(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 October 2016 (06.10.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/156330 A1

(51) **International Patent Classification**:
A61K 9/20 (2006.01) *A61K 31/00* (2006.01)

(21) **International Application Number**:
PCT/EP2016/056820

(22) **International Filing Date**:
29 March 2016 (29.03.2016)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
15161687.7 30 March 2015 (30.03.2015) EP

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

WO 2016/156330 A1

(54) **Title**: SOLID PHARMACEUTICAL COMPOSITION COMPRISING AMORPHOUS SOFOSBUVIR AND A PHOSPHOLIPID

(57) **Abstract**: The present invention relates to a solid pharmaceutical composition comprising amorphous sofosbuvir and at least one phospholipid, preferably in the form of a tablet. The patent also relates to a process for preparing such compositions and to the use of the solid pharmaceutical composition for the treatment of hepatitis C virus infections.

Solid pharmaceutical composition comprising amorphous sofosbuvir and a phospholipid

The present invention relates to a solid pharmaceutical composition comprising amorphous sofosbuvir and at least one phospholipid, preferably in the form of a tablet. The patent also relates to a process for preparing such compositions and to the use of the solid pharmaceutical composition for the treatment of hepatitis C virus (HCV) infections.

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®.

The recommended dose of sofosbuvir is 400 mg administered orally once daily. Thus, it is advantageous if a pharmaceutical composition containing sofosbuvir contains 400 mg of the active ingredient so that it only needs to be administered once per day. Accordingly, the commercial product Sovaldi® is in the form of a tablet which contains 400 mg of crystalline sofosbuvir. However, sofosbuvir is difficult to handle and to formulate. The tablet Sovaldi® has a total weight of 1200 mg, thus providing a drug load of only 33.33 %. Tablets with a total weight of 1200 mg containing 400 mg of crystalline sofosbuvir are also described in WO 2013/082003. Pharmaceutical compositions 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 Sovaldi® tablet has a high weight and large size which renders it difficult to swallow the tablet is a clear indication of the problems which occur in formulating sofosbuvir.

WO 2014/120981 describes combination tablets which comprise crystalline sofosbuvir and amorphous ledispavir. The crystalline sofosbuvir drug content is described to be up to 50 % in these tablets. The tablets contain no surfactant and a solid dispersion of ledispavir in copovidone. With crystalline drugs the problem of conversion between polymorphs exists.

There exists a need for a pharmaceutical composition which allows for high sofosbuvir drug loading, wherein the pharmaceutical composition has a small size and a low weight. The pharmaceutical composition should also dissolve fast in order to provide a suitable bioavailability. In this respect, it is also advantageous if dissolution is pH independent and dissolution profiles are highly reproducible. The pharmaceutical composition should have further suitable properties such as e.g. being easy to manufacture and to handle.

In order to solve these problems, the present inventors have carried out significant studies concerning suitable excipients for preparing sofosbuvir containing solid pharmaceutical compositions. The present invention therefore provides a solid pharmaceutical composition comprising amorphous sofosbuvir and at least one phospholipid. The solid pharmaceutical composition is for oral use. Preferably, the solid pharmaceutical composition of the present invention is in form of a tablet. The tablet is optionally coated. The solid pharmaceutical composition usually does not contain liposomes.

The term amorphous denotes a physical state which is not crystalline and may be verified by x-ray diffraction and/or other means including but not limited to observation with a polarized light microscope and differential scanning calorimetry.

Examples of preparing crystalline and amorphous forms of sofosbuvir (GS-7977) are disclosed in US patent applications No. 2010/0298257 and 2011/0251152. With respect to sofosbuvir and methods for its production it can also be referred to e.g. US patent 7,964,580 and patent application US 2010/0016251.

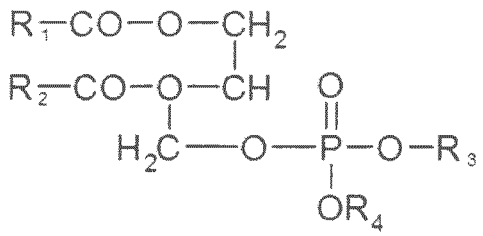
To obtain the solid pharmaceutical composition of the present invention, amorphous sofosbuvir can be used directly as starting compound for preparation of the solid pharmaceutical composition of the present invention. Alternatively, it is also possible to work with crystalline sofosbuvir as a starting compound and convert it into amorphous sofosbuvir during preparation of the solid pharmaceutical composition. In this respect, it was e.g. found that amorphous sofosbuvir can be obtained when melt extruding a phospholipid together with crystalline sofosbuvir.

In a preferred embodiment, the solid pharmaceutical composition of the present invention comprising amorphous sofosbuvir and at least one phospholipid comprises no or

essentially (less than 20%, preferably less than 10%, more preferably less than 5% or less than 2%) no crystalline sofosbuvir.

As the at least one phospholipid preferably a phosphoglyceride (glycerophospholipid) or sphingophosphatide (sphingophospholipid) can be used in the present invention. Phospholipids can e.g. be obtained from animal or plant material, such as soybean. The phospholipids are preferably surfactants.

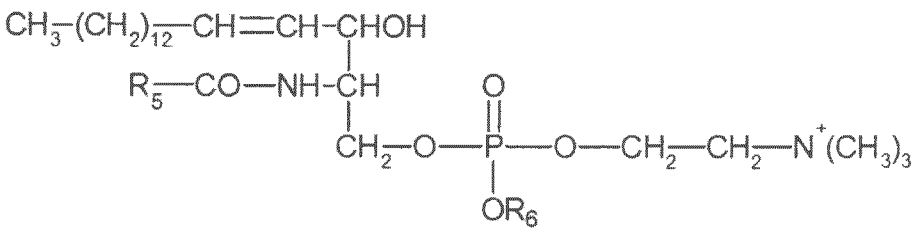
Phosphoglycerides to be used in the present invention are e.g. those of formula I below:



(I)

wherein R1 and R2 are independently selected from H and C1-C24 optionally substituted straight or branched alkyl, alkenyl, or alkynyl chains,
R3 is H, -CH2-CHNH2-COOH, CH2-CHOH-CH2OH, or -CH2-CH2-$N^+(CH3)_nH_{3-n}$ wherein n is 0, 1, 2 or 3, and
R4 is a negative charge, H or a C1-C24 optionally substituted straight or branched alkyl, alkenyl, or alkynyl chain.

Sphingophosphatides are e.g. those of formula II below:



(II)

wherein R5 is defined as R1 in formula (I) above, and
R6 is defined as R4 in formula (I) above.

In one embodiment of the present invention, the at least one phospholipid comprised in the composition is thus a phosphoglyceride as defined above or a sphingophosphatide as defined above.

In a preferred embodiment of the present invention, the at least one phospholipid is a phosphoglyceride of formula I, wherein R1 and R2 are independently selected from C4-C24 alkyl or alkenyl chains, R3 is CH2-CH2-$N^+(CH3)_3$ and R4 is a negative charge or H.

Preferably, the at least one phospholipid in the present invention is selected from one member of the group consisting of phosphatidylcholine, phosphatidic acid, phosphatidylethanolamine, phosphatidylglycerol and phosphatidylserine.

The at least one phospholipid can e.g. be selected from table 1 below.

Table 1. Phospholipids

Abbreviation	**CAS**	**Name**	**Type**
DDPC	3436-44-0	1,2-Didecanoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DEPA-NA	80724-31-8	1,2-Dierucoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DEPC	56649-39-9	1,2-Dierucoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DEPE	988-07-2	1,2-Dierucoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DEPG-NA		1,2-Dierucoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DLOPC	998-06-1	1,2-Dilinoleoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DLPA-NA		1,2-Dilauroyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DLPC	18194-25-7	1,2-Dilauroyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DLPE		1,2-Dilauroyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DLPG-NA		1,2-Dilauroyl-*sn*-glycero-	Phosphatidylglycerol

Abbreviation	CAS	Name	Type
		3[Phospho-rac-(1-glycerol...) (Sodium Salt)	
DLPG-NH4		1,2-Dilauroyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt)	Phosphatidylglycerol
DLPS-NA		1,2-Dilauroyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
DMPA-NA	80724-3	1,2-Dimyristoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DMPC	18194-24-6	1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DMPE	988-07-2	1,2-Dimyristoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DMPG-NA	67232-80-8	1,2-Dimyristoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DMPG-NH4		1,2-Dimyristoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt)	Phosphatidylglycerol
DMPG-NH4/NA		1,2-Dimyristoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium/Ammonium Salt)	Phosphatidylglycerol
DMPS-NA		1,2-Dimyristoyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
DOPA-NA		1,2-Dioleoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DOPC	4235-95-4	1,2-Dioleoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DOPE	4004-5-1-	1,2-Dioleoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DOPG-NA	62700-69-0	1,2-Dioleoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DOPS-NA	70614-14-1	1,2-Dioleoyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
DPPA-NA	71065-87-7	1,2-Dipalmitoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
	63-89-8	1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DPPE	923-61-5	1,2-Dipalmitoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine

Abbreviation	CAS	Name	Type
DPPG-NA	67232-81-9	1,2-Dipalmitoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DPPG-NH4	73548-70-6	1,2-Dipalmitoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt)	Phosphatidylglycerol
DPPS-NA		1,2-Dipalmitoyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
DSPA-NA	108321-18-2	1,2-Distearoyl-*sn*-glycero-3-phosphate (Sodium Salt)	Phosphatidic acid
DSPC	816-94-4	1,2-Distearoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
DSPE	1069-79-0	1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine	Phosphatidylethanolamine
DSPG-NA	67232-82-0	1,2-Distearoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt)	Phosphatidylglycerol
DSPG-NH4	108347-80-4	1,2-Distearoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt)	Phosphatidylglycerol
DSPS-NA		1,2-Distearoyl-*sn*-glycero-3-phosphoserine (Sodium Salt)	Phosphatidylserine
EPC		Egg-PC	Phosphatidylcholine
HEPC		Hydrogenated Egg PC	Phosphatidylcholine
HSPC		Hydrogenated Soy PC	Phosphatidylcholine
LYSOPC MYRISTIC	18194-24-6	1-Myristoyl-*sn*-glycero-3-phosphocholine	Lysophosphatidylcholine
LYSOPC PALMITIC	17364-16-8	1-Palmitoyl-*sn*-glycero-3-phosphocholine	Lysophosphatidylcholine
LYSOPC STEARIC	19420-57-6	1-Stearoyl-*sn*-glycero-3-phosphocholine	Lysophosphatidylcholine
Milk Sphingomyelin MPPC		1-Myristoyl-2-palmitoyl-*sn*-glycero 3-phosphocholine	Phosphatidylcholine
MSPC		1-Myristoyl-2-stearoyl-*sn*-glycero-3–phosphocholine	Phosphatidylcholine
PMPC		1-Palmitoyl-2-myristoyl-*sn*-glycero-3–phosphocholine	Phosphatidylcholine
POPC	26853-31-6	1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
POPE		1-Palmitoyl-2-oleoyl-*sn*-glycero-3-	Phosphatidylethanolamine

Abbreviation	CAS	Name	Type
		phosphoethanolamine	
POPG-NA	81490-05-3	1-Palmitoyl-2-oleoyl-*sn*-glycero-3[Phospho-rac-(1-glycerol)...] (Sodium Salt)	Phosphatidylglycerol
PSPC		1-Palmitoyl-2-stearoyl-*sn*-glycero-3–phosphocholine	Phosphatidylcholine
SMPC		1-Stearoyl-2-myristoyl-*sn*-glycero-3–phosphocholine	Phosphatidylcholine
SOPC		1-Stearoyl-2-oleoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine
SPPC		1-Stearoyl-2-palmitoyl-*sn*-glycero-3-phosphocholine	Phosphatidylcholine

In a more preferred embodiment of the present invention, the at least one phospholipid is a phosphatidylcholine. Of course, the solid pharmaceutical composition of the present invention can also comprise two or more different phospholipids.

In one more preferred embodiment, the solid pharmaceutical composition of the present invention comprises a lecithin which comprises phosphatidylcholine, such as Lipoid S 75.

While the inventors of the present invention found that dissolution of unformulated amorphous sofosbuvir was slow and variable, and dissolution became even worse in a dissolution medium comprising Tween 80 (see figure 4), surprisingly, the solid pharmaceutical composition comprising amorphous sofosbuvir and a phospholipid shows fast dissolution with little variation between individual tablets and independently of the pH of the dissolution medium. This has been demonstrated in examples 1 and 2 of the specification where figures 1 and 2 show the dissolution behavior of tablets according to the present invention containing 40 or even 45 wt.-% sofosbuvir and a phospholipid. It can be seen that the dissolution is very fast with little inter tablet variability. Figure 3 shows the dissolution of tablets containing 40 wt.-% sofosbuvir and poloxamer instead of a phospholipid. Dissolution is clearly not as fast as with the composition of the present invention and some variability is observed dependent on the pH of the dissolution medium and between individual tablets. Also, dissolution of Sovaldi tablets containing 33 wt.-% crystalline sofosbuvir is slower than for the pharmaceutical composition of the present invention and the Sovaldi tablets show a higher dependency on the pH of the dissolution medium.

The solid pharmaceutical composition of the present invention can e.g. comprise 10-70 %, preferably 20-60 %, more preferably30-50 % or 35-55 %, and even more preferably 40 to 50 % sofosbuvir. The use of a phospholipid in a sofosbuvir composition has been shown to be particularly favorable when the composition comprises a high drug load.

All percentages in the present specification are on a weight basis and refer to the total weight of the solid pharmaceutical 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).

In one embodiment the solid pharmaceutical composition according to the present invention contains about 400 mg of sofosbuvir. In an alternative embodiment the solid pharmaceutical formulation according to the present invention contains less than 400mg of sofosbuvir, such as about 300, about 250 or about 200 mg of sofosbuvir. The term "about" means ± 10 % in this connection.

The solid pharmaceutical composition according to the present invention preferably has a weight of not more than 1020 mg, preferably 700 to 1020 mg, such as 700 to 950 mg, more preferably 750 to 900 mg (900 - 1050mg).

The volume of the solid pharmaceutical composition, in particular when the composition is in form of a tablet, is preferably 400 - 700 mm^3, preferably 450 to 700 mm^3, such as 500 to 700 mm^3. The dimensions of the pharmaceutical composition, in particular when the composition is in form of a tablet, are preferably less than 20 x 9 mm, more preferably less than 19 x 9 mm, such as less than 18 x 9 mm, for example equal or less than 18 x 8.7 mm. The tablet according to the present invention may for example be oval, oblong or baguette-shaped.

The solid pharmaceutical composition according to the present invention contains preferably at least 3 % phospholipids in total, more preferably at least 5 % in total, such as at least 7 % in total based on the total weight of the pharmaceutical composition. The use of phospholipids in solid pharmaceutical compositions, such as tablets is unusual, particularly in the amounts indicated. In one embodiment, the solid pharmaceutical

composition comprises at least 5 % phosphatidylcholine based on the total weight of the pharmaceutical composition.

The solid pharmaceutical composition according to the present invention preferably contains one or more glidants. Glidants are well known in the art and include e.g. colloidal silicon dioxide or talc and the preferred glidant is colloidal silicon dioxide such as the commercial product Syloid 244FP.

The glidant can be comprised in the solid pharmaceutical composition of the present invention in a relative high amount. A solid pharmaceutical composition comprising one or more glidants is preferred wherein the total amount of glidants is at least 10 % based on the total weight of the composition, preferably at least 15 % or even at least 20 wt.-%.

Lubricants can also be comprised in the solid pharmaceutical composition of the present invention. Examples of lubricants are magnesium stearate, stearic acid, silica, sodium stearyl fumarate etc., preferred is sodium stearyl fumarate, e.g. the brandname Pruv.

The solid pharmaceutical composition according to the present invention preferably comprises one more binders and one or more disintegrants. In one embodiment the solid pharmaceutical composition comprises one or more binders, one or more disintegrants and optionally one or more lubricants.

Examples of typical binders that can be comprised in the solid pharmaceutical composition include microcrystalline cellulose (MCC), hydroxypropyl cellulose, hydroxypropylmethyl cellulose, povidone and copovidone. The most preferred binder according to the present invention is microcrystalline cellulose and here it is particularly preferred to use Avicel PH 200. As disintegrants preferably one or more so-called "superdisintegrants" are used in the present invention. Preferred superdisintegrants are modified cellulose (croscarmellose sodium), sodium carboxymethyl starch (sodium starch gylcolate), cross-linked polyvinyl pyrrolidone (crospovidone), cross-linked alginic acid and Xanthan gum. More preferred is the modified cellulose, such as croscarmellose sodium, e.g. the commercial product Ac-Di-Sol.

The solid pharmaceutical dosage form can contain one or more surfactants (ionic surfactant or a non-ionic surfactant) other than phospholipids. 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 (e.g, Lutrol F127). In one embodiment of the present invention, the solid pharmaceutical composition comprises less than 5 % by weight based on the total weight of the composition, preferably less than 2.5 % and more preferably less than 1.0 % or no surfactant other than phospholipids.

Very often, pharmaceutical compositions also contain diluents and fillers and it is not excluded that the solid pharmaceutical composition of the present invention also contains diluents or fillers. However, in view of a high relative amount of sofosbuvir in the composition of the present invention it is preferred that the solid pharmaceutical composition contains no diluents and no fillers.

In one embodiment, the solid pharmaceutical composition of the present invention contains one or more glidants, one or more binders and one or more disintegrants (preferably superdisintegrants), and optionally at least one or more lubricants in addition to sofosbuvir and the phospholipid.

The solid pharmaceutical composition of the present invention e.g. comprises an amount of disintegrants (preferably superdisintegrants) of less than 20 %, preferably less than 15 % based on the total weight of the composition. However, the disintegrants (preferably superdisintegrants) in the solid pharmaceutical composition of the present invention can also be present in an amount of at least 10 %, or at least 12 %, or at least 14 % by weight based on the total weight of the composition. The amount of binder is preferably in the range of 4 to 20 %. The amount of binder can, e.g., be in the range of 10 to 18 %, or in the range of 12 to 17 %.

A process for preparing solid pharmaceutical compositions in the form of tablets according to the present invention, e.g., comprises the following process steps:

i) preparing granules comprising amorphous sofosbuvir, phospholipid and optionally one or more glidants,
ii) compressing the granules together with at least one or more binders and one or more disintegrants and optionally one or more lubricants to form tablets,

iii) iii) optionally coating the tablets.

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

Ingredient	Preferred embodiment 1	Preferred embodiment 2	Preferred embodiment 3
Sofosbuvir	40-50	40-50	40-50
one or more phospholipids	3-15	5-15	7-13
one or more glidants	10-30	15-25	17-25
one or more disintegrants	7-20	7-15	7-16
one or more binders	3-20	15-18	15-17
one or more lubricants	0-5	0-3	0-3

The above total amounts are in percent and the total amount of all components add up to 100 % if no other ingredients are present

In the above table in a preferred embodiment the solid pharmaceutical composition comprises phosphatidylcholine.

In a further preferred embodiment silicium dioxide is contained as glidant.

It is further preferred embodiment croscarmellose sodium is contained as disintegrant.

In a further preferred embodiment MCC is contained as binder.

An embodiment which comprises the relative amounts indicated in the above table and wherein the phospholipids, glidants disintegrants and binders all comprise the preferred embodiments as indicated above is also preferred.

In addition to the active ingredient sofosbuvir, the solid pharmaceutical composition of the present invention can comprise one or more other active ingredients. A skilled person is

well aware of the distinction between pharmaceutically active ingredients and pharmaceutical excipients.

Of course, the solid pharmaceutical composition according to the present invention can also be administered with one or more other active ingredients than sofosbuvir in a combination therapy wherein the one or more other active ingredient is/are comprised in (a) separate pharmaceutical composition(s) from the sofosbuvir composition. 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, the one or more other therapeutic agents can be for treating HCV and/or other conditions such as HIV infections. In one embodiment, non-limiting examples of suitable other therapeutic agents include 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 therapeutic agents agent may further be those which treat other conditions, such as HIV infections. Accordingly, the one or more other therapeutic agents 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 therapeutic agents are particularly listed WO 2014/120981 to which it is explicitly referred.

In one embodiment, the solid pharmaceutical 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 solid pharmaceutical 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 solid pharmaceutical composition does not contain ledispavir. The solid pharmaceutical composition of the present invention may then also be administered in combination with a separate pharmaceutical composition comprising ledispavir.

In one embodiment, the solid pharmaceutical 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 solid pharmaceutical 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 solid pharmaceutical composition does not contain velpatasvir. The solid pharmaceutical composition of the present invention may then also be administered in combination with a separate pharmaceutical composition comprising velpatasvir.

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

In one embodiment, the present invention relates to a solid pharmaceutical composition wherein the composition comprises a melt extrudate comprising amorphous sofosbuvir, phospholipid and optionally further constituents, and wherein the extrudate is obtainable by melt extruding the phospholipid together with crystalline sofosbuvir and optionally further

constituents. The present invention further also relates to a process for preparing solid pharmaceutical compositions according to the present invention comprising the step of melt extruding the phospholipid together with crystalline sofosbuvir and optionally further constituents to obtain an extrudate comprising amorphous sofosbuvir, phospholipid and optionally further constituents.

The solid pharmaceutical composition according to the present invention is preferably one wherein the composition comprises granules comprising amorphous sofosbuvir, phospholipid and optionally further constituents, and wherein the granules are obtainable by melt extruding the phospholipid together with crystalline sofosbuvir and optionally further constituents and shaping the extrudate into granules. The shaping can e.g. be performed by cutting, breaking, spheronizing or sieving the extrudate to form granules.

The present invention further also relates to a process for preparing solid pharmaceutical compositions according to the present invention comprising the following process step:

a) melt extruding the phospholipid together with crystalline sofosbuvir and optionally further constituents and shaping the extrudate into granules comprising amorphous sofosbuvir, phospholipid and optionally further constituents.

In one embodiment at least a glidant, e.g. colloidal silicon dioxide, is used as further constituent.

In one embodiment, step a) in the process comprises steps

a1) granulating the phospholipid onto one or more glidants and drying the obtained glidant/phospholipid granules
a2) blending the dried glidant/phospholipid granules with crystalline sofosbuvir and optionally sieving the blend
a3)melt extruding the blend and shaping the extrudate into granules comprising amorphous sofosbuvir, phospholipid and glidant(s).

The granules can of course also comprise further constituents than sofosbuvir, phospholipid and glidant(s).

During melt extrusion a temperature above the melting temperature of the employed crystalline sofosbuvir should be used. In the melt extrusion process crystalline sofosbuvir should be converted into amorphous sofosbuvir. In one embodiment, the phospholipid and crystalline sofosbuvir and optionally further constituents are melt-extruded using an extrusion temperature above 100 °C, preferably above 110 °C, 120 or 125 °C.

For example, granules comprising amorphous sofosbuvir can e.g. be prepared by melt extruding the blend of the dried glidant/phospholipid granules with crystalline sofosbuvir on a twin screw extruder, preferably using a temperature of at least 100 °C, preferably above 110 °C, 120 or 125 °C, and sieving the extrudate to obtain the granules.

The granules can be further processed; for example, tablets can be compressed using the granules or capsules can be filled with the granules. In the present invention, the tablets e.g. have a hardness between 100 and 200 N.

Preferably, the process according to the present invention and by which the solid pharmaceutical compositions of the present invention are obtainable comprises the following process steps after step a):

b) compressing the granules together at least with one or more binders and one or more disintegrants and optionally one or more lubricants to form tablets
c) optionally coating the tablets.

In one embodiment, the solid pharmaceutical compositions according to the present invention are prepared by a method as shown in the example of this application.

Instead of solid pharmaceutical compositions comprising amorphous sofosbuvir and at least one phospholipid, also solid pharmaceutical compositions comprising crystalline sofosbuvir and at least one phospholipid can be prepared for obtaining compositions with favorable properties.

The crystalline sofosbuvir can have any of the crystalline forms as described in US patent applications Nos. 2010/0298257, 2011/0251152, 2010/0016251 and US patent 7,964,580. Other crystalline forms can also be used.

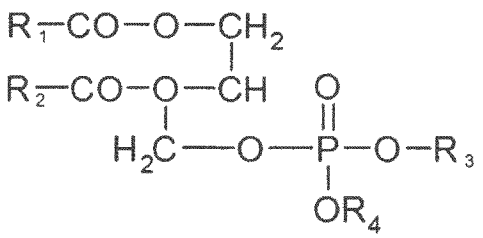
Preferably, in the solid pharmaceutical compositions comprising crystalline sofosbuvir and at least one phospholipid the crystalline sofosbuvir is a crystal form of sofosbuvir as described in CN 104130302 A to which it is explicitly referred. Preferably, crystalline sofosbuvir as described in any of claims 1-10 of CN 104130302 A is used. In one embodiment of the solid pharmaceutical compositions comprising crystalline sofosbuvir and at least one phospholipid, a crystal form A of sofosbuvir having an X-ray powder diffraction pattern comprising peaks expressed in degrees 2θ at 8.19, 12.47 and 19.47 ± 0.2, wherein the X-ray powder diffraction pattern is obtained using copper K-alpha radiation, is thus comprised in the solid pharmaceutical composition.

In the following, some embodiments of solid pharmaceutical compositions comprising crystalline sofosbuvir and at least one phospholipid and a preparation process thereof are described:

Embodiment 1: Solid pharmaceutical composition comprising crystalline sofosbuvir and at least one phospholipid.

Embodiment 2: Solid pharmaceutical composition according to embodiment 1, wherein the composition is in the form of a tablet.

Embodiment 3: Solid pharmaceutical composition according to embodiment 1 or 2, wherein the at least one phospholipid is a phosphoglyceride of formula I



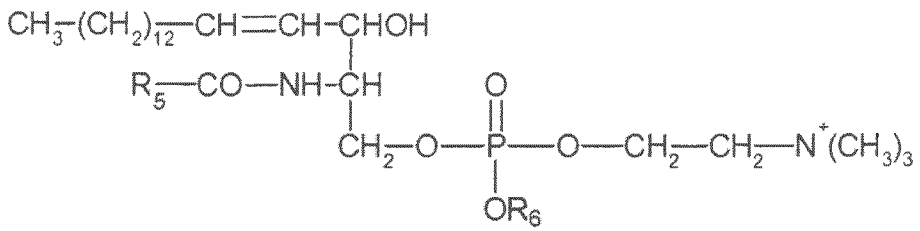
(I)

wherein R1 and R2 are independently selected from H and C1-C24 optionally substituted straight or branched alkyl, alkenyl, or alkynyl chains,

R3 is H, -CH2-CHNH2-COOH, CH2-CHOH-CH2OH, or $-CH_2-CH_2-N^+(CH_3)_nH_{3-n}$ wherein n is 0, 1, 2 or 3, and

R4 is a negative charge, H or a C1-C24 optionally substituted straight or branched alkyl, alkenyl, or alkynyl chain.

or a sphingophosphatide of formula II



(II)

wherein R5 is defined as R1 in formula (I) above, and
R6 is defined as R4 in formula (I) above.

Embodiment 4: Solid pharmaceutical composition according to any of embodiments 1-3, wherein the at least one phospholipid is a phosphoglyceride of formula I, wherein R1 and R2 are independently selected from C4-C24 alkyl or alkenyl chains, R3 is CH2-CH2-N+(CH3)3 and R4 is a negative charge or H.

Embodiment 5: Solid pharmaceutical composition according to any of embodiments 1-4, wherein the at least one phospholipid is a phosphatidylcholine.

Embodiment 6: Solid pharmaceutical composition according to any of embodiments 1-5, wherein the composition comprises sofosbuvir in an amount of 35 to 55 %, more preferably 40 to 50, based on the total weight of the composition.

Embodiment 7: Solid pharmaceutical composition according to any of embodiments 1-6, wherein the composition comprises about 400 mg sofosbuvir.

Embodiment 8: Solid pharmaceutical composition according to any of embodiments 1-7, wherein the composition comprises at least 5 % phospholipids in total based on the total weight of the composition.

Embodiment 9: Solid pharmaceutical composition according to any of embodiments 1-8, wherein the composition comprises one or more glidants in a total amount of at least 10 % based on the total weight of the composition.

Embodiment 10: Solid pharmaceutical composition according to any of claims 1-9, wherein the composition comprises one or more other active ingredients in addition to sofosbuvir.

Embodiment 11: Solid pharmaceutical composition according to any of embodiments 1-10, wherein the composition comprises ledispavir.

Embodiment 12: Solid pharmaceutical composition according to any of embodiments 1-11, wherein the composition comprises velpatasvir.

Embodiment 13: Solid pharmaceutical composition according to any of embodiments 1-12, wherein the composition is for use in the treatment of hepatitis C virus infections.

Embodiment 14: Process for preparing solid pharmaceutical compositions in the form of tablets according to any of embodiments 2-13 comprising the following process steps:

a) preparing granules comprising sofosbuvir, phospholipid and optionally one or more glidants
b) compressing the granules together with at least one or more binders and one or more disintegrants and optionally one or more lubricants to form tablets
c) optionally coating the tablets.

Furthermore, features and embodiments that have been described above for the solid pharmaceutical composition of the present invention comprising amorphous sofosbuvir also apply for the solid pharmaceutical composition comprising crystalline sofosbuvir and at least one phospholipid and the preparation process thereof (if nothing else is obvious to the skilled person). For example, when it is described above that in one more preferred embodiment, the solid pharmaceutical composition of the present invention comprises a lecithin which comprises phosphatidylcholine, such as Lipoid S75, this means - applied to the solid pharmaceutical composition comprising crystalline sofosbuvir and at least one phospholipid - that in one more preferred embodiment of such pharmaceutical composition

comprising crystalline sofosbuvir and at least one phospholipid the composition comprises a lecithin which comprises phosphatidylcholine, such as Lipoid S75.

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

Example 1: Pharmaceutical composition with Phospholipid

Composition	Brand Name	Functionality	Amount	
			[mg]	[%]
Sofosbuvir	-	active ingredient	402.29*	40.23
Phosphatidylcholine	Lipoid S 75	surfactant	100.00**	10.00
Colloidal silicon dioxide	Syloid 244FP	glidant	201.15	20.12
Crosscarmellose Sodium	Ac-Di-Sol	disintegrant	130.00	13.00
MCC	Avicel PH 200	binder	150.00	15.00
Natriumstearylfumarat	Pruv	lubricant	16.56	1.66
		TOTAL	1000.00	100.0

*adjusted to potency of the active
**amount of Lipoid S 75 (according to the manufacturer Lipoid S 75 contains approximately 70 wt.-% phosphatidylcholine

Manufacturing:

Lipoid was dissolved in Ethanol and granulated on the Syloid 244 FP and dried in a cabinet dryer at 40°C. Syloid 244FP/Lipoid granules were mixed together with crystalline Sofosbuvir (Form I) for 5 min in a tumble blender. The mixture was sieved through a 1000µm sieve and blended in a tumble blender for 5 minutes. The mixture was extruded on a 9mm twin screw extruder with 30 RpM and temperatures Zone 1: 80°C, Zone 2: 100°C, Zone 3: 110 °C without die. The extrudate was sieved step wise through a 500 µm, 250µm and 125µm sieve. 1/3 of sieved (mesh size 500µm) PRUV was added and mixed for 5 min in a tumble blender. Avicel and Ac-Di-Sol were sieved (mesh size 500µm) added and mixed together for 5 min in a tumble blender. Residual PRUV was added through a sieve (mesh size 500µm) and the final blend was mixed for further 3min in a tumble blender. The final blend was compressed into oblong tablets on an eccentric press with a hardness of about 120 N. The tablets contained amorphous sofosbuvir due to a conversion of crystalline sofosbuvir to amorphous sofosbuvir during the melt extrusion process.

The tablets 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 1.2 (0.1 M HCl) (n=3), 4.5 (50 mM acetate buffer) (n=3) or 6.8 (50 mM phosphate buffer) (n=2) at 37°C and 75 rpm.

Figure 1 shows the dissolution of the tablets of example 1.

Example 2: Pharmaceutical composition with Phospholipid

Composition	Brand Name	Functionality	Amount	
			[mg]	[%]
Sofosbuvir	-	active ingredient	402.29*	44.70
Phosphatidylcholine	Lipoid S 75	surfactant	100.00**	11.11
Colloidal silicon dioxide	Syloid 244FP	glidant	201.15	22.35
Crosscarmellose Sodium	Ac-Di-Sol	disintegrant	130.00	14.44
MCC	Avicel PH 200	binder	50.00	5.56
Natriumstearylfumarat	Pruv	lubricant	16.56	1.84
		TOTAL	900.00	100.0

*adjusted to potency of the active
**amount of Lipoid S 75 (according to the manufacturer Lipoid S 75 contains approximately 70 wt.-% phosphatidylcholine

Manufacturing and dissolution tests (at pH = 6.8) were performed as described in example 1. The tablets contained amorphous sofosbuvir due to a conversion of the employed crystalline sofosbuvir Form I to amorphous sofosbuvir during the melt extrusion process. The tablet size was 18 x 8.7 mm.

Figure 2 shows the dissolution of 3 tablets of example 2.

Comparative Example 1: Pharmaceutical composition with Poloxamer

Composition	Brand Name	Functionality	Amount	
			[mg]	[%]
Sofosbuvir	-	active ingredient	402.29*	40.23
Poloxamer F127	Lutrol F127	surfactant	150.00**	15.00
Colloidal silicon dioxide	Syloid 244FP	glidant	201.15	20.12
Crosscarmellose Sodium	Ac-Di-Sol	disintegrant	110.00	11.00
MCC	Avicel PH 200	binder	120.00	12.00
Natriumstearylfumarat	Pruv	lubricant	16.56	1.66
		TOTAL	1000	*100.0*

**adjusted to potency of the active*

Manufacturing:

Lutrol was dissolved in Ethanol/Water 1:1 and granulated on the Syloid 244 FP and dried in a cabinet dryer at 40°C. Syloid 244FP/Lutrol granules were mixed together with crystalline Sofosbuvir for 5 min in a tumble blender. The mixture was sieved through a 100µm sieve and blended in a tumble blender for 5 minutes. The mixture was extruded on a 9mm twin screw extruder with 30 RpM and temperatures Zone 1: 80 °C, Zone 2: 100°C, Zone 3: 110°C without die. The extrudate was sieved step wise through a 500µm, 250µm and 125µm sieve. 1/3 of sieved (mesh size 500pm) PRUV was added and mixed for 5 min in a tumble blender. Avicel and Ac-Di-Sol were sieved (mesh size 500µm) added and mixed together for 5 min in a tumble blender. Residual PRUV was added through a sieve (mesh size 500µm) and the final blend was mixed for further 3min in a tumble blender. The final blend was compressed into oblong tablets 21 x 10 mm on an eccentric press with a hardness of about 120 N. The tablets contained amorphous sofosbuvir due to a conversion of crystalline sofosbuvir to amorphous sofosbuvir during the melt extrusion process.

The tablets were subjected to dissolution tests as described in the example above (pH 1.2 (n=3), 4.5 (n=3) or 6.8 (n=2)).

Figure 3 shows the dissolution of the tablets of comparative example 1.

Comparative Example 2: Amorphous active ingredient

Method 1: Amorphous sofosbuvir from Ethanol

Form 1 of Sofosbuvir (8 g) was dissolved in ethanol (20 mL). The solvent was removed on a rotary evaporator (bath temperature 50°C). The resulting solid was further dried in a vacuum oven at 40°C / 10 mbar for two days.

Method 2: Amorphous sofosbuvir by grinding
Form 1 of Sofosbuvir (8 g) was milled in a planetary ball mill (Fritsch Pulverisette 6) with 6 Zirkonium oxide grinding balls (25 mm diameter) for 1h at 300 rpm.

400 mg of the samples as obtained above were subjected to dissolution tests. Dissolution tests at pH = 6.8 (50 mM phosphate buffer) were performed as described in example 1 above (n= 2)). Additionally, a dissolution test was performed with amorphous sofosbuvir (as obtained according to method 1) wherein a dissolution medium containing Tween was used (pH = 6.0, 1.5 % Tween 80, 10 mM phosphate buffer).

Figure 4 shows the dissolution of amorphous sofosbuvir samples of comparative example 2 (amorph (from EtOH) in pH 6.0 1.5 % Tween 80 (n = 2), amorph (from grinding) in pH 6.8 (n = 2), amorph (from EtOH) in pH 6.8 (n = 2)).

Comparative Example 3: Sovaldi tablets

Sovaldi tablets (Batch MXHVD) were subjected to dissolution tests as described in the example above (pH 1.2 (n=3), 4.5 (n=3) or 6.8 (n=6)).

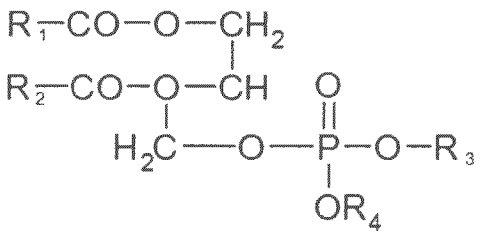
Figure 5 shows the dissolution of the Sovaldi tablets of comparative example 3.

Claims

1. Solid pharmaceutical composition comprising amorphous sofosbuvir and at least one phospholipid.

2. Solid pharmaceutical composition according to claim 1, wherein the composition is in the form of a tablet.

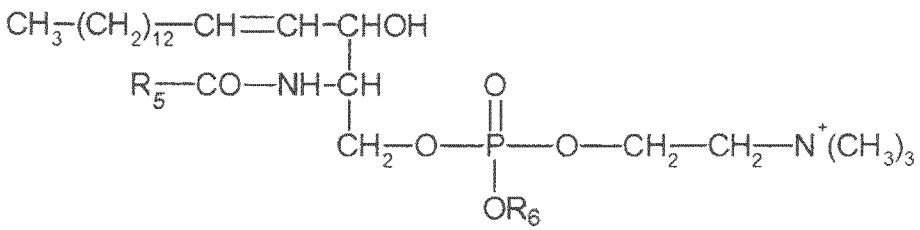
3. Solid pharmaceutical composition according to claim 1 or 2, wherein the at least one phospholipid is a phosphoglyceride of formula I



(I)

wherein R1 and R2 are independently selected from H and C1-C24 optionally substituted straight or branched alkyl, alkenyl, or alkynyl chains,
R3 is H, -CH2-CHNH2-COOH, CH2-CHOH-CH2OH, or $-CH_2-CH_2-N^+(CH_3)_nH_{3-n}$ wherein n is 0, 1, 2 or 3, and
R4 is a negative charge, H or a C1-C24 optionally substituted straight or branched alkyl, alkenyl, or alkynyl chain.

or a sphingophosphatide of formula II



(II)

wherein R5 is defined as R1 in formula (I) above, and
R6 is defined as R4 in formula (I) above.

4. Solid pharmaceutical composition according to any of claims 1-3, wherein the at least one phospholipid is a phosphoglyceride of formula I,
wherein R1 and R2 are independently selected from C4-C24 alkyl or alkenyl chains, R3 is CH2-CH2-N+(CH3)3 and R4 is a negative charge or H.

5. Solid pharmaceutical composition according to any of claims 1-4, wherein the at least one phospholipid is a phosphatidylcholine.

6. Solid pharmaceutical composition according to any of claims 1-5, wherein the composition comprises sofosbuvir in an amount of 35 to 55 % based on the total weight of the composition.

7. Solid pharmaceutical composition according to any of claims 1-6, wherein the composition comprises about 400 mg sofosbuvir.

8. Solid pharmaceutical composition according to any of claims 1-7, wherein the composition comprises at least 5 % phospholipids in total based on the total weight of the composition.

9. Solid pharmaceutical composition according to any of claims 1-8, wherein the composition comprises one or more glidants in a total amount of at least 10 % based on the total weight of the composition.

10. Solid pharmaceutical composition according to any of claims 1-9, wherein the composition comprises one or more other active ingredients in addition to sofosbuvir.

11. Solid pharmaceutical composition according to any of claims 1-10, wherein the composition comprises ledispavir.

12. Solid pharmaceutical composition according to any of claims 1-11, wherein the composition comprises velpatasvir.

13. Solid pharmaceutical composition according to any of claims 1-12, wherein the composition comprises granules comprising amorphous sofosbuvir, phospholipid

and optionally further constituents, and wherein the granules are obtainable by melt-extruding the phospholipid together with crystalline sofosbuvir and optionally further constituents and shaping the extrudate into granules.

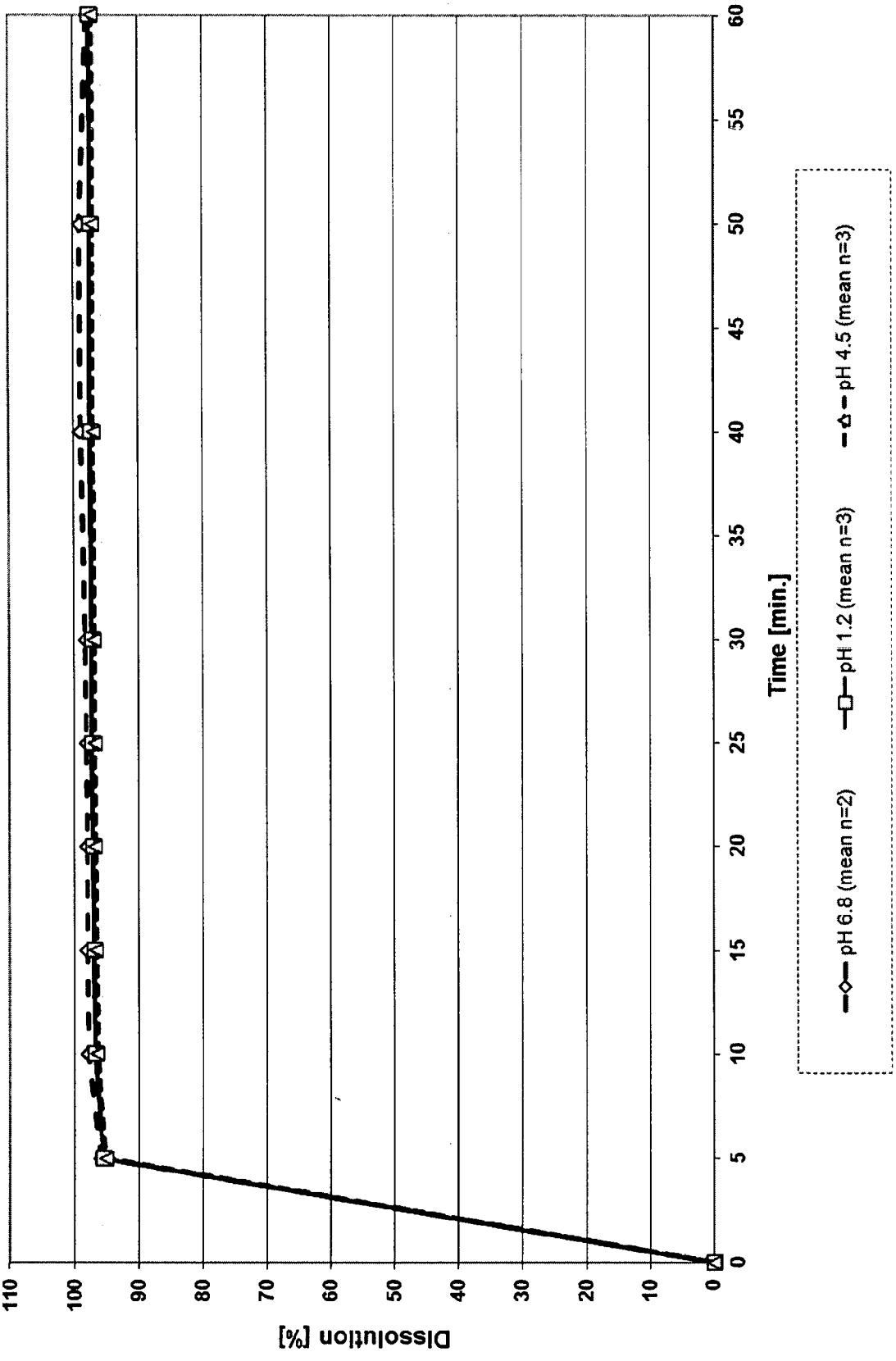
14. Solid pharmaceutical composition according to any of claims 1-13, wherein the composition is for use in the treatment of hepatitis C virus infections.

15. Process for preparing solid pharmaceutical compositions according to any of claims 1-14 comprising the following process step:

    a) melt extruding the phospholipid together with crystalline sofosbuvir and optionally further constituents and shaping the extudate into granules comprising amorphous sofosbuvir, phospholipid and optionally further constituents.

16. Process according to claim 15 further comprising the following process steps:

    b) compressing the granules together with at least one or more binders and one or more disintegrants and optionally one or more lubricants to form tablets
    c) optionally coating the tablets.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pH 4.5 (mean n=3)

Figure 1

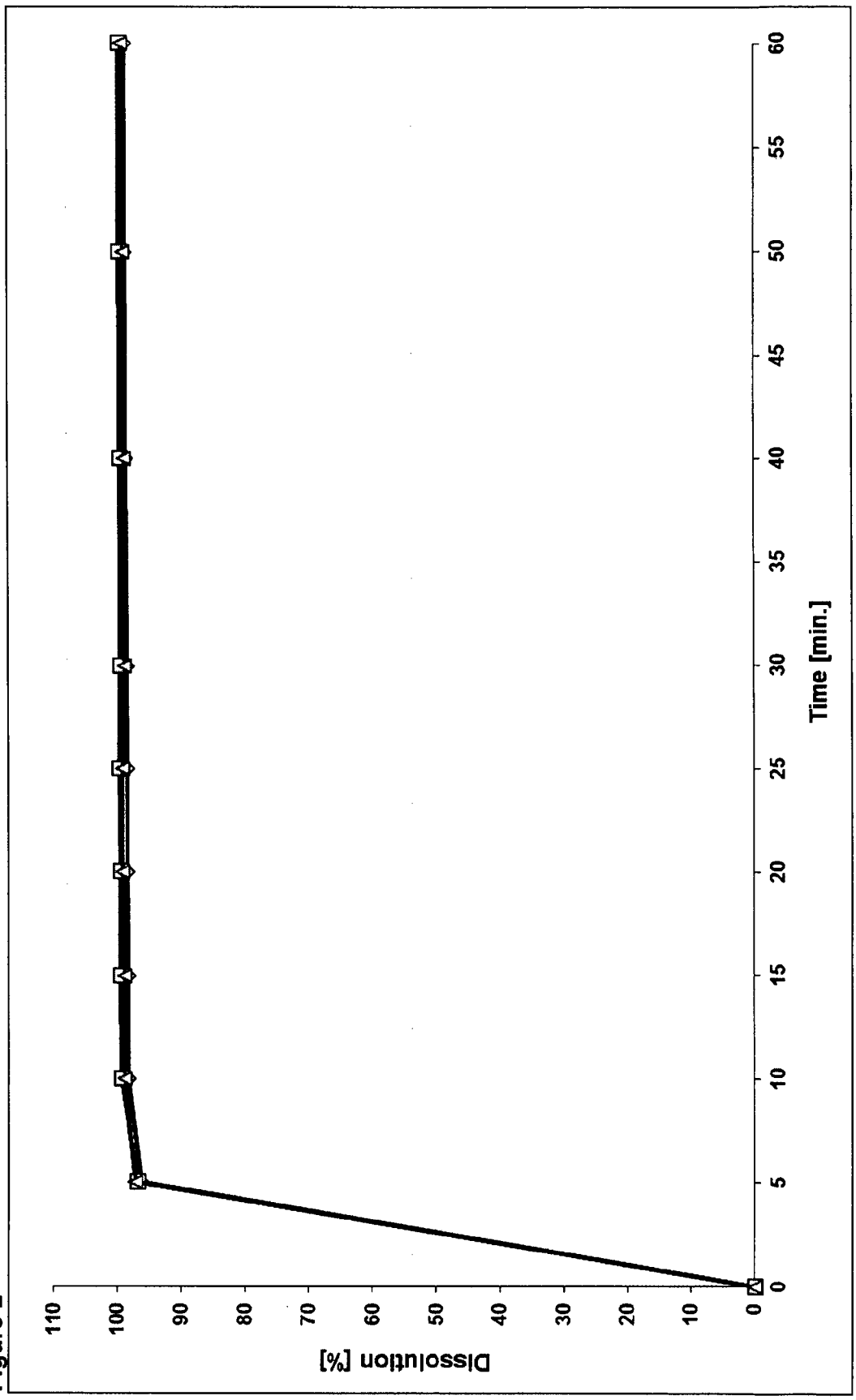
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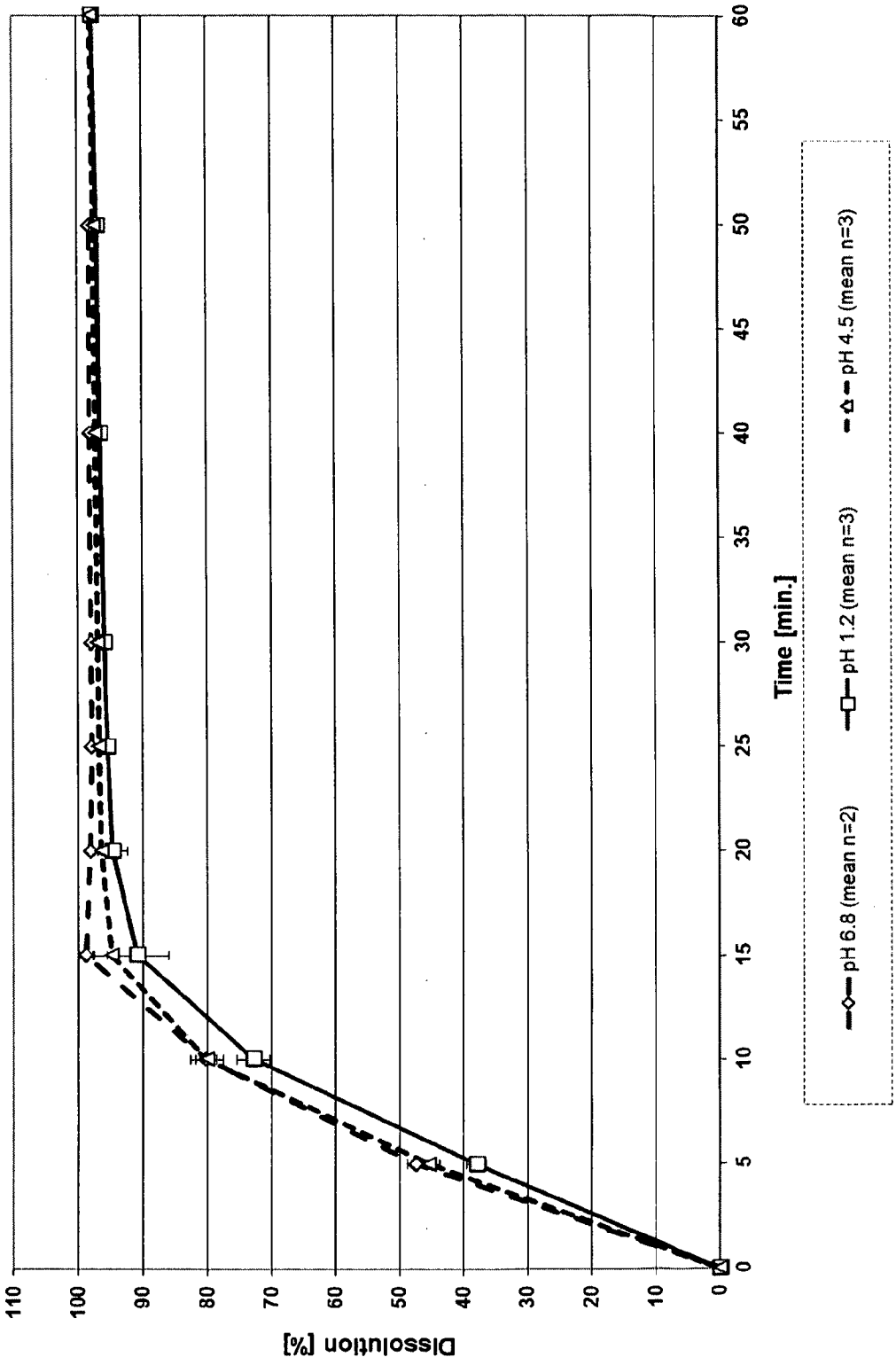
Figure 2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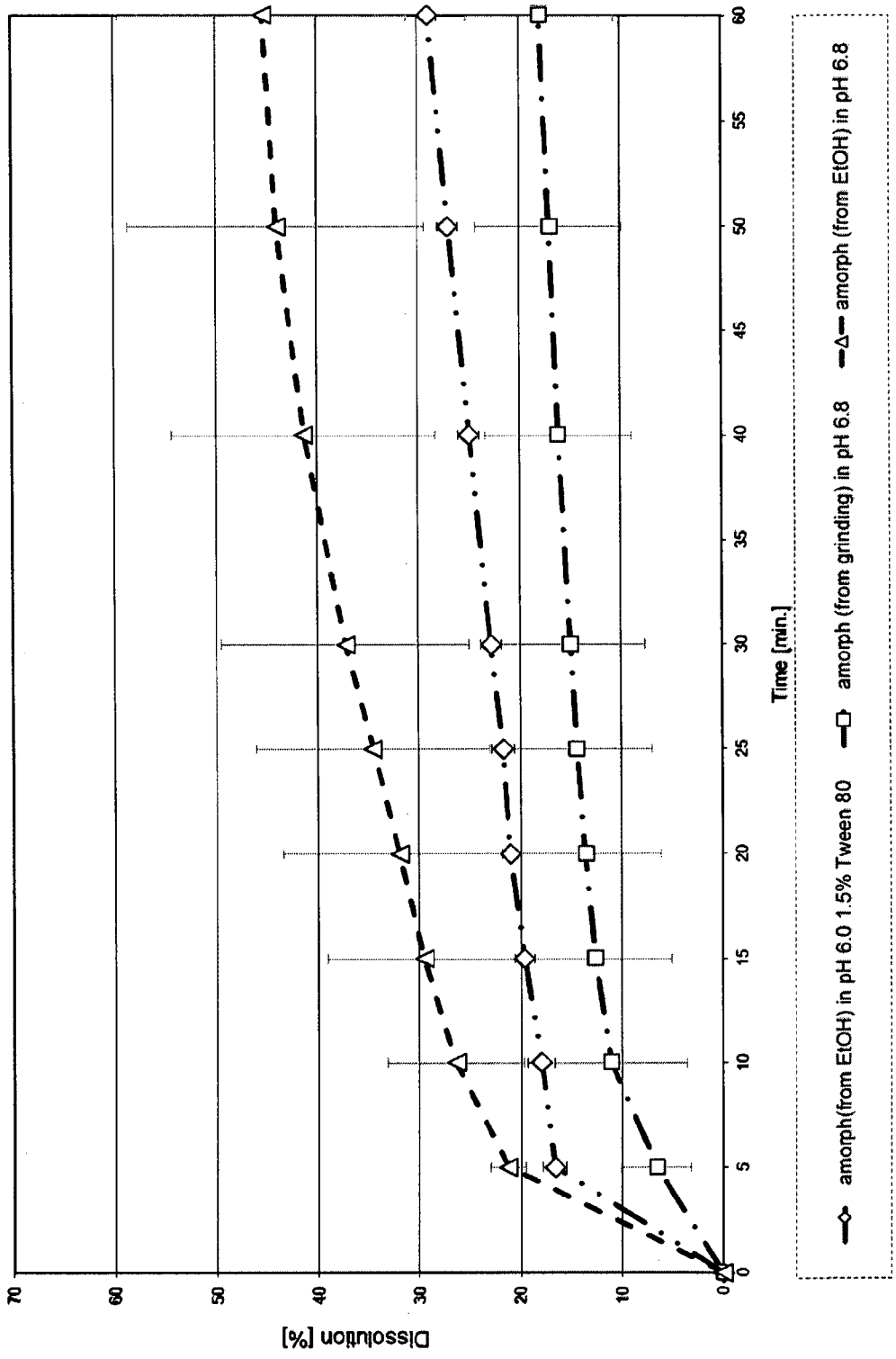
pH 6.8 (mean n=2)
pH 1.2 (mean n=3)
pH 4.5 (mean n=3)

Figure 3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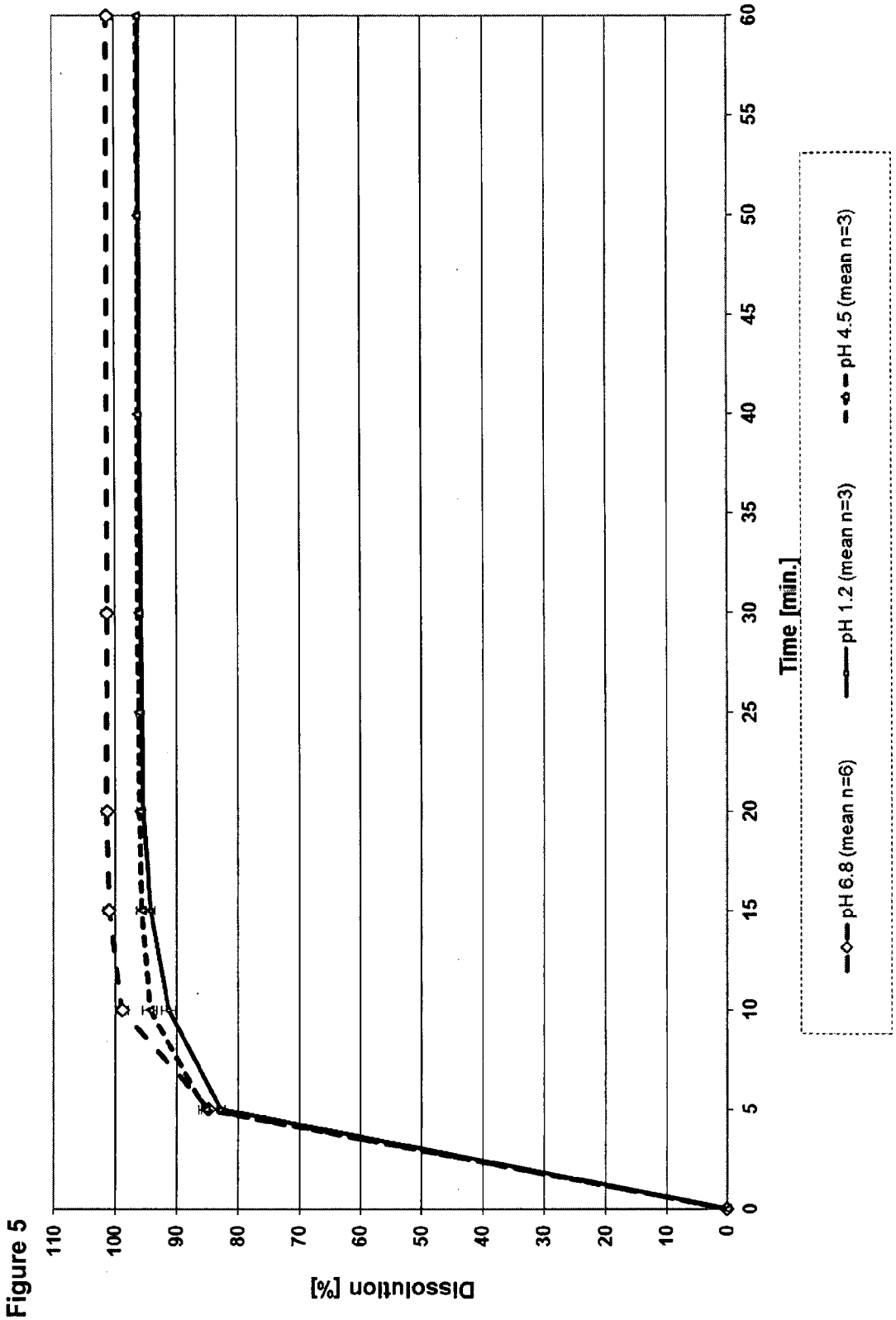
amorph(from EtOH) in pH 6.0 1.5% Tween 80
amorph (from grinding) in pH 6.8
amorph (from EtOH) in pH 6.8

Figure 4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pH 6.8 (mean n=6)
pH 1.2 (mean n=3)
pH 4.5 (mean n=3)

Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/056820

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/00
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, 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.
A	WO 2013/082003 A1 (GILEAD PHARMASSET LLC [US]) 6 June 2013 (2013-06-06) cited in the application tables 1-5 -----	1-16

☐ 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
30 May 2016	08/06/2016

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	Konter, Jörg

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/056820

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
		US 2015150896 A1	04-06-2015
		WO 2013082003 A1	06-06-2013