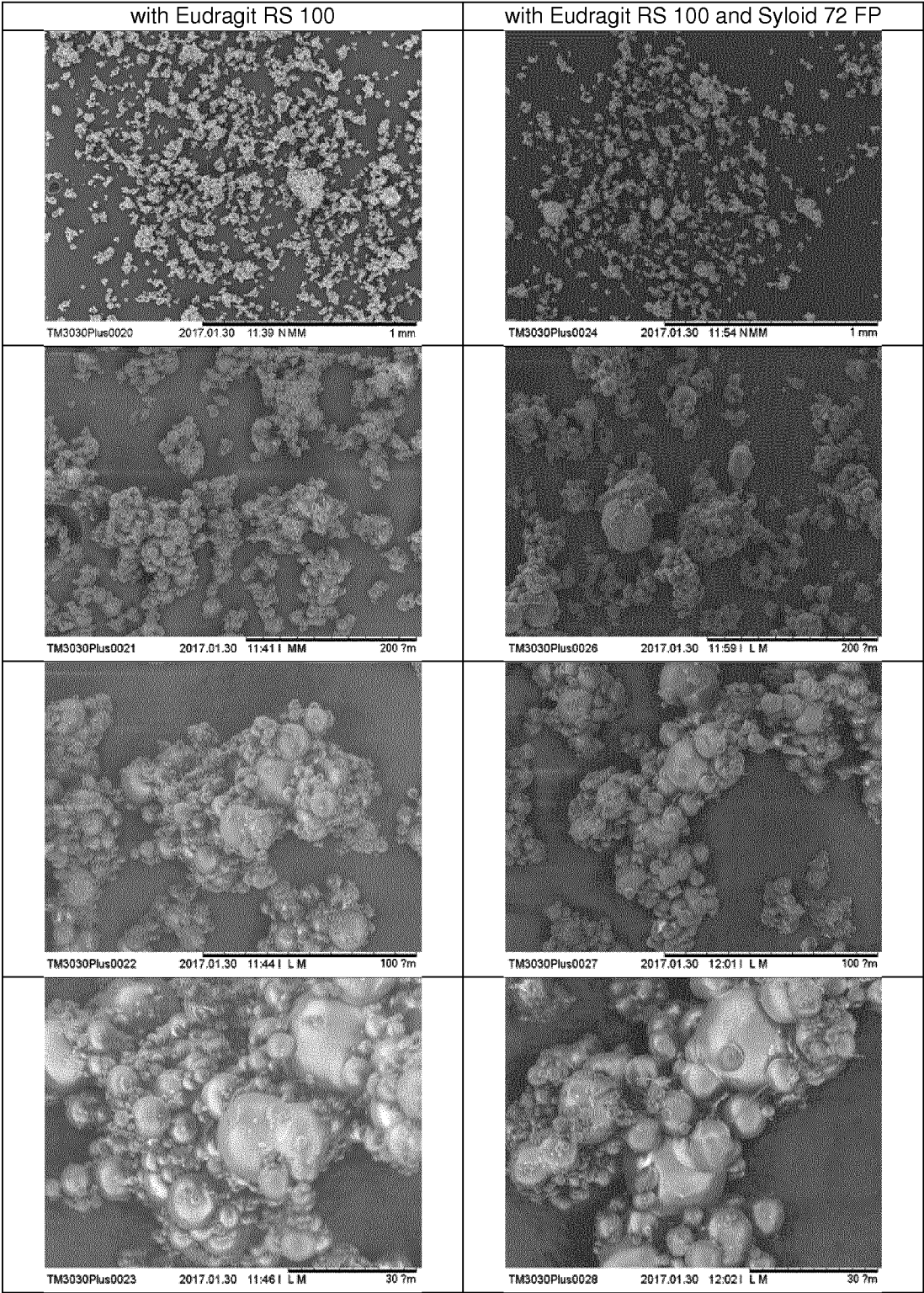


Figure 4

SEM images of spray dried batches of Examples 7 to 9

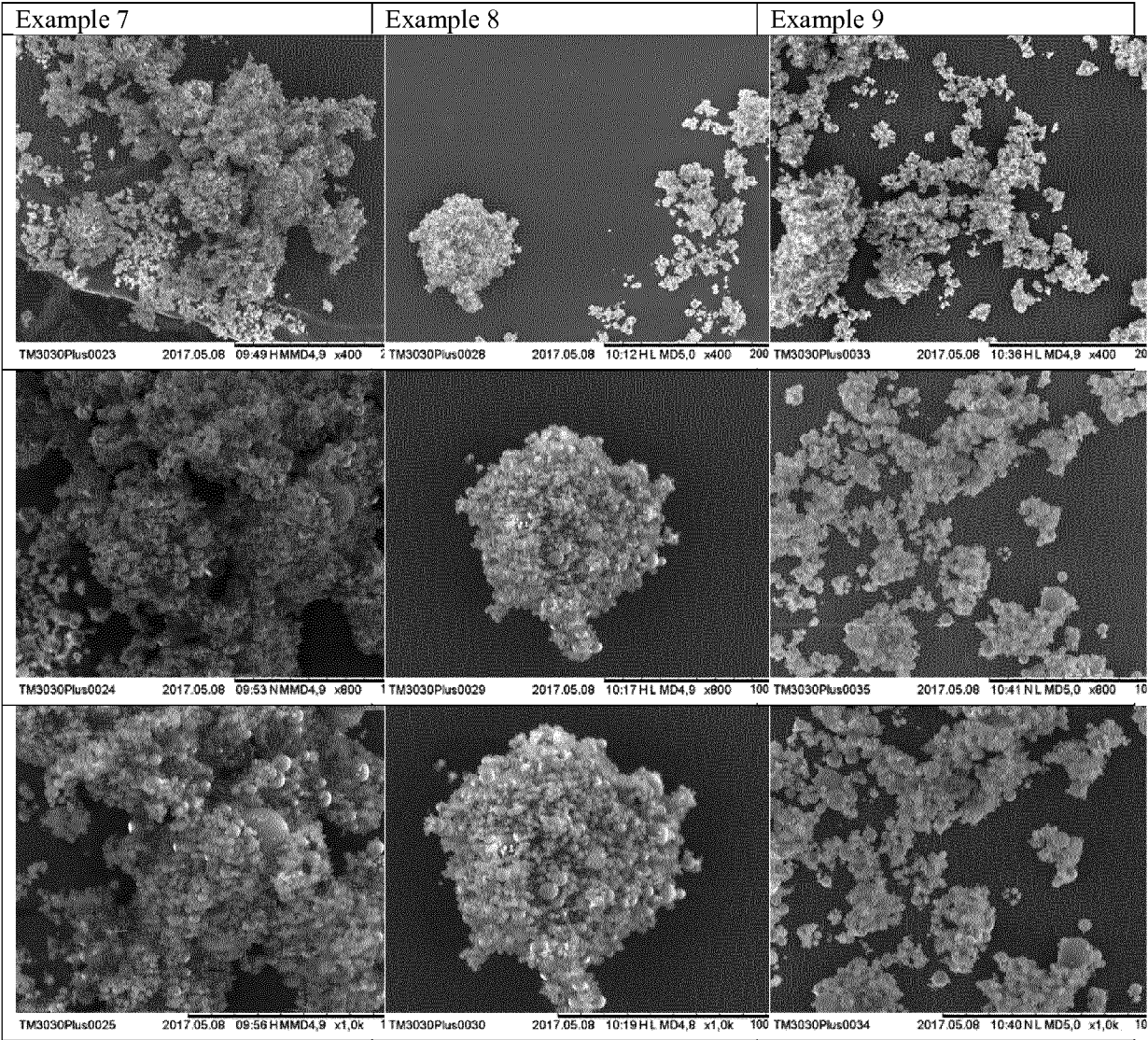


Figure 5

SEM images of spray dried batches of Examples 10 to 12

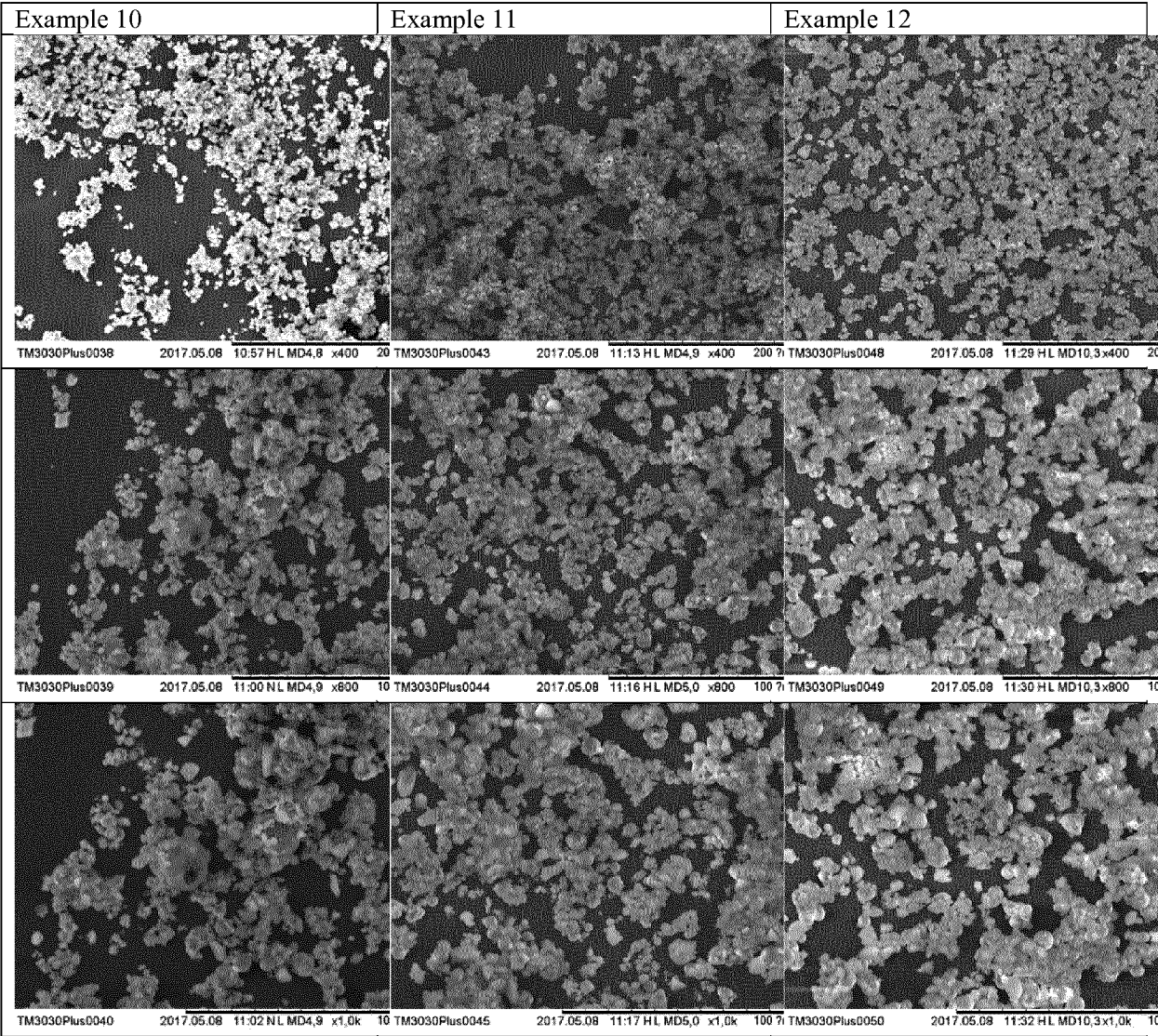
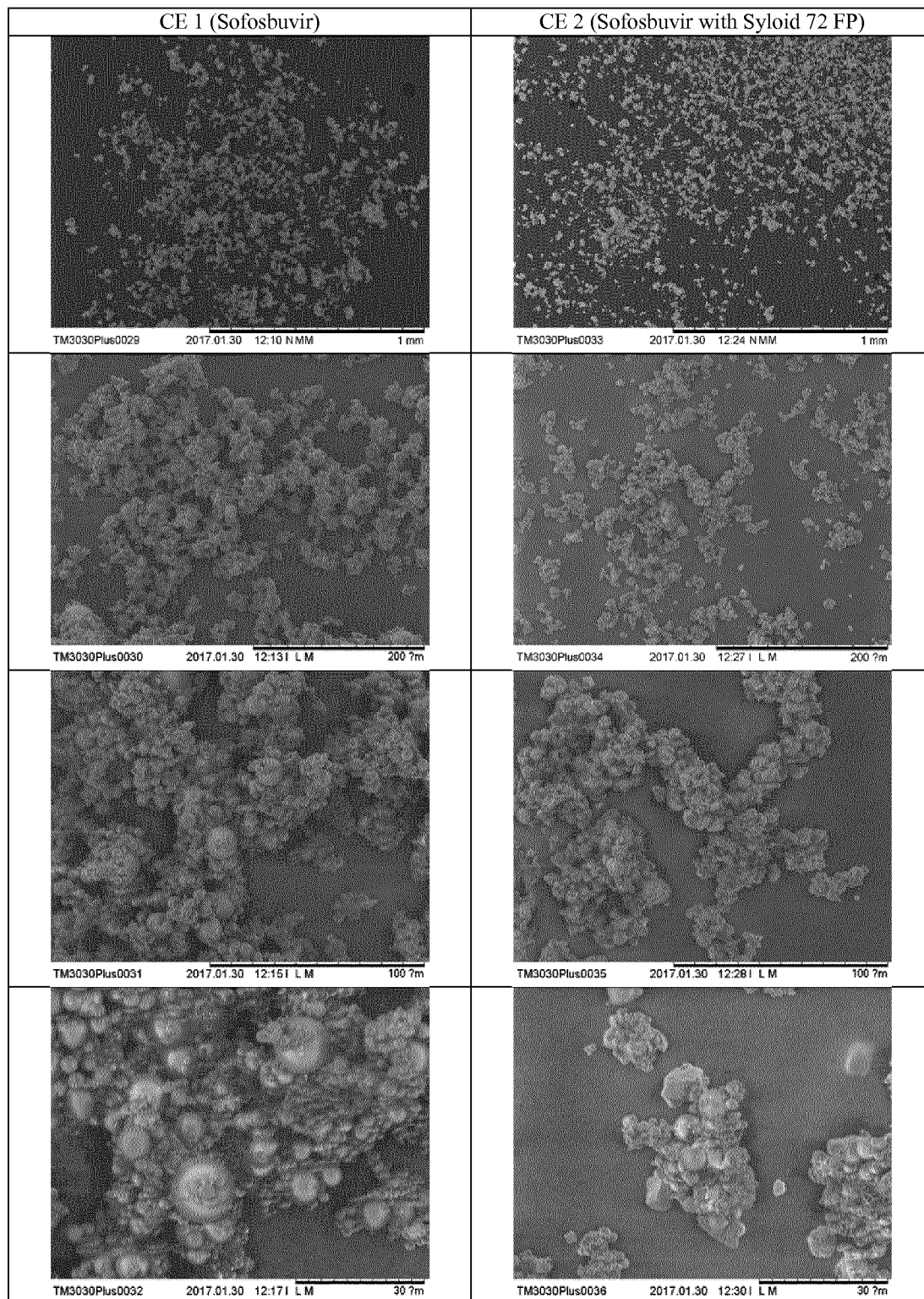
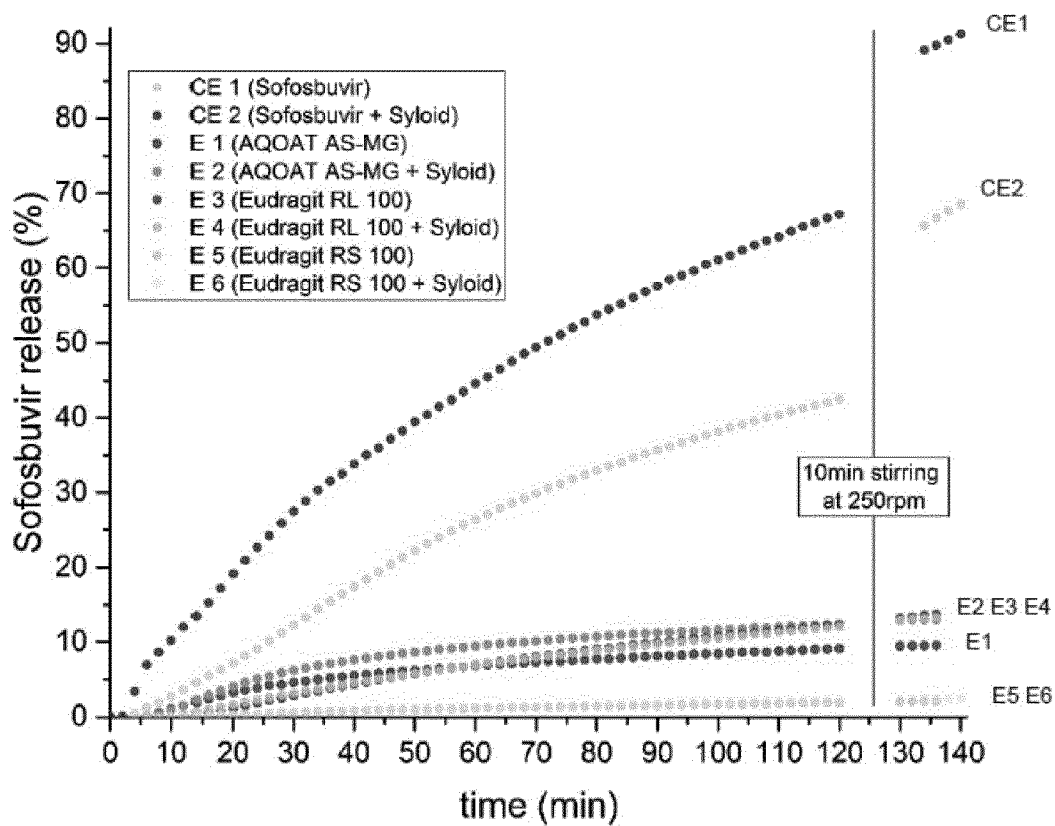


Figure 6

SEM images of spray dried batches of Comparative Examples 1 and 2**Figure 7**

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Dissolution profile of examples 1-6 and comparative examples 1 and 2 in 0.1 N HCl**Figure 8**

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Dissolution profile of examples 1-6 and comparative examples 1 and 2 in phosphate buffer pH 6.8

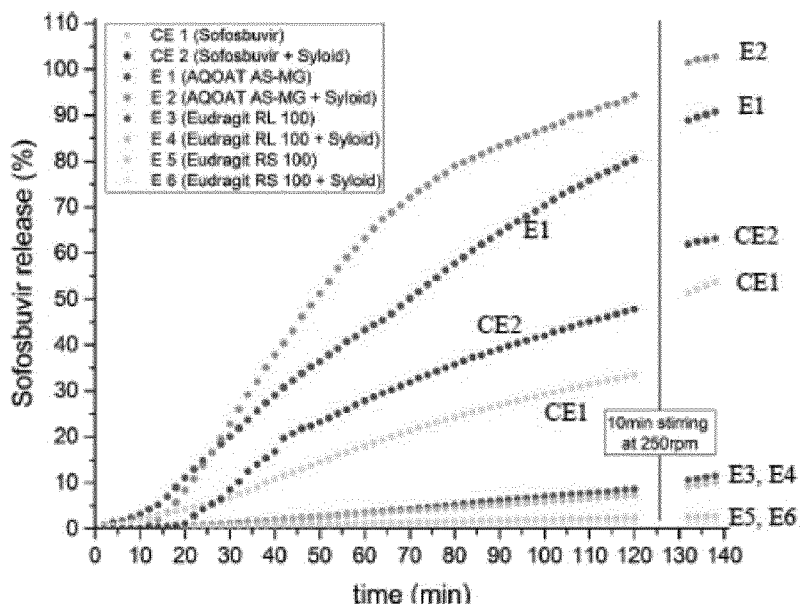


Figure 9

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Dissolution profile of Example 2, Comparative Example 2 and physical mixtures of example 13 (10% E2+90% CE2 and 90% E2+10%CE2) in 0.1 N HCl

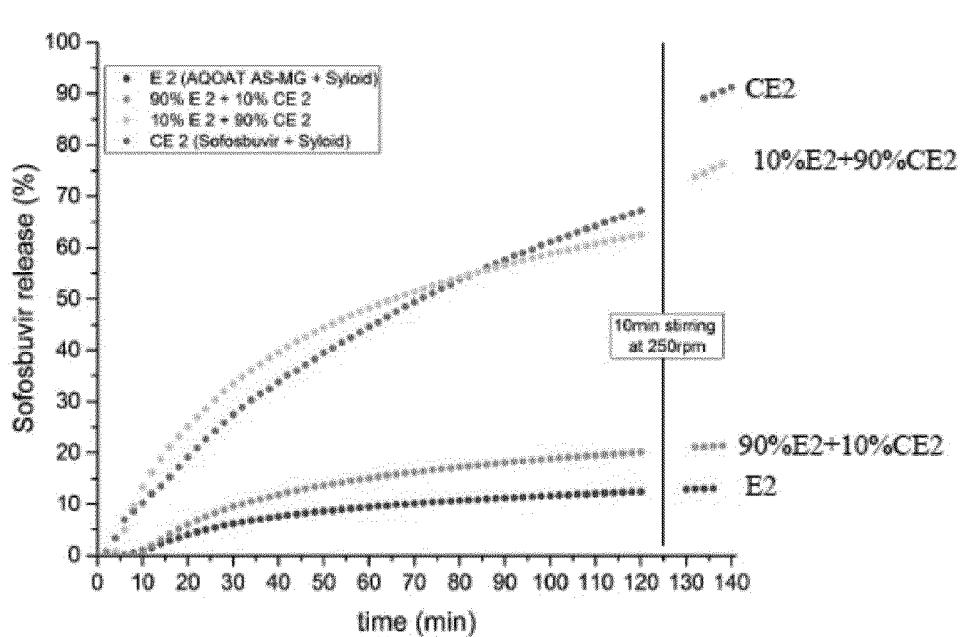


Figure 10

Dissolution profile of Example 2, Comparative Example 2 and physical mixtures of example 13 (10 % E2+90 % CE2 and 90 % E2+10 % CE2) in phosphate buffer pH 6.8

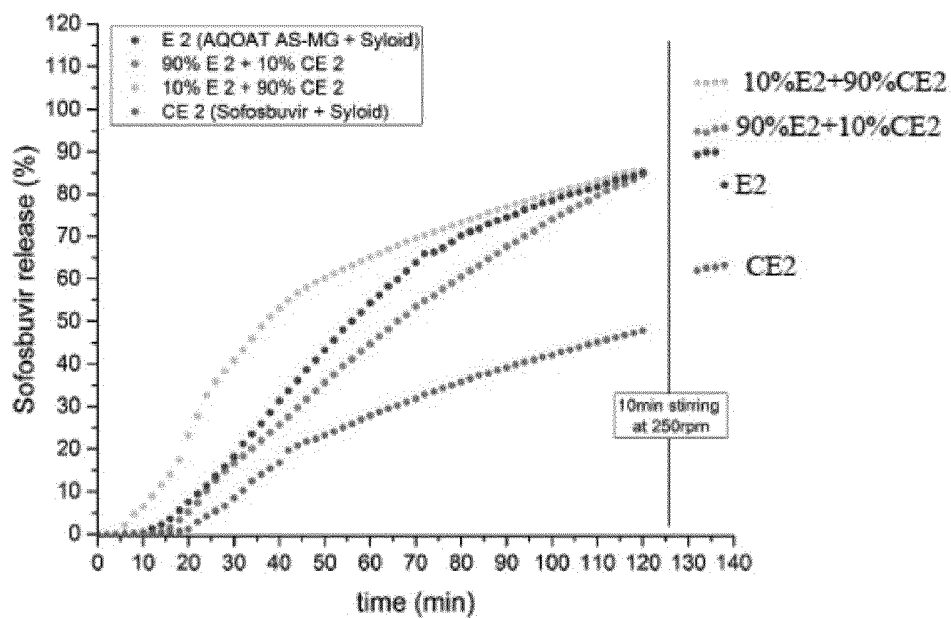


Figure 11

Dissolution profile of Examples 3, 7, 8 and 9 with comparative example 1 in 0.1 N HCl

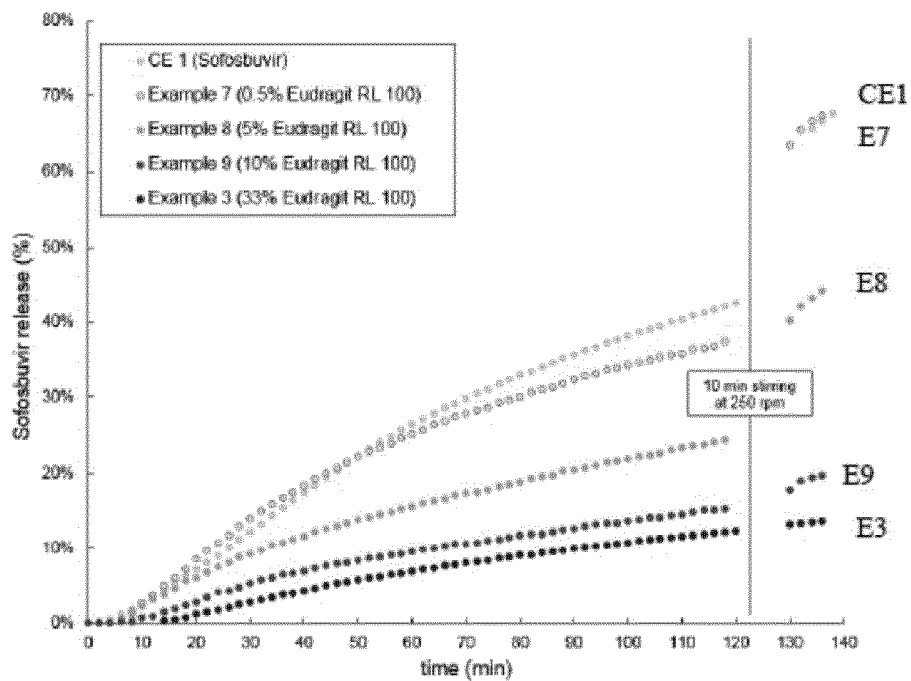


Figure 12

**Dissolution profile of Examples 3, 7, 8, and 9 with comparative example 1
in phosphate buffer pH 6.8**

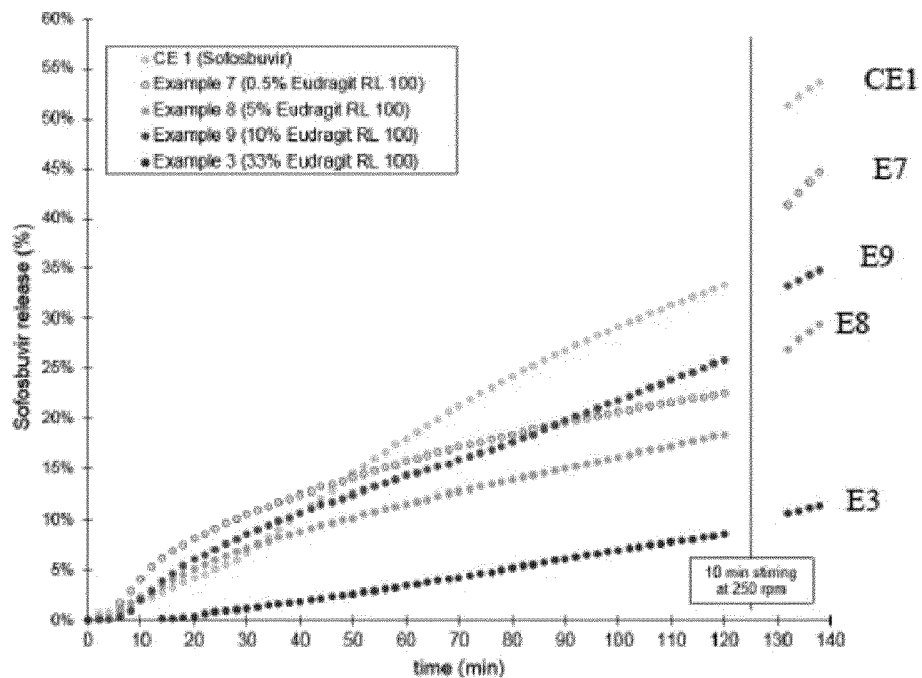


Figure 13

**Dissolution profile of Examples 2, 10, 11 and 12
with comparative example 2 in 0.1 N HCl**

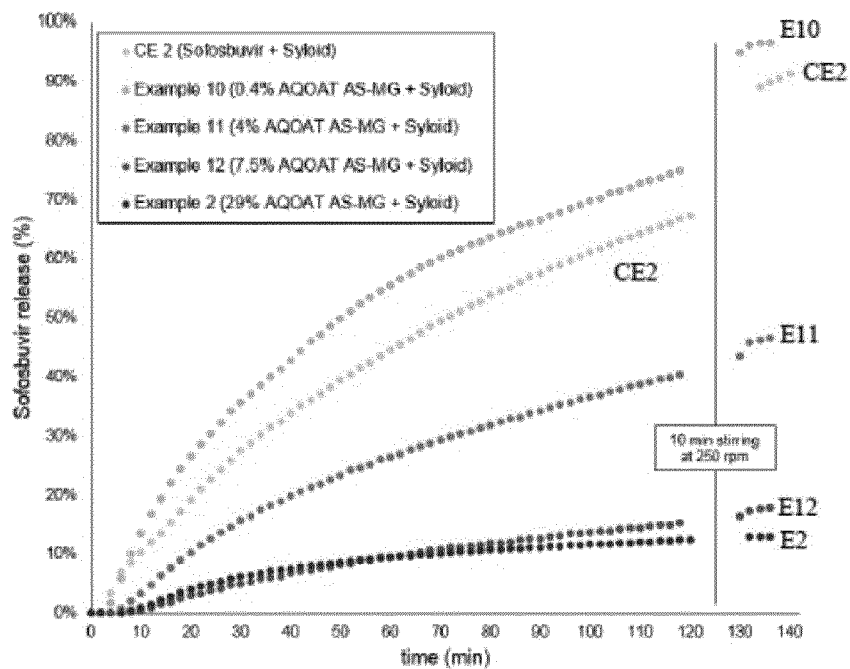


Figure 14

Dissolution profile of Examples 2, 10, 11 and 12 with
comparative example 2 in phosphate buffer pH 6.8

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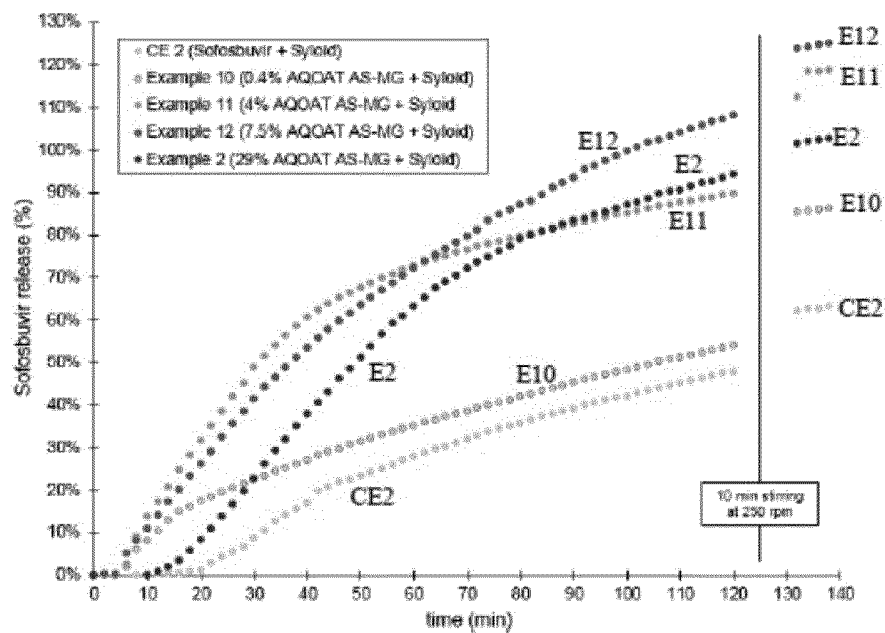


Figure 15

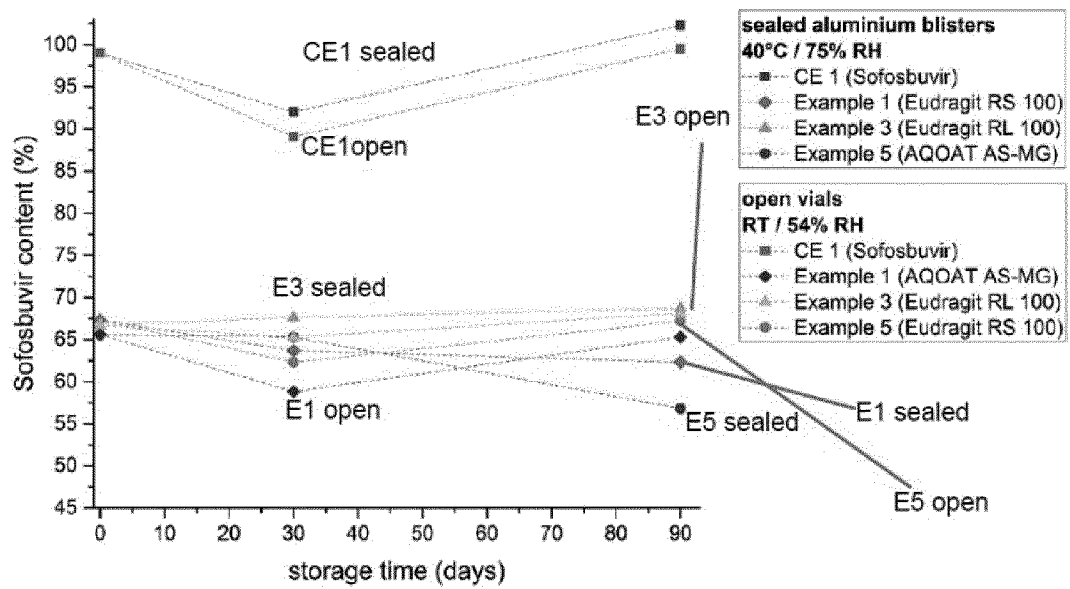


Figure 16

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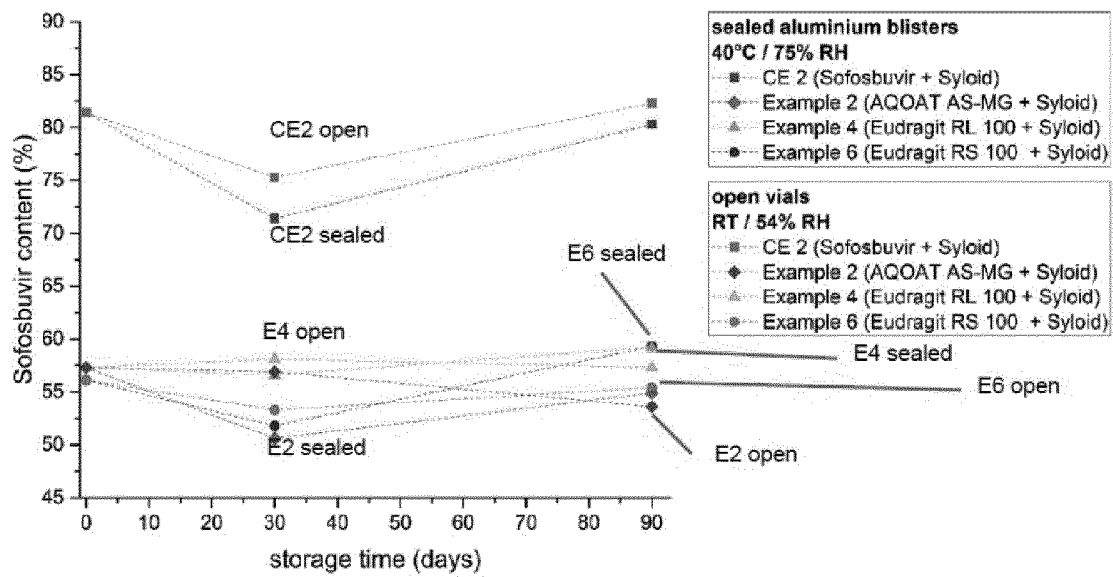


Figure 17

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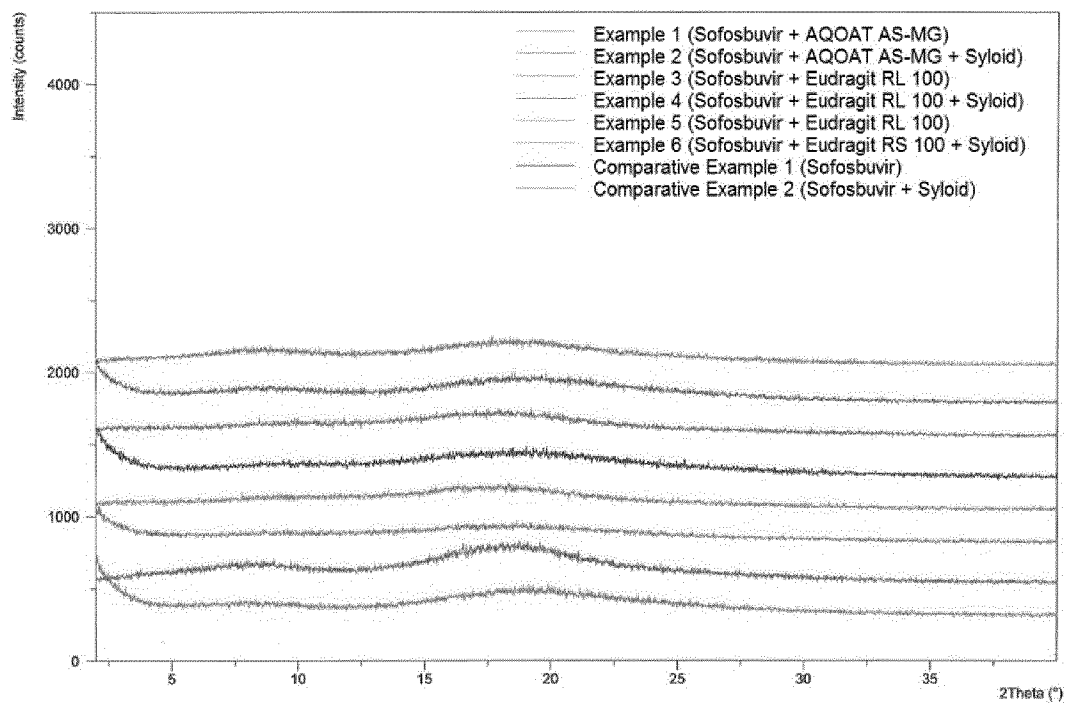
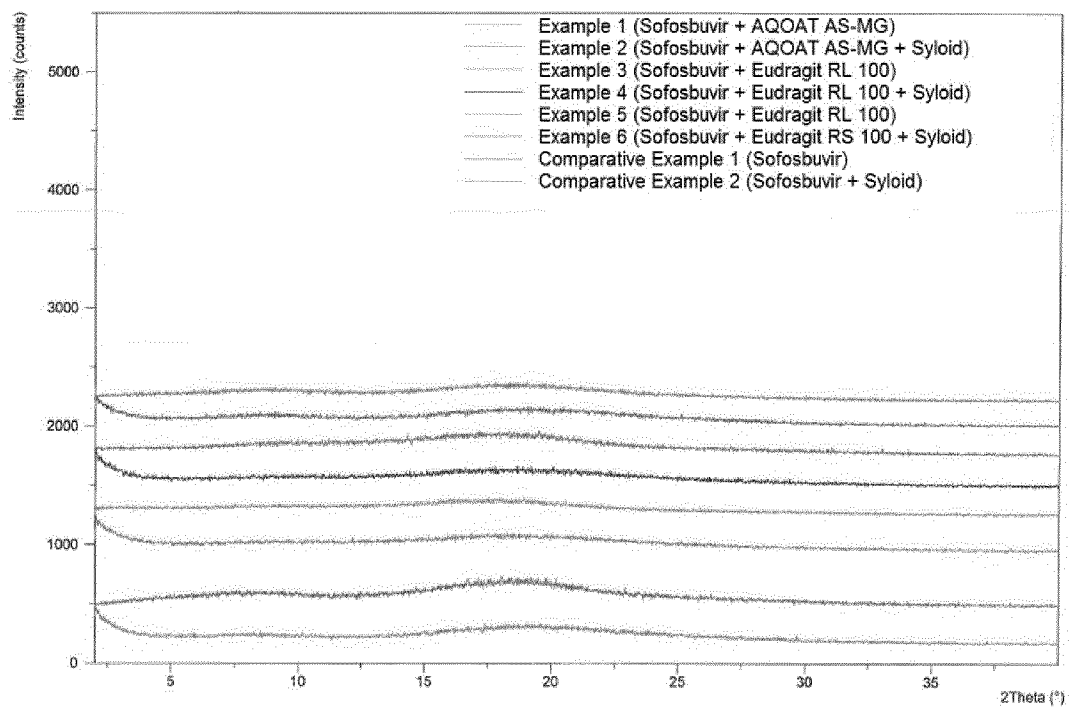


Figure 18

**Figure 19**

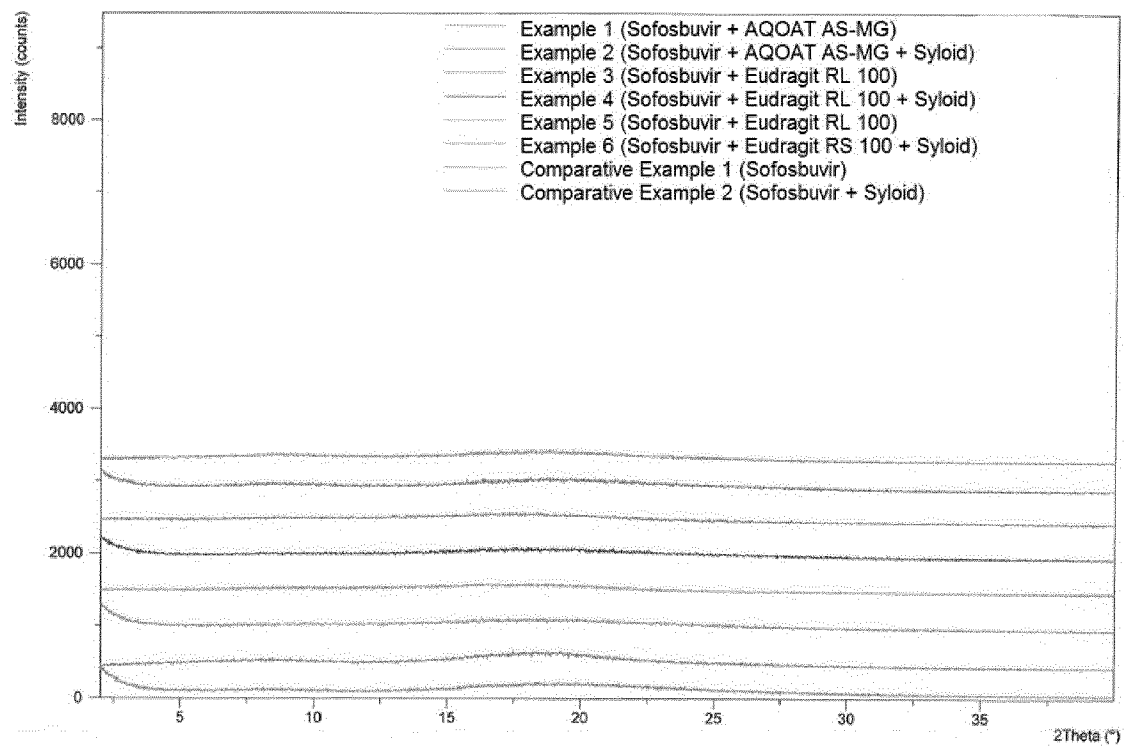


Figure 20

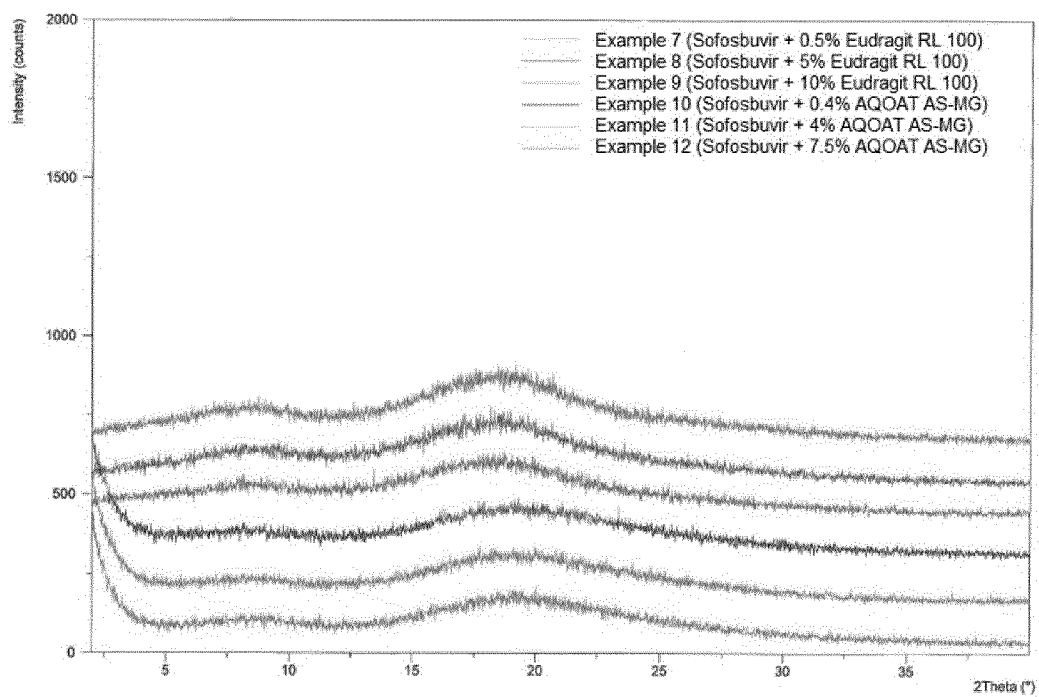


Figure 21

Figure 22

Influence of different polymers and Syloid 72 FP on stability in humid surrounding






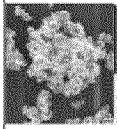















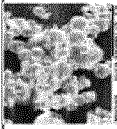


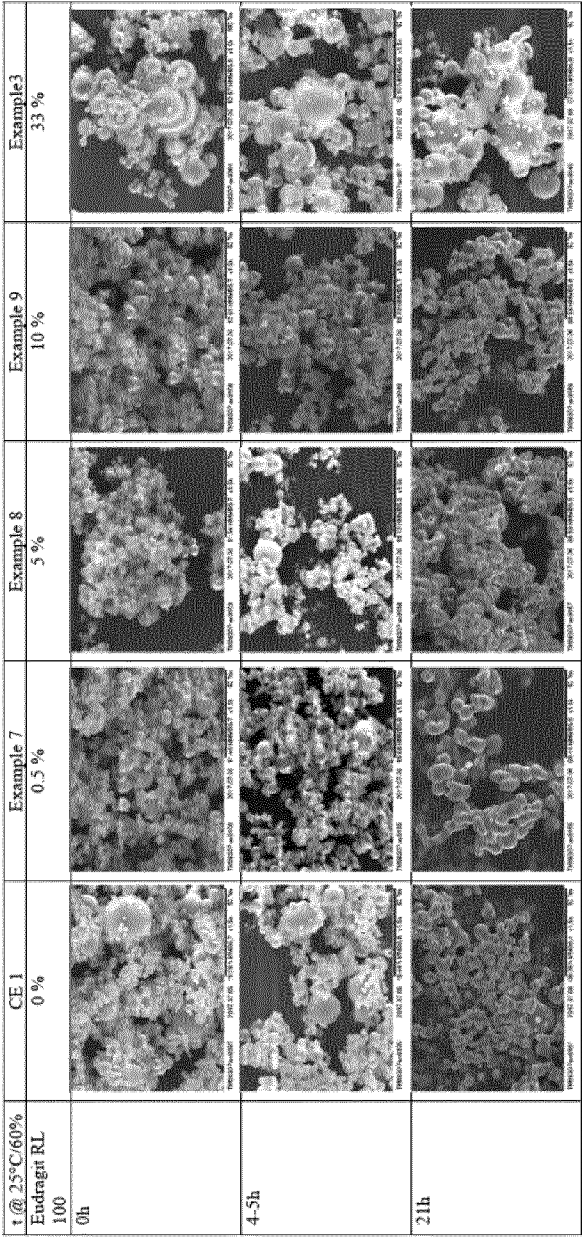
t @ 25°C/60 %	Example 1		Example 2		Example 3		Example 4		Example 5		Example 6		CE 1		CE 2	
	AQOAT AS-MG		AQOAT AS-MG + Syloid 72 FP		Eudragit RL 100		Eudragit RL 100 + Syloid 72 FP		Eudragit RS 100		Eudragit RS 100 + Syloid 72 FP		without coating/encapsula tion		without coating/encapsula tion + Syloid 72 FP	
0 h																
4+5 h																
21 h																

Figure 23
Influence of increasing amount of polymer on stability in humid surrounding



The Eudragit content is expressed as percent related to the Sofosbuvir content in the sample.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/050162

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/16 A61K31/44 A61K31/7072 A61P7/02 A61P31/12 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 A61P		
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, BIOSIS, CHEM ABS Data, EMBASE, 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 Y	US 2013/224301 A1 (CURATOLO WILLIAM J [US] ET AL) 29 August 2013 (2013-08-29) figure 1 paragraphs [0002], [0005], [0013] - [0018], [0040] - [0046] tables I-II claims 1-6; example 15 -----	1-13, 15-20 1-20
X Y	US 2007/218138 A1 (BITTORF KEVIN J [US] ET AL) 20 September 2007 (2007-09-20) figure 2 paragraphs [0008] - [0012], [0018] - [0019], [0240] - [0241] examples 1-13; tables 10-14 claims 1,5,9,10,83 ----- -/--	1-13, 15-20 1-20
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex. </div>		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-size: 1.2em;">8 February 2019</div>		Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">20/02/2019</div>
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-size: 1.2em;">Hillers, Nathalie</div>

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Y	paragraphs [0005] - [0006], [0079] - [0082], [0087] claims 1,2,5-11	1-20

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Y	examples 1-2 paragraphs [0080] - [0081], [0099] - [0100], [0124] claims 1,4,16,18,20,21	1-20

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Y	examples 5,9-12,15,16 claims 5-8,12,13 page 3, paragraph 1-3	1-20

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Y	paragraphs [0001], [0008], [0009], [0014], [0034], [0043], [0059] - [0062], [0090], [0093]; claims 1-8 example 3	1-20

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Y	example 2 page 43, lines 24-32 page 44, lines 7-12 page 45, lines 13-15 page 9, lines 12-14 page 8, lines 9-11 the whole document	1-20

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INTERNATIONAL SEARCH REPORT

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	page 3, lines 9-14 claims; examples the whole document -----	1-20

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