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(54) Title: COMPOSITION WITH A HIGH DRUG LOAD OF SOFOSBUVIR

(57) Abstract: The present invention relates to a pharmaceutical composition containing the active ingredient sofosbuvir. The composition, preferably in the form of a tablet, contains a high relative amount of active ingredient of 35 to 75 %. The patent also relates to the use of such a composition for the treatment of hepatitis C virus infections and to a process for preparing sofosbuvir tablets with such high drug load.

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Composition with a high drug load of sofosbuvir

The present invention relates to a pharmaceutical composition containing the active ingredient sofosbuvir. The composition, preferably in the form of a tablet, contains a high relative amount of active ingredient of 35 to 75 %. The patent also relates to the use of such a composition for the treatment of hepatitis C virus infections and to a process for preparing sofosbuvir tablets with such high drug load.

Sofosbuvir is an active ingredient which is known to be useful for treating hepatitis C virus infections. In this connection, it can be referred to WO 2013/082003 where sofosbuvir is designated as GS-7977. A sofosbuvir containing medicament is also on the market under the tradename Sovaldi®. Sovaldi® is available as immediate release tablets.

The recommended dose of sofosbuvir is 400 mg administered orally once daily. Thus, it is advantageous if a tablet containing sofosbuvir contains 400 mg of the active ingredient so that a patient has to take only one tablet per day. Accordingly, the commercial product Sovaldi® is in the form of a tablet which contains 400 mg of sofosbuvir. However, sofosbuvir is difficult to handle and to formulate into tablets. The tablet Sovaldi® has a total weight of 1200 mg, thus providing a drug load of only 33.33 %. Tablets with a weight of more than about 1000 mg are difficult to swallow and, therefore, there are often problems with patient compliance. The fact that the only marketed product with sofosbuvir is a tablet with a tablet weight which is difficult to swallow is a clear indication of the problems which occur in preparing small tablets having a high drug load.

Besides the active ingredient Sovaldi® tablets also contain glidant. More specifically, the SOVALDI ® tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

WO 2013/082003 and WO 2014/120981 also describes tablets containing sofosbuvir. The tablets of all examples comprise at least 0.5 % silicon dioxide which is a typical glidant.

Glidant materials are generally added to pharmaceutical compositions to facilitate the flow of a material to be processed by reducing interparticulate friction. Low flowability and stickiness is particularly a problem of small particle size particles. Furthermore, oral dosage forms comprising a high loading of the active material usually require glidant in order to overcome the flowability problem associated with the lack of flowability of the API.

Glidant materials, especially colloidal silicon dioxide, are, however, typically extremely fluffy and bulky, and they often require a sieving stage during which a significant amount of airborne particles is produced. Such airborne particles are a potential safety hazard, and, thus, require the use of safety equipment and other safety precautions by workers handling the materials. Moreover, because particles of glidant materials, such as colloidal silicon dioxide, are extremely small, the total surface area of a sample of such a material is extremely large, relative to the volume of the sample.

There exists a need for a pharmaceutical composition, preferably in the form of a tablet, containing sofosbuvir which has a higher drug load and therefore has a smaller size and lower weight. Moreover having a high relative amount of active ingredient in a pharmaceutical composition, such as a tablet, is also an advantage in case of fixed dose combinations with a second or further active ingredient. Nevertheless, fast dissolution is required in order to provide a suitable bioavailability. Preferably dissolution of a composition in the form of a tablet is as fast or even faster as for a tablet providing a drug load of 33.33 % of sofosbuvir. To reduce hazards to workers and provide a manufacturing process that can be easily handled, substantially glidant free sofosbuvir formulations and methods of preparing such formulations would further be advantageous.

In order to solve these problems, the present inventors have carried out significant studies concerning suitable excipients and preparation methods for preparing sofosbuvir containing compositions, preferably in the form of a tablet.

The present invention therefore provides a pharmaceutical composition comprising sofosbuvir in an amount of 35 to 75 %, preferably of 40 to 70 %, such as 40 to 65 % or 40 to 60 %, more preferred 40 to 55 %, such as 40 to 50%, based on the total weight of the

composition. In one particularly preferred embodiment the composition of the present invention comprises sofosbuvir in an amount of 35-55 % based on the total weight of the composition. In another particularly preferred embodiment the composition of the present invention comprises sofosbuvir in an amount of 40-50% based on the total weight of the composition. Preferably, the composition of the present invention is a solid pharmaceutical composition. More preferably, the composition of the present invention is in the form of a tablet and the tablet preferably comprises one or more pharmaceutically acceptable excipients. The tablet is for oral use.

All percentages in the present specification are on a weight basis and refer to the total weight of the composition, if nothing else is especially indicated or obvious under the circumstances. It is to be understood that a value of e.g. 40 % includes all values from 39.50 % to 40.49 %. The same applies to all other percentages disclosed herein (if nothing else is explicitly mentioned or obvious under the circumstances).

The pharmaceutical composition (in particular when in form of a tablet) according to the present invention contains preferably about 400 mg of sofosbuvir. The term "about" means ± 10 % in this connection. If a tablet contains 400 mg sofosbuvir, only one tablet has to be taken per day.

A composition (in particular when in form of a tablet) according to the present invention preferably has a weight of not more than 1020 mg, preferably not more than 800 mg. Preferably a composition (in particular when in form of a tablet) according to the present invention has a weight between 700 and 1020 mg, such as between 700 and 920 mg, more preferred between 700 and 820 mg.

In a preferred composition of the present invention the sofosbuvir is small particle size sofosbuvir and the composition comprises no glidants. Glidants are known to the skilled person. They reduce interparticle friction and cohesion and thus increase flowability of particles or mixtures. Colloidal silicon dioxide is the most known glidant. In contrast to glidants, lubricants prevent ingredients from sticking to e.g. tablet punches. Magnesium stearate is a typical lubricant (not a glidant). The present inventors surprisingly found that sofosbuvir can be formulated into pharmaceutical compositions without a glidant even though the sofosbuvir is used in a small particle size form.

In one embodiment, the present invention relates to a composition, wherein the composition contains sofosbuvir as sole active ingredient and one or more pharmaceutically acceptable excipients.

The pharmaceutical compositions of the present invention may, however, also contain more than one active ingredient in another embodiment. That is besides sofosbuvir another active ingredient may be present in this case. In one embodiment, the composition of the present invention thus comprises one or more other active ingredients in addition to sofosbuvir, preferably ledispavir or velpatasvir. A skilled person is well aware of the distinction between pharmaceutically active ingredients and pharmaceutical excipients.

Of course, the pharmaceutical composition according to the present invention can also be administered with one or more other active ingredients than sofosbuvir in a combination therapy. In particular, the solid pharmaceutical composition of the present invention can be used in known combination therapies, e.g. in the same way as the known commercial product Sovaldi®.

For example, herein the one or more other active ingredients can be for treating HCV and/or other conditions such as HIV infections. In one embodiment, non-limiting examples of suitable other active ingredients include one or more interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs or therapeutic agents for treating HCV.

The one or more other active ingredients may further be those which treat other conditions, such as HIV infections. Accordingly, the one or more other active ingredients may be compounds useful in treating HIV, for example HIV protease inhibiting compounds, non-nucleoside inhibitors of HIV reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gpl20 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

Suitable one or more other active ingredients are particularly listed in WO 2014/120981 to which it is explicitly referred.

In one embodiment, the composition of the present invention comprises ledispavir. Ledispavir is in this case preferably comprised in the composition of the present invention in an amount of 10 to 25 % based on the total weight of the pharmaceutical composition. The present invention, e.g., relates to a composition comprising ledispavir and wherein the total amount of sofosbuvir is 100-400 mg, preferably 300-400 mg and more preferably 400 mg. Such pharmaceutical compositions are, e.g., administered to a patient once a day. In one embodiment the pharmaceutical composition of the present invention comprises about 400 mg sofosbuvir and about 90 mg ledispavir. In another embodiment, the composition does not contain ledispavir. The composition of the present invention may then also be administered in combination with a separate pharmaceutical composition comprising ledispavir.

In one embodiment, the composition of the present invention comprises velpatasvir. Velpatasvir is in this case preferably comprised in the pharmaceutical composition of the present invention in an amount of 1 to 15 % based on the total weight of the pharmaceutical composition. The present invention, e.g., relates to a composition comprising velpatasvir and wherein the total amount of sofosbuvir is 100-400 mg, preferably 300-400 mg and more preferably 400 mg. In another preferred embodiment the present invention, e.g., relates to a solid pharmaceutical composition comprising velpatasvir and wherein the total amount of sofosbuvir is below 350 mg or below 300 mg, preferably 200-350 mg or 250-350 mg. Such pharmaceutical compositions are, e.g., administered to a patient once a day. In one embodiment, the pharmaceutical composition of the present invention comprises sofosbuvir in one of the afore-described amounts and 10-150 mg velpatasvir. In another embodiment, the composition does not contain velpatasvir. The composition of the present invention may then also be administered in combination with a separate pharmaceutical composition comprising velpatasvir.

In one embodiment, the composition of the present invention is in form of a tablet, wherein the tablet contains sofosbuvir as active ingredient and one or more pharmaceutically acceptable excipients and wherein the tablet contains one or more disintegrants and the

relative amount of disintegrants in the composition is more than 10 %, preferably more than 12 % by weight based on the weight of the total composition.

The sofosbuvir is present in crystalline form in the composition of the present invention. Sofosbuvir is, e.g., described in US 7,964,580 and in US 8,334,270. Solid state forms of Sofosbuvir are, e.g., described in WO 2010/135569, US 2011/251152, WO2011/123645, CN 104130302, CN 104277088 and CN 104447924. The sofosbuvir for use in the present application can have any of the crystalline forms as described in one of those patent publications.

Preferably, sofosbuvir is present in crystalline form in the pharmaceutical composition (in particular when in the form of a tablet) according to the present invention. The crystalline form of Sofosbuvir to be used in the pharmaceutical compositions of the present invention (preferably in the tablets of the present invention) is preferably crystalline sofosbuvir form E. Sofosbuvir form E is sometimes also designated as sofosbuvir form 7. Preferably, the crystalline sofosbuvir (form E) used in the present invention has an X-ray powder diffraction pattern comprising peaks at 12.4, 16.2, 17.2, 25.0 and 25.3 degrees two theta ± 0.1 degrees two theta. More preferably, the crystalline sofosbuvir (form E) used in the present invention has an X-ray powder diffraction pattern comprising peaks at 12.4, 16.2, 17.2, 25.0 and 25.3 degrees two theta ± 0.1 degrees two theta and peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern.

In one embodiment the crystalline sofosbuvir (form E) used in the present invention has an X-ray powder diffraction pattern comprising peaks 12.4, 13.5, 16.2, 25.3 and 27.2 degrees two theta ± 0.2 degrees two theta.

In one embodiment the crystalline sofosbuvir (form E) used in the present invention has an X-ray diffraction pattern having peaks at 8.1, 12.1, 12.4, 13.5, 16.2 and 17.2 degrees two theta ± 0.1 degrees two theta.

In one embodiment the crystalline sofosbuvir (form E) used in the present invention has an X-ray powder diffraction pattern comprising peaks at 8.1, 12.1, 12.4, 13.5, 16.2 and 17.2 degrees two theta ± 0.2 degrees two theta and peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern.

In one embodiment the crystalline sofosbuvir (form E) used in the present invention has an X-ray powder diffraction pattern comprising peaks at 8.1, 10.4, 13.5, 18.0 and 18.7 degrees two theta ± 0.1 degrees two theta.

In one embodiment the crystalline sofosbuvir (form E) used in the present invention has an X-ray powder diffraction pattern comprising peaks at 8.1, 10.4, 13.5, 18.0 and 18.7 degrees two theta ± 0.2 degrees two theta and peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern.

In a preferred embodiment the crystalline sofosbuvir (form E) used in the present invention has an X-ray powder diffraction pattern comprising peaks at 8.1, 10.4, 12.1, 12.4, 13.5, 16.2, 17.2, 18.0, 18.7, 25.0, 25.3 and 27.2 degrees two theta ± 0.2 degrees two theta, preferably ± 0.1 degrees two theta. In a more preferred embodiment sofosbuvir (form E) used in the present invention has an X-ray powder diffraction pattern comprising peaks at 8.1, 10.4, 12.1, 12.4, 13.5, 16.2, 17.2, 18.0, 18.7, 25.0, 25.3 and 27.2 degrees two theta ± 0.2 degrees two theta, preferably ± 0.1 degrees two theta, and peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern. Even more preferably, the crystalline sofosbuvir used in the present invention has an X-ray powder diffraction pattern as depicted in figure 1. The X-ray powder diffraction pattern is obtained using CuK_ radiation (λ = 1.5418 Å) as described in the examples.

However, the crystalline form of the sofosbuvir for use in the present application is not particularly limited and other crystalline forms can also be used. In one embodiment of the present invention the sofosbuvir is sofosbuvir of form 6 (see US 2011/251152).

With respect to sofosbuvir and methods for its production it can also be referred to e.g. US patent 7,964,580 and patent publications US 2010/0016251 and 2012/010278.

Surprisingly, the pharmaceutical compositions in the form of a tablet according to the present invention show fast dissolution with little variations between individual tablets. This has been shown in the examples of the specification where figures 2-4 show the dissolution behavior of tablets of the present invention prepared in examples 4-6. It is also referred to example 7. It can be seen that the dissolution is very fast with little inter tablet variability. Preferably after 5 minutes more than 90%, more preferably more than 95% of

the amount of sofosbuvir in the pharmaceutical composition has dissolved in 900 ml of an aqueous solution pH 6.8, USP paddle apparatus II at 75 rpm, 37 °C. More preferably after 10 minutes more than 95%, even more preferred more than 97% of the amount of sofosbuvir in the pharmaceutical composition has dissolved in 900 ml of an aqueous solution pH 6.8, USP paddle apparatus II at 75 rpm, 37 °C.

Preferably, the composition of the present invention comprises not more than 1.5 % of lubricants based on the weight of the total composition. In particular, the composition of the present invention preferably comprises not more than 1.5 % of magnesium stearate, more preferably not more than 1 %, mostly preferred not more than 0.6% of magnesium stearate based on the weight of the total composition.

The pharmaceutical compositions (preferably tablets) of the present invention preferably contain the sofosbuvir in form of small particle size sofosbuvir. The small particle size sofosbuvir preferably used in the present invention preferably has a d(0.5) of less than 20 µm, preferably less than 10 µm, more preferably less than 5 µm and most preferably between 1-2 µm. The particle size is measured herein by laser diffraction (preferably using the Malvern Mastersizer 2000). In one embodiment of the present invention, the small particle size sofosbuvir has a d(0.1) of 0.4-0.6 µm, a d(0.5) of 1.0-2.0 µm and a d(0.9) of 3.2-5.0 µm. The d(0.1), d(0.5) and d(0.9) values are based on a volume distribution. For measurement of the sofosbuvir particle size it is also referred to example 7.

The small particle size sofosbuvir may be directly obtainable by different processes, for example it may be obtained through chemical synthesis or by micronization techniques. Micronization is a technique known to the skilled person. E.g., by milling as a commonly known micronization technique small particles sizes can be achieved.

In one embodiment, the small particle size sofosbuvir is sofosbuvir of form E. In a further preferred embodiment of the present invention, the pharmaceutical composition is a composition, wherein the small particle size sofosbuvir is sofosbuvir of form E and the composition is a solid pharmaceutical composition and the sofosbuvir is contained in an amount of 35 to 75%, based on the total weight of the composition, preferably in an amount of 40-50 % based on the total weight of the composition.

Solid pharmaceutical compositions according to the present invention are, e.g., powders, granules, pellets, capsules or tablets. A tablet is particularly preferred as the solid pharmaceutical composition of the present invention. It is in particular envisaged that the term "pharmaceutical composition" in the present specification can be replaced by the term "tablet".

In one embodiment of the present invention the pharmaceutical composition is in the form of a tablet, wherein the tablet contains one or more disintegrant, wherein the one or more disintegrant is one or more superdisintegrant preferably selected from the group consisting of sodium carboxymethyl starch, crospovidone and croscarmellose sodium. Preferably, the composition of the present invention contains at least one disintegrant which is a superdisintegrant and the total amount of superdisintegrants in the composition is at least 10 %, more preferably at least 12 %, still more preferably at least 14 % by weight based on the total amount of the pharmaceutical composition, such as between 10 to 20%, more preferably 12 to 20% by weight based on the total amount of the pharmaceutical composition in the form of a tablet.

In one embodiment of the present invention the pharmaceutical compositions is in the form of a tablet, wherein the tablet contains one or more disintegrants and one or more binders. Disintegrants and binders are known in the art.

Examples of typical binders include hydroxypropyl cellulose, hydroxypropylmethyl cellulose, povidone and copovidone. The most preferred binder according to the present invention is hydroxypropyl cellulose and here it is particularly preferred to use low substituted hydroxypropyl cellulose, e.g. the hydroxypropyl cellulose known under the brandname L-HPC LH11.

Preferred superdisintegrants are sodium carboxymethyl starch (sodium starch glycolate), cross-linked polyvinyl pyrrolidone (crospovidone), modified cellulose (croscarmellose sodium), cross-linked alginic acid and Xanthan gum. In one embodiment of the present invention the superdisintegrant crospovidone, e.g. the commercial products Kollidon CL-F and Polyplasdone XL, is preferred.

Furthermore, in one embodiment of the present invention the pharmaceutical dosage form is in the form of a tablet, wherein the tablet preferably contains one or more surfactants,

e.g. an ionic surfactant or a non-ionic surfactant. Ionic surfactants can be anionic surfactants such as sodium lauryl sulfate or cationic surfactants such as cetyl pyridinium chloride and cetyltriethylammonium bromide. Non-ionic surfactants are e.g. polysorbates (such as polysorbate 20, 21, 40, 60, 61, 65, 80, 81, 85 and 120) which are sold under the tradenames span and tween and poloxamer. A preferred non-ionic surfactant is a poloxamer, e.g., Lutrol F127. In another embodiment the pharmaceutical composition of the present invention does not comprise a poloxamer and does not comprise a phospholipid.

In one embodiment of the present invention, the composition can contain usual lubricants. Examples of lubricants are magnesium stearate, stearic acid, sodium stearyl fumarate etc., preferred is sodium stearyl fumarate, e.g. the brandname Pruv. In the embodiment of the present invention in which the tablet can comprise a glidant (in another embodiment no glidant is present, as described above) a glidant can be used which is well known in the art, e.g. colloidal silicon dioxide. The preferred glidant is colloidal silicon dioxide such as the commercial product Syloid 244FP. In this embodiment it is preferred that the compositions of the present invention contain a relatively high amount of glidant of e.g. at least 7 %.

Very often, pharmaceutical compositions also contain diluents and fillers and it is not excluded that the pharmaceutical composition of the present invention also contains diluents or fillers. However, in view of the high relative amount of active ingredient in the compositions of the present invention and the high amount of other excipients it is preferred that the pharmaceutical composition contains no diluents and no filler.

Therefore, in one embodiment the pharmaceutical composition of the present invention contains one or more binders and one or more disintegrants (preferably superdisintegrants) and preferably at least one surfactant, and optionally at least one lubricant in addition to the active ingredient.

Regarding the amounts of the pharmaceutically acceptable excipients, the compositions of the present invention in one embodiment contain a relative high amount of one or more disintegrants (preferably superdisintegrants) and a relative low amount of binder. It was found that the pharmaceutical compositions of the invention can be prepared by using a higher amount of disintegrants (preferably superdisintegrants) than binder in the

composition. Preferably, in one embodiment of the present invention, wherein the pharmaceutical composition is in the form of a tablet and wherein the tablet contains disintegrant, the disintegrant in the composition of the present invention is a superdisintegrant and is present in an amount of at least 10 %, more preferably at least 12 %, still more preferably at least 14 % by weight based on the total amount of the pharmaceutical composition in the form of a tablet. In one embodiment, the amount of binder is less than the amount of disintegrant and is preferably in the range of 10 to 18 %, more preferably in the range of 12 to 17 %, particular preferably in the range of 13 to 16 %.

The ratio of the one or more binder to the one or more disintegrants (preferably the superdisintegrants) is preferably in the range of 0.85 to 0.99, more preferably in the range of 0.88-0.95.

Furthermore, in one embodiment the compositions of the present invention may contain a relatively high amount of one or more surfactants, preferably 5 % or more, more preferably 7 % or more. This is a usually high amount for pharmaceutical compositions in the form of a tablet. In one embodiment of the present invention, wherein the pharmaceutical compositions is in the form of a tablet, the tablet contains a surfactant in an amount of 7 % or more based on the total weight of the pharmaceutical composition.

In the following tables, preferred compositions of the present invention, wherein the compositions are in the form of tablets, are summarized. The tablets preferably contain the corresponding ingredient in the indicated amounts. Preferably, the tablets consist of the indicated ingredients in the indicated amounts, which means that no other ingredients are present.

Table I

Ingredient	Preferred embodiment 1	Preferred embodiment 2	Preferred embodiment 3
Sofosbuvir	40-50	40-50	40-50
one or more disintegrants	12-20	12-17	14-17
one or more binders	10-18	12-17	13-16
one or more surfactants	7-20	7-20	7-20
one or more glidants	7-20	7-12	7-12
one or more lubricants	0-5	0-3	0-3

The total amount of all components add up to 100 % if no other ingredients are present

Table II (no glidants present)

Ingredient	Preferred embodiment 1	Preferred embodiment 2	Preferred embodiment 3
Small particle size Sofosbuvir	39-50	40-50	40-50
one or more disintegrants	1-20	1-12	1-8
one or more fillers	20-60	30-55	40-50
one or more lubricants	0-3	0-1.5	0-1

The total amount of all components add up to 100 % if no other ingredients are present

In the above tables in a preferred embodiment the one or more disintegrants are one or more superdisintegrants selected from the group consisting of sodium carboxymethyl starch, crospovidone and croscarmellose sodium. In a further preferred embodiment, in the above table I the one or more disintegrants are crospovidone. In a further preferred embodiment, in the above table II the one or more disintegrants are sodium croscarmellose.

In a further preferred embodiment in the above table I the one or more binders are low substituted hydroxypropyl cellulose or hydroxypropylmethyl cellulose, preferably low substituted hydroxypropyl cellulose.

In a further preferred embodiment in the above table II the fillers are microcrystalline cellulose and/or mannitol.

It is furthermore preferred that in the above table I the one or more disintegrants are superdisintegrants as defined above and the one or more binders are low substituted hydroxypropyl cellulose.

It is furthermore preferred that in the above table I the one or more surfactants are anionic surfactants, e.g. a poloxamer. An embodiment which comprises the relative amounts indicated in the above table I and wherein the disintegrants, binders and surfactants are all the preferred embodiments as indicated above is also preferred. An embodiment which comprises the relative amounts indicated in the above table II and wherein the disintegrants and fillers are all the preferred embodiments as indicated above is also preferred.

The pharmaceutical compositions preferably in the form of a tablet according to the present invention are preferably for use in treating hepatitis C virus infections as is known in the art. As indicated above, in such a use the compositions in the form of a tablet according to the present invention can be used alone or in the form of a combination therapy as is known in the art.

Processes for preparing the pharmaceutical compositions in the form of a tablet according to the invention are known in the art. The sofosbuvir may be dry-granulated or wet-granulated before tableting, or the tablet blends may be directly compressed. Granulation is preferred for preparing sofosbuvir tablets, and dry granulation is most preferred. Tablets in accordance with the invention may be coated to facilitate swallowing and/or to enhance the appearance of the tablet.

In the process for preparing the pharmaceutical compositions in the form of a tablet according to the invention in one embodiment preferably an extrusion method can be used in which all components are mixed together and extruded to form a granulate. This granulate can then be compressed into tablets using usual tableting machines. Preparing extrusion granules and compressing those granules to tablets is a standard procedure in the art.

In a preferred embodiment the pharmaceutical compositions in the form of a tablet according to the present invention are prepared by dry granulation. Well-known dry

granulation methods are shown in the examples of this application. It is preferred that in the dry granulation method first a comprimate is formed, the comprimate is then crushed in order to obtain particles which are easier to handle than the original mixture. The crushed particles are sieved, optionally blended in a mixer such as a tumble mixer and then pressed to the pharmaceutical composition in the form of a tablet as described herein. This method is a well-known variant of the dry compression technology.

According to the invention the following embodiments A1-A14 and B1-B15 of pharmaceutical compositions and preparation processes are preferred. Disclosed in this specification are also embodiments C1-C17 and those parts of the above specification which are not in contradiction with these embodiments are also applicable to these embodiments.

Embodiment A1: Pharmaceutical composition in the form of a tablet which contains sofosbuvir as sole active ingredient and one or more pharmaceutically acceptable excipients, wherein the tablet contains the sofosbuvir in an amount of 35 to 55 %, based on the total weight of the tablet.

Embodiment A2: Pharmaceutical composition in the form of a tablet according to embodiment A1, wherein the tablet contains the active ingredient sofosbuvir in an amount of 40 % to 50 %, based on the total weight of the tablet.

Embodiment A3: Pharmaceutical composition in the form of a tablet according to embodiment A1 or A2, wherein the tablet contains about 400 mg sofosbuvir.

Embodiment A4: Pharmaceutical composition in the form of a tablet according to any of the embodiments A1 to A3, wherein sofosbuvir is present in crystalline form.

Embodiment A5: Pharmaceutical composition in the form of a tablet according to any of the embodiments A1 to A4 wherein the total tablet weight is not more than 1020 mg.

Embodiment A6: Pharmaceutical composition in the form of a tablet according to any of embodiments A1 to A5, wherein the tablet contains one or more binders and one or more disintegrants.

Embodiment A7: Pharmaceutical composition in the form of a tablet according to embodiment A6, wherein the total amount of disintegrants present in the pharmaceutical composition is higher than the total amount of binders in the pharmaceutical composition.

Embodiment A8: Pharmaceutical composition according to embodiment A7, wherein the ratio of the one or more binders / one or more disintegrants is in the range of 0.85 to 0.99.

Embodiment A9: Pharmaceutical composition in the form of a tablet according to any of embodiments A6 to A8 wherein the relative amount of disintegrants in the composition is more than 10 %, preferably more than 12 % by weight based on the weight of the total composition.

Embodiment A10: Pharmaceutical composition in the form of a tablet according to any of embodiments A6 to A9 wherein the one or more disintegrant is one or more superdisintegrant preferably selected from the group consisting of sodium carboxymethyl starch, crospovidone and croscarmelose sodium.

Embodiment A11: Pharmaceutical composition in the form of a tablet according to any of embodiments A1 to A10, wherein the composition contains a surfactant in an amount of 7 % or more based on the total weight of the pharmaceutical composition.

Embodiment A12: Pharmaceutical composition in the form of a tablet according to any of embodiments A1 to A11 consisting of sofosbuvir, one or more surfactants, one or more disintegrants, one or more binders, optionally one or more glidants, and optionally one or more lubricants.

Embodiment A13: Pharmaceutical composition in the form of a tablet according to any of embodiments A1 to A12 for use in the treatment of hepatitis C virus infections.

Embodiment A14: Process for preparing pharmaceutical compositions in the form of a tablet according to any of embodiments A1 to A12 comprising the process steps wherein the active ingredient and the one or more pharmaceutically acceptable excipients are compacted, the compacted mass is crushed, optionally sieved and compressed to the pharmaceutical composition in the form of a tablet according to any of embodiments A1 to A12.

Embodiment B1: Pharmaceutical composition in the form of a tablet which contains sofosbuvir as active ingredient and one or more pharmaceutically acceptable excipients, wherein the tablet contains the sofosbuvir in an amount of 35 to 75 %, based on the total weight of the tablet and wherein the tablet contains one or more disintegrants and the relative amount of disintegrants in the composition is more than 10 %, preferably more than 12 % by weight based on the weight of the total composition.

Embodiment B2: Pharmaceutical composition in the form of a tablet according to embodiment B1, wherein the tablet contains the sofosbuvir as sole active ingredient in an amount of 35 to 55 %, based on the total weight of the tablet.

Embodiment B3: Pharmaceutical composition in the form of a tablet according to embodiment B1 or B2, wherein the tablet contains the active ingredient sofosbuvir in an amount of 40 % to 50 %, based on the total weight of the tablet.

Embodiment B4: Pharmaceutical composition in the form of a tablet according to any one of embodiments B1 to B3, wherein the tablet contains about 400 mg sofosbuvir.

Embodiment B5: Pharmaceutical composition in the form of a tablet according to any of the embodiments B1 to B4, wherein sofosbuvir is present in crystalline form.

Embodiment B6: Pharmaceutical composition in the form of a tablet according to embodiment B5, wherein the crystalline sofosbuvir has an X-ray powder diffraction pattern comprising peaks at 12.4, 16.2, 17.2, 25.0 and 25.3 degrees two theta ± 0.1 degrees two theta, and preferably peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern.

Embodiment B7: Pharmaceutical composition in the form of a tablet according to any of the embodiments B1 to B6 wherein the total tablet weight is not more than 1020 mg.

Embodiment B8: Pharmaceutical composition in the form of a tablet according to any of embodiments B1 to B7, wherein the tablet contains one or more binders and one or more disintegrants.

Embodiment B9: Pharmaceutical composition in the form of a tablet according to embodiment 8, wherein the total amount of disintegrants present in the pharmaceutical composition is higher than the total amount of binders in the pharmaceutical composition.

Embodiment B10: Pharmaceutical composition according to embodiment 9, wherein the ratio of the one or more binders / one or more disintegrants is in the range of 0.85 to 0.99.

Embodiment B11: Pharmaceutical composition in the form of a tablet according to any of embodiments B1 to B10 wherein the one or more disintegrant is one or more superdisintegrant preferably selected from the group consisting of sodium carboxymethyl starch, crospovidone and croscarmelose sodium.

Embodiment B12: Pharmaceutical composition in the form of a tablet according to any of embodiments B1 to B11, wherein the composition contains a surfactant in an amount of 7 % or more based on the total weight of the pharmaceutical composition.

Embodiment B13: Pharmaceutical composition in the form of a tablet according to any of embodiments B1 to B12 consisting of sofosbuvir, one or more surfactants, one or more disintegrants, one or more binders, optionally one or more glidants, and optionally one or more lubricants.

Embodiment B14: Pharmaceutical composition in the form of a tablet according to any of embodiments B1 to B13 for use in the treatment of hepatitis C virus infections.

Embodiment B15: Process for preparing pharmaceutical compositions in the form of a tablet according to any of embodiments B1 to B14 comprising the process steps wherein the active ingredient and the one or more pharmaceutically acceptable excipients are compacted, the compacted mass is crushed, optionally sieved and compressed to the pharmaceutical composition in the form of a tablet according to any of embodiments B1 to B14.

Embodiment C1: Pharmaceutical composition comprising small particle size sofosbuvir and no glidants.

Embodiment C2: The pharmaceutical composition of embodiment C1, wherein the composition comprises not more than 1.5 % of lubricants based on the weight of the total composition.

Embodiment C3: The pharmaceutical composition of embodiment C1 or C2, wherein the small particle size sofosbuvir has a d(0.5) of less than 20 µm, preferably less than 10 µm, more preferably less than 5 µm and most preferably between 1-2 µm.

Embodiment C4: The pharmaceutical composition of any of embodiments C1-C3, wherein the small particle size sofosbuvir has a d(0.1) of 0.4-0.6 µm, a d(0.5) of 1.0-2.0 µm and a d(0.9) of 3.2-5.0 µm.

Embodiment C5: Pharmaceutical composition of any of embodiments C1-C4, wherein the small particle size sofosbuvir is present in crystalline form.

Embodiment C6: The pharmaceutical composition of embodiment C5, wherein the crystalline sofosbuvir has an X-ray powder diffraction pattern comprising peaks at 12.4, 16.2, 17.2, 25.0 and 25.3 degrees two theta ± 0.1 degrees two theta, and preferably peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern.

Embodiment C7: The pharmaceutical composition of embodiment C5, wherein the small particle size sofosbuvir is sofosbuvir of form 6.

Embodiment C8: The pharmaceutical composition of embodiment C5, wherein the small particle size sofosbuvir is sofosbuvir of form E.

Embodiment C9: The pharmaceutical composition of embodiment of C8, wherein the composition is a solid pharmaceutical composition and the sofosbuvir is contained in an amount of 35 to 75%, based on the total weight of the composition, preferably in an amount of 40-50 % based on the total weight of the composition.

Embodiment C10: The pharmaceutical composition of any of embodiments C1-C9, wherein the composition is in form of a tablet comprising one or more pharmaceutically acceptable excipients.

Embodiment C11: The pharmaceutical composition of embodiment C10, wherein the sofosbuvir is contained in an amount of 35 to 75%, based on the total weight of the tablet, preferably in an amount of 40-50 % based on the total weight of the tablet.

Embodiment C12: The pharmaceutical composition of embodiment C10 or C11, wherein the tablet contains the sofosbuvir as sole active ingredient in an amount of 35 to 55 %, based on the total weight of the tablet.

Embodiment C13: The pharmaceutical composition of any of embodiments C10-C12, wherein the tablet contains one or more disintegrants and the relative amount of disintegrants in the composition is more than 10 %, preferably more than 12 % by weight based on the weight of the total composition.

Embodiment C14: The pharmaceutical composition of any of embodiments C10-C13, wherein the tablet contains about 400 mg sofosbuvir and wherein preferably the total tablet weight is not more than 1020 mg.

Embodiment C15: The pharmaceutical composition of any of embodiments C10-C14, wherein the tablet contains one or more binders and one or more disintegrants.

Embodiment C16: The pharmaceutical composition of any of embodiments C1-C15 for use in the treatment of hepatitis C virus infections.

Embodiment C17: Process for preparing pharmaceutical compositions in the form of a tablet according to any of embodiments C10-C15 comprising the process steps wherein the active ingredient and the one or more pharmaceutically acceptable excipients are compacted, the compacted mass is crushed, optionally sieved and compressed to the pharmaceutical composition in the form of a tablet according to any of embodiments C10-C15.

The following examples are illustrative without restricting the scope of protection. If in the examples a process detail is not explicitly described, a skilled person can easily find such detail according to the general practice in the art.

Preparation of Crystalline form E of sofosbuvir

Example 1: Preparation of Crystalline form E of Sofosbuvir:

Sofosbuvir (1g, Form 1) was dissolved in the acetone (3 mL) under stirring at 25±5°C (Form 1 of Sofosbuvir may be obtained according to the process described in WO 2010/135569). Then di-iso-propyl-ether (DIPE) (10 mL) was added under stirring to get turbidity. The mass was stirred for 2 h at 25±5°C to give a white solid. To this mass DIPE (15 mL) was added and the mass was stirred for 48 h at 25±5°C. The mass was filtered and the obtained solid was dried at 50 °C under vacuum for 12 h to provide form E of Sofosbivir (as confirmed by XRPD).

Example 2: Preparation of Crystalline form E of sofosbuvir:

MIBK (5 L) and water (1% of MIBK) were added to Sofosbuvir Form-1 (1 Kg) at 9±3 °C (Form 1 of Sofosbuvir may be obtained according to the process described in WO 2010/135569). The resulting suspension was stirred at 50 – 200 RPM until the solution becomes clear. Solution was filtered to remove any foreign particles. Washed with MIBK (0.5 L). The filtered solution was charged, stirred at 9±3 °C, seeded with Form E crystals and solution was stirred as such for 4±0.5 h at 50-200 RPM. Cyclohexane (10 L) was then added and solution was stirred for 1±0.5 h at 9±3 °C. Slurry was filtered and the cake was washed with cyclohexane (2 X 2 L). Solid was dried under vacuum for 12 h at Tj 40-50 °C to afford Sofosbuvir Form E in 80 to 90% yield.

Example 3: Preparation of micronized Crystalline form E of Sofosbuvir:

Micronized crystalline form E of sofobuvir was prepared using a 100 mm plate airjet micronizer, feed rate 0.5 Kg/hr, feeding pressure is 6.5 bars+/- 0.5 bar, milling pressure is 6 bars+/- 0.5 bar.

X-Ray Powder Diffraction

X-ray powder diffraction analyses were performed on X-Ray powder diffractometer Bruker D8 Advance; CuK_ radiation (λ = 1.5418 Å); Lynx eye detector; laboratory temperature 22-25 °C; PMMA specimen holder ring. Prior to analysis, the samples were gently ground by means of mortar and pestle in order to obtain a fine powder. The ground sample was adjusted into a cavity of the sample holder and the surface of the sample was smoothed by means of a cover glass.

Measurement parameters:

Scan range: 2 – 40 degrees 2-theta;

Scan mode: continuous;

Step size: 0.05 degrees;

Time per step: 0.5 s;

Sample spin: 30 rpm;

Sample holder: PMMA specimen holder ring.

The described peak positions were determined using silicon powder as an internal standard in an admixture with the sample measured. The position of the silicon (Si) peak was corrected to silicone theoretical peak: 28.45 degrees two-theta, and the positions of the measured peaks were corrected respectively. Figure 1 shows the X-ray powder diffraction pattern of sofosbuvir Form E.

Formulations

Example 4: Tablet formulation with 40 % drug load

Composition	Brand Name	Functionality	Amount	
			[mg]	[%]
Sofosbuvir Form 1	-	active ingredient	402.29*	40.07
Poloxamer F127	Lutrol F127	surfactant	190.00	18.92
Colloidal silicon dioxide	Syloid 244FP	glidant	100.00	9.96
Crospovidone	Kollidon CL-F	disintegrant	90.00	8.96
Hydroxypropyl cellulose, low-substituted	L-HPC LH 11	binder	141.72	14.12
Crospovidone	Polyplasdone XL	disintegrant	64.00	6.37
Natriumstearylfumarate	Pruv	lubricant	16.00	1.59
		TOTAL	1004.01	100.0

*adjusted to potency of the active

Manufacturing:

Sofosbuvir, Lutrol F127, Syloid 244FP, Kollidon CL-F, L-HPC LH 11 and Polyplasdone XL were sieved through a 630µm sieve and blended in a tumble mixer for 10 minutes. Pruv were sieved through a 125µm sieve and blending was continued for a further 4 minutes. The blend was compacted on an eccentric press. Afterwards the tablets (compacted mass)

were crushed and passed through a 630µm sieve and blended in a tumble mixer for 5 minutes. The final blend was compressed on an eccentric press (18mm x 8,7mm oblong).

Example 5: Tablet formulation with 50 % drug load

Composition	Brand Name	Functionality	Amount	
			[mg]	[%]
Sofosbuvir Form 1	-	active ingredient	402.29*	50.14
Poloxamer F127	Lutrol F127	surfactant	74.00	9.22
Colloidal silicon dioxide	Syloid 244FP	glidant	74.00	9.22
Crospovidone	Kollidon CL-F	disintegrant	74.00	9.22
Hydroxypropyl cellulose, low-substituted	L-HPC LH 11	binder	112.00	13.96
Crospovidone	Polyplasdone XL	disintegrant	50.00	6.23
Natriumstearylfumarate	Pruv	lubricant	16.00	1.99
		TOTAL	802.29	100.0

*adjusted to potency of the active

Manufacturing:

Sofosbuvir, Lutrol F127, Syloid 244FP, Kollidon CL-F, L-HPC LH 11 and Polyplasdone XL were sieved through a 630µm sieve and blended in a tumble mixer for 10 minutes. Pruv were sieved through a 125µm sieve and blending was continued for a further 4 minutes. The blend was compacted on an eccentric press. Afterwards the tablets (compacted mass) were crushed and passed through a 630µm sieve and blended in a tumble mixer for 5 minutes. The final blend was compressed on an eccentric press (18mm x 8,7mm oblong).

Example 6: Formulation with 50% drug load

Composition	Brand Name	Functionality	Amount	
			[mg]	[%]
Sofosbuvir Form E		active ingredient	400.0	50.0
Mannitol	(Partek M200)	filler	107.2	13.4
Microcrystalline Cellulose	(Avicel PH 102)	filler	107.2	13.4
Croscarmellose-Sodium	(Ac-Di-Sol)	disintegrant	120.0	15.0
Colloidal Siliciumdioxide	(Syloid 244 FP)	glidant	56.0	7.0
Magnesium stearate		lubricant	9.6	1.2
TOTAL			**800.0**	**100.0**

Manufacturing:

Sofosbuvir (sieved through a 250 µm sieve), Mannitol, MCC, Croscarmellose-Na and Siliciumdioxide were sieved through a 630µm sieve and blended in a tumble mixer for 10 minutes. Mg-stearate was added through a sieve (125µm) and the mixture was blended for further 3 min. The final blend was compressed to tablets.

The tablets prepared in example 4, example 5 and example 6 were subjected to dissolution tests. The conditions were the usual conditions of the US Pharmacopeia with paddle apparatus II in 900 ml of an aqueous solvent with a pH of 6.8 at 37°C and 75 rpm. Figure 2 shows the dissolution of two tablets of example 4 with 40 % drug load, figure 3 shows the dissolution of two tablets of example 5 with 50 % drug load, figure 4 shows the dissolution of tablets of example 6 with 50 % drug load in comparison to the dissolution of Sovaldi® tablets.

Example 7: Tablet formulations that are free of glidant

Intragranular ingredients (mg)		
	Sofosbuvir Form E formulation	Sofosbuvir Form 6 formulation
Part I		
Small particle size Sofosbuvir	400	400
Microcrystalline Cellulose	215	215
Croscarmellose Sodium	30	30
Mannitol	270	270
Silicon Dioxide	-	-
Part II		
Magnesium stearate	5	5
Extragranular ingredients		
Part III		
Microcrystalline Cellulose	45	45
Croscarmellose Sodium	30	30

Part IV		
Magnesium stearate	5	5
Silicon Dioxide	-	-
Total core weight	1000	1000

Method of preparation:

The batches were prepared by a dry granulation method. The intra-granular ingredients of Part I were blended for 10 minutes, Magnesium Stearate of Part II was added to the mix and blended for additional 5 minutes. The obtained blend was granulated by the roller compactor and milled through 0.8mm screen and blended with the Part III extra-granular excipients for 10 minutes. Part IV Magnesium Stearate added to the blend and blended for additional 5 minutes. The final blend was compressed into tablets.

Particle size measurement of small particle size sofosbuvir

Dry cell measurement

Mastersizer 2000

Analysis model: General purpose

Powder RI: 1.573

Absorption: 0.5

Dispersant name: Dry Dispersion (Air)

Dispersant RI: 1.0

Sensitivity: Normal (fine powder)

Filtering obscuration: On (0.5-3%)

Measuring time: 5 seconds (5000 snaps)

Background measuring time: 5 seconds (5000 snaps)

Repeats aliquots: 1

Repeat Measurements: 1

Pressure: 2.5 Bar

Feed rate of the flow cell: 30%

Funnel gap: 5mm

Feeder with small sieve filled with balls (2/3by volume)

Between samples runs, clean the cell with air for 30 seconds.

A background measurement was performed before each measurement.

0.5gm sofosbuvir powder was added with a spatula directly into the feeder. The feeder work was started. The obscuration should be in the range 0.5-3%.

Physical results

	Sofosbuvir Form E formulation	Sofosbuvir Form 6 formulation
Hausner Ratio	1.22	1.22
Carr's Index	18	18
Tablet Weight (mg)	1000	1000
Tablet Hardness (scu)	41	40
Disintegration Time (min)	1:21	1:37

The Hausner ratio and Carr's is frequently used as an indication of the flowability of a powder. The Hausner factor is the ratio of bulk volume to compacted volume, calculated by the formula bulk density/tapped density. Bulk and tapped density are measured according to the general Pharmacopoeia method. Hausner ratio of <1.25 indicates a powder that is free flowing. A Carr's Index > 23 indicates poor flow.

Claims

1. Pharmaceutical composition comprising sofosbuvir in an amount of 35 to 75 %, based on the total weight of the composition.

2. Pharmaceutical composition according to claim 1, wherein the composition is in the form of a tablet and preferably comprises one or more pharmaceutically acceptable excipients.

3. Pharmaceutical composition according to claim 1 or 2, wherein the sofosbuvir is small particle size sofosbuvir and the composition comprises no glidants.

4. Pharmaceutical composition according to any of claims 1-3, wherein the composition contains sofosbuvir as sole active ingredient and one or more pharmaceutically acceptable excipients.

5. Pharmaceutical composition according to any of claims 1-3, wherein the composition comprises one or more other active ingredients in addition to sofosbuvir, preferably ledispavir or velpatasvir.

6. Pharmaceutical composition according to any of claims 2-5, wherein the tablet contains sofosbuvir as active ingredient and one or more pharmaceutically acceptable excipients and wherein the tablet contains one or more disintegrants and the relative amount of disintegrants in the composition is more than 10 %, preferably more than 12 % by weight based on the weight of the total composition.

7. Pharmaceutical composition according to any of claims 1-6, wherein the composition comprises sofosbuvir in an amount of 35-55 % based on the total weight of the composition.

8. Pharmaceutical composition according to any of claims 1-7, wherein the composition comprises sofosbuvir in an amount of 40-50 % based on the total weight of the composition

9. Pharmaceutical composition according to any one of claims 1-8, wherein the composition contains about 400 mg sofosbuvir.

10. Pharmaceutical composition according to any of the claims 1-9, wherein the weight of the pharmaceutical composition is not more than 1020 mg.

11. Pharmaceutical composition according to any of claims 1-10, wherein the sofosbuvir is present in crystalline form.

12. Pharmaceutical composition according to claim 11, wherein the crystalline sofosbuvir has an X-ray powder diffraction pattern comprising peaks at 12.4, 16.2, 17.2, 25.0 and 25.3 degrees two theta ± 0.1 degrees two theta, and preferably peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern.

13. Pharmaceutical composition according to claim 11, wherein the crystalline sofosbuvir has an X-ray powder diffraction pattern comprising peaks at 8.1, 12.1, 12.4, 13.5, 16.2 and 17.2 degrees two theta ± 0.1 degrees two theta.

14. Pharmaceutical composition according to claim 11, wherein the crystalline sofosbuvir has an X-ray powder diffraction pattern comprising peaks at 8.1, 12.1, 12.4, 13.5, 16.2 and 17.2 degrees two theta ± 0.2 degrees two theta and peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern.

15. Pharmaceutical composition according to claim 11, wherein the crystalline sofosbuvir has an X-ray powder diffraction pattern comprising peaks at 8.1, 10.4, 13.5, 18.0 and 18.7 degrees two theta ± 0.1 degrees two theta.

16. Pharmaceutical composition according to claim 11, wherein the crystalline sofosbuvir has an X-ray powder diffraction pattern comprising peaks at 8.1, 10.4, 13.5, 18.0 and 18.7 degrees two theta ± 0.2 degrees two theta and peaks at 10.9 and 14.2 degrees two theta ± 0.2 degrees two theta are absent in the X-ray powder diffraction pattern.

17. Pharmaceutical composition according to claim 11, wherein the sofosbuvir is sofosbuvir of form 6.

18. Pharmaceutical composition according to any of claims of claim 1-17, wherein the composition comprises not more than 1.5 % of lubricants based on the weight of the total composition.

19. Pharmaceutical composition according to any of claims 3-18, wherein the small particle size sofosbuvir has a d(0.5) of less than 20 µm, preferably less than 10 µm, more preferably less than 5 µm and most preferably between 1-2 µm.

20. Pharmaceutical composition according to any of claims 3-19, wherein the small particle size sofosbuvir has a d(0.1) of 0.4-0.6 µm, a d(0.5) of 1.0-2.0 µm and a d(0.9) of 3.2-5.0 µm.

21. Pharmaceutical composition according to any of claims 2-20, wherein the tablet contains one or more disintegrant, wherein the one or more disintegrant is one or more superdisintegrant preferably selected from the group consisting of sodium carboxymethyl starch, crospovidone and croscarmelose sodium.

22. Pharmaceutical composition according to any of claims 2-21, wherein the tablet contains one or more binders and one or more disintegrants.

23. Pharmaceutical composition according to claim 22, wherein the total amount of disintegrants present in the pharmaceutical composition is higher than the total amount of binders in the pharmaceutical composition.

24. Pharmaceutical composition according to claim 23, wherein the ratio of the one or more binders / one or more disintegrants is in the range of 0.85 to 0.99.

25. Pharmaceutical composition according to any of claims 2-24, wherein the tablet contains a surfactant in an amount of 7 % or more based on the total weight of the pharmaceutical composition.

26. Pharmaceutical composition according to any of claims 1-25 for use in the treatment of hepatitis C virus infections.

27. Pharmaceutical composition in the form of a tablet according to any of claims 2-25 prepared by dry granulation, wherein preferably in the dry granulation method first a comprimate is formed, the comprimate is crushed, the crushed particles are sieved,

optionally blended in a mixer such as a tumble mixer and then pressed to the pharmaceutical composition in the form of a tablet.

28. Process for preparing pharmaceutical compositions in the form of a tablet according to any of claims 2-25 comprising the process steps wherein the active ingredient and the one or more pharmaceutically acceptable excipients are compacted, the compacted mass is crushed, optionally sieved and compressed to the pharmaceutical composition in the form of a tablet according to any of claims 2-25.

Figure 1

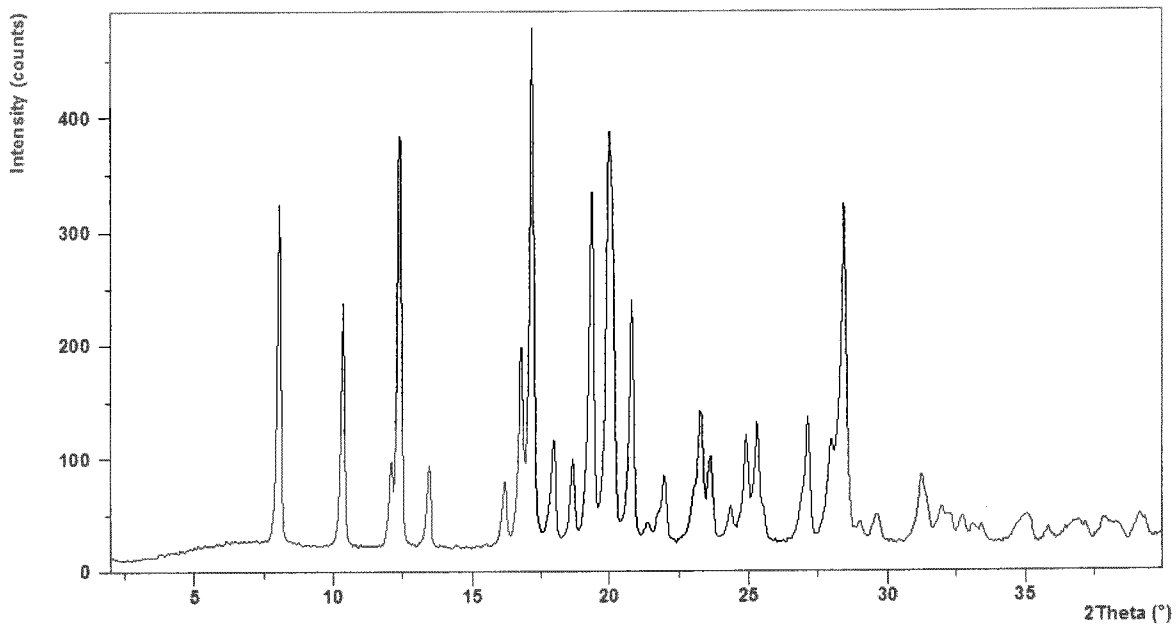

Figure 2

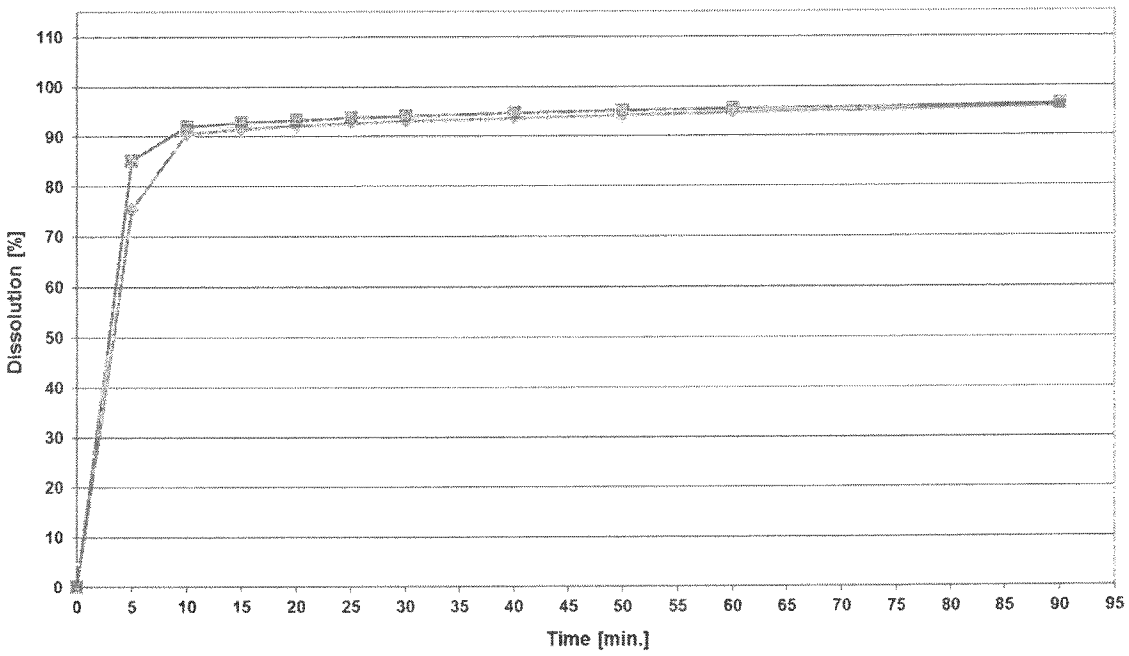
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Figure 3

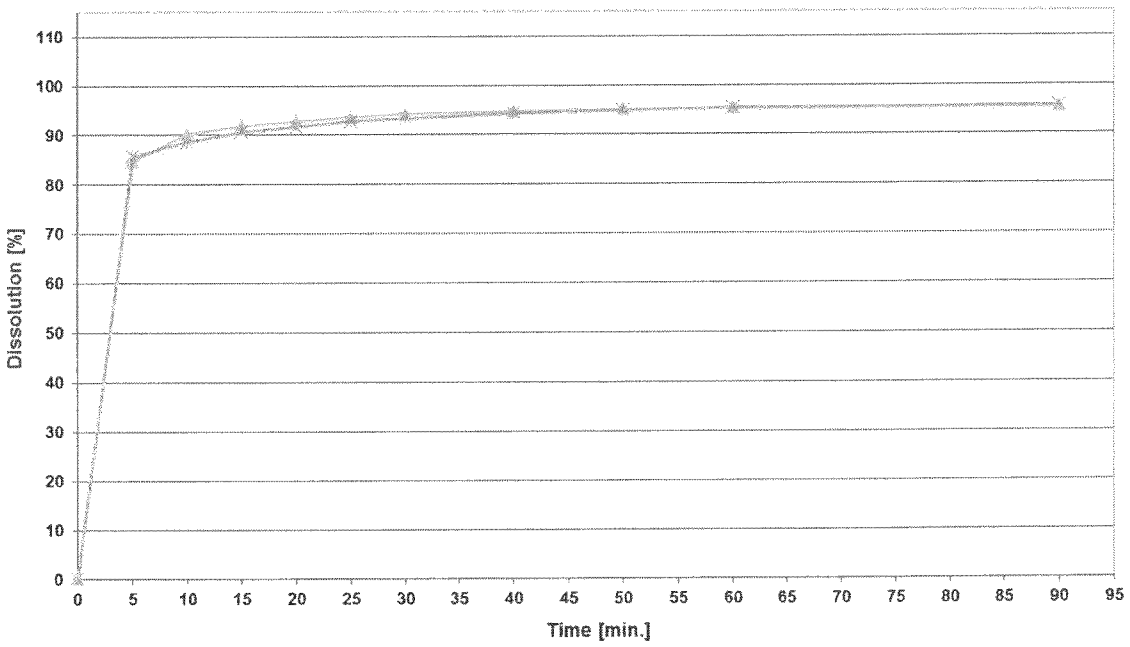
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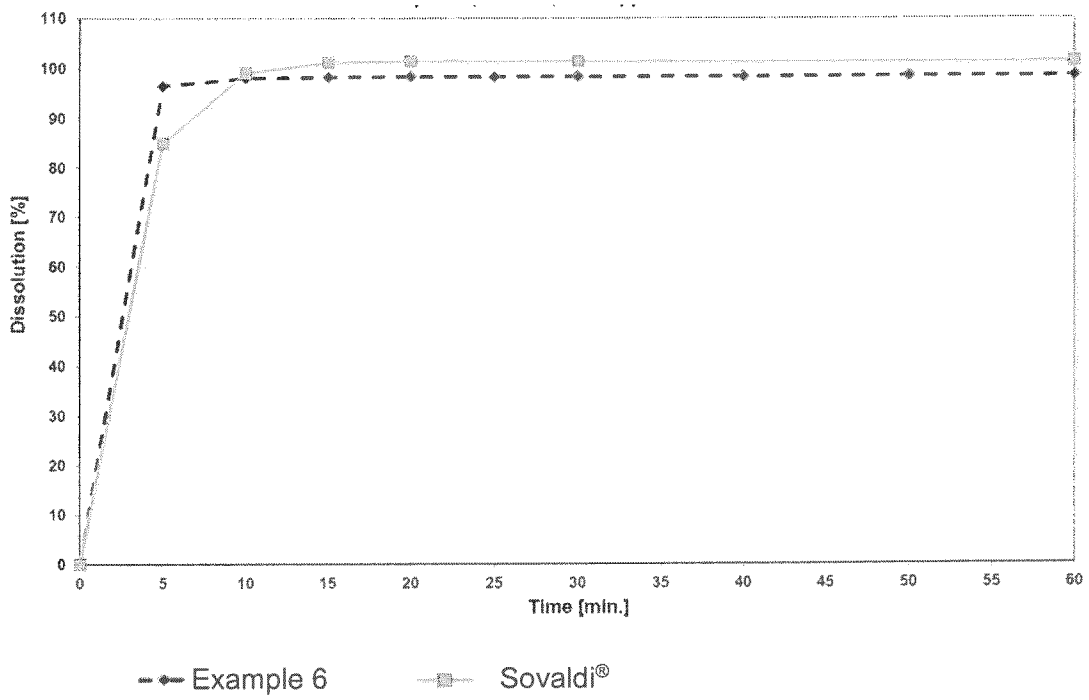
Figure 4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100
90
80
70
60
50
40
30
20
10
0
Dissolution [%]
0
5
10
15
20
25
30
35
40
45
50
55
60
Time [min.]
Example 6
Sovaldi®

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/063163

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/4196 A61P31/14 A61K31/4184 A61K31/7072
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, 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	WO 2013/082003 A1 (GILEAD PHARMASSET LLC [US]) 6 June 2013 (2013-06-06) cited in the application examples claims	1-28

X,P	WO 2014/120981 A1 (CHAL BEN [US] ET AL) 7 August 2014 (2014-08-07) cited in the application tables 3,5,18 claims	1-25

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2015	08/09/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	S. von Eggelkraut-G.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/063163

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013082003 A1	06-06-2013	US 2013136776 A1	30-05-2013
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		WO 2014120981 A1	07-08-2014