develop a more convenient immediate release oral solid dosage form of suitable size, offering good physical and chemical stability upon storage, and facilitating simple and accurate dosing.

Poor aqueous solubility and slow dissolution rate are known to lead to low bioavailability or negatively affect pharmacokinetic performance and limit the orally absorbed dose. Therefore, there is a need for oral formulations containing Vamorolone with increased dissolution rate and solubility, capable of providing suitable bioavailability at a palatable oral solid dose(s).

Overall, there is a need for overcoming the problems arising from the Vamorolone formulation provided by US 2020/0281942. Especially, there is a need for providing higher doses of Vamorolone in a convenient pharmaceutical dosage form, preferably an immediate release solid dosage form, containing Vamorolone with enhanced solubility and dissolution rate when compared to crystalline drug, which is able to deliver Vamorolone as a stable formulation, more preferably with improved bioavailability at an optimized dose. Further, there is a need to provide an immediate release solid oral dosage form containing Vamorolone.

SUMMARY

The present disclosure fulfils this need by providing Vamorolone as an amorphous solid composition. The composition of the present disclosure comprises an amorphous solid dispersion of Vamorolone in a polymer matrix, i.e. amorphous Vamorolone dispersed in a polymer matrix.

In an aspect of the present disclosure, there is provided an amorphous solid dispersion comprising Vamorolone and at least one pharmaceutically acceptable polymer

The terms “composition of the present invention (or disclosure)” and the “amorphous solid dispersion of the present invention (or disclosure)” are used as synonyms through the specification.

The presence of the polymer alone in a composition comprising Vamorolone, but not as amorphous solid dispersion of the present disclosure does not result in an increase of solubility as is seen for the solid dispersion. Just blending Vamorolone (be it crystalline or amorphous) with a polymer does lead to the same solubility as amorphous Vamorolone alone – see Figure 3.

The amorphous solid dispersion of the present disclosure, hence, was found to be a formulation with increased dissolution properties and that is capable of stabilizing the solubility of Vamorolone in aqueous media.

It has been surprisingly found that the composition of the present disclosure exhibits a drastically enhanced kinetic solubility in aqueous media, which can allow for a better bioavailability,

regardless of the co-administration of food, compared to the Vamorolone compositions in the prior art.

It has further been surprisingly found that the composition of the present disclosure comprising an amorphous solid dispersion of Vamorolone dissolved in an aqueous medium is stable over a long time period, without recrystallization, in a form of a supersaturated aqueous solution, so that the solubilized form can be efficiently absorbed *in vivo.*

The composition of the present disclosure comprising an amorphous solid dispersion of Vamorolone is preferably obtained by spray drying. This technology was found to be superior compared to other alternatives such as hot melt extrusion, since it allows for a high drug load while preventing the composition from degradation and demonstrates good processability to pharmaceutical dosage forms.

A suitable polymer or a mixture of suitable polymers are employed to stabilize Vamorolone in the amorphous state. In general, the polymer is pharmaceutically acceptable. Typical examples of polymers include cellulose or cellulose derivatives, povidone and copovidone, and derivatives of methacrylic acid and methyl methacrylate. Such polymers may comprise co-polymers.

"Cellulose derivatives" comprise cellulose ethers, cellulose esters and cellulose ester ethers or respective co-polymers thereof. Preferred cellulose derivatives are selected from hydroxy propyl methyl cellulose (HPMC), hydroxyethyl cellulose, methyl cellulose, ethyl cellulose and cellulose acetate.

"Derivatives of methacrylic acid, ethyl acrylate and/or methyl methacrylate" comprise vinyl polymers, constituted by acrylate or methacrylate monomers, in which the vinyl group has been involved in polymerization, while the carboxyl group is the target of a derivatization reaction. "Derivatives of methacrylic acid, ethyl acrylate and/or methyl methacrylate", thus, comprise vinyl polymers with a functionalized carboxyl group, e.g. esters or carboxylate salts. Preferred derivatives of methacrylic acid, ethyl acrylate and/or methyl methacrylate are poly(methacrylic acid) polymers and polyacrylate polymers or respective co-polymers thereof. More preferred derivatives of methacrylic acid, ethyl acrylate and/or methyl methacrylate are selected from ethyl acrylate-methyl methacrylate copolymer, such as Eudragit® E PO, methacrylic acid-ethyl acrylate copolymer, such as Eudragit® L, methacrylic acid-methyl methacrylate copolymer, such as Eudragit® S, ethyl acrylate-methyl methacrylate copolymer, such as Eudragit® RS, methacrylic acid-ethyl acrylate copolymer, such as Eudragit® NE.

Polymers are preferably selected from hydroxy propyl methyl cellulose (HPMC), hydroxyethyl cellulose, methyl cellulose, ethyl cellulose and cellulose acetate and are more preferably selected from hydroxypropylmethylcellulose (HPMC), copovidone (polyvinylpyrrolidone-vinyl acetate copolymer), and hydroxypropylmethylcellulose acetate succinate (HPMCAS, grade L, M or H). In most preferred examples, the Vamorolone polymer is hydroxypropylmethylcellulose acetate succinate.

In specific examples, the polymer is selected from cellulose derivatives, preferably hydroxypropylmethyl cellulose derivatives, more preferably hydroxypropylmethyl cellulose acetate succinate grade L, H or M. In one preferred example, the polymer is hydroxypropylmethyl cellulose acetate succinate (HPMCAS) grade M that dissolves at pH values above 6.0. Preferably, HPMCAS grade L, H or M is characterized by an acetyl content of about 7 – 11% and a succinoyl content of about 10-14%.

The kinetic solubility of Vamorolone in the amorphous state is increased in the presence of one or more of the polymers of the disclosure, leading to supersaturated solutions when dissolving the composition of the present disclosure. Such supersaturated solutions of Vamorolone are stable for at least 10 hours in a concentration of more than 50 µg/ml, preferably more than 100 µg/ml, even more preferably more than 150 µg/ml, even more preferably more than 200 µg/ml, even more preferably more than 250 µg/ml, even more preferably more than 300 µg/ml and most preferably more than 350 µg/ml. All concentrations above refer to solubility in an aqueous medium at 37°C. Typically the aqueous medium is fasted stated simulated intestinal fluid (FASSIF) at 37°C.

In one example**,** the amorphous solid dispersion of the present disclosure comprises at least 20 wt% of Vamorolone by weight of the amorphous solid dispersion and 80 wt% of total polymer by weight of the amorphous solid dispersion. Some amorphous solid dispersions comprise from about 20 wt% to about 80 wt% of Vamorolone by weight of the amorphous solid dispersion. Preferably, the amorphous solid dispersions of the present disclosure contain about 30 wt% to 70 wt% of Vamorolone. More preferably, the amorphous solid dispersions contain about 40 wt% to 60 wt% of Vamorolone. More preferably, the amorphous solid dispersions contain about 45 wt% to 55 wt% of Vamorolone. The total amount of polymers preferably is 100 wt% minus the Vamorolone amount, e.g. total polymer amount of 80 wt% to 20 wt% of the amorphous solid dispersion, if the Vamorolone amount is 20 wt% to 80wt% of the amorphous solid dispersion. The same calculation applies to all the preferred Vamorolone amounts as set forth above. In another preferred example, the disclosure relates to an amorphous solid

dispersion containing an amount of 50 wt% of Vamorolone, in a 1:1 ratio with the total amount of polymer.

The polymers in an alternatively preferred example have an amount of 99 wt% minus the Vamorolone amount, e.g total polymer.in an amount of 79 wt% to 19 wt% of the amorphous solid dispersion, if the Vamorolone amount is 20 wt% to 80wt% of the amorphous solid dispersion. The total polymer amount is 69 wt% to 29 wt% of the amorphous solid dispersion, if the Vamorolone amount is 30 wt% to 70 wt% of the amorphous solid dispersion. The total polymer amount is 59 wt% to 39 wt% of the amorphous solid dispersion, if the Vamorolone amount is 40 wt% to 60 wt% of the amorphous solid dispersion. The total polymer amount is 54 wt% to 34 wt% of the amorphous solid dispersion, if the Vamorolone amount is 45 wt% to 55 wt% of the amorphous solid dispersion.

The polymers in still another preferred example have an amount of 97 wt% minus the Vamorolone amount, e.g. total polymer in an amount of 77 wt% to 17 wt% of the amorphous solid dispersion, if the Vamorolone amount is 20 wt% to 80wt% of the amorphous solid dispersion. The total polymer amount is 67 wt% to 27 wt% of the amorphous solid dispersion, if the Vamorolone amount is 30 wt% to 70 wt% of the amorphous solid dispersion. The total polymer amount is 57 wt% to 37 wt% of the amorphous solid dispersion, if the Vamorolone amount is 40 wt% to 60 wt% of the amorphous solid dispersion The total polymer amount is 52 wt% to 32 wt% of the amorphous solid dispersion, if the Vamorolone amount is 45 wt% to 55 wt% of the amorphous solid dispersion.

In yet another preferred example, the disclosure relates to an amorphous solid dispersion containing amorphous Vamorolone in a polymer matrix together with one or more further active ingredients.

Higher amounts of Vamorolone, above 67 wt% of the solid dispersion, have been linked to physical instability. When exposed to stress conditions during storage (40°C/75% relative humidity, for 1 week) partial re-crystallization of the amorphous form was observed, then. Also, despite an initial increase in kinetic solubility in water or aqueous media, the ability to maintain supersaturation was negatively impacted when Vamorolone loads of about 67 wt% or higher in the solid dispersion were used.

In preferred examples, the composition of the disclosure does not comprise any additional ingredients apart from polymer and Vamorolone. In another example, the composition of the disclosure comprises up to 3 wt%, or up to 2 wt% or up to 1 wt% of total amount of any

additional ingredients. Additional ingredients are for example additional ingredients for stabilizing Vamorolone in the amorphous phase.

In still further examples, a pharmaceutical composition is provided comprising the amorphous solid dispersion of Vamorolone and one or more pharmaceutically acceptable excipients. Such a pharmaceutical composition might contain pharmaceutically acceptable excipients of different functional categories, including, but not limited to, diluents, binders, disintegrants, lubricants, glidants, surfactants and polymeric film coatings. In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the amorphous solid dispersion as disclosed herein and a pharmaceutically acceptable excipient.

In one particular example the pharmaceutical composition is a solid oral dosage form. In a more preferred example, the solid dosage form is an immediate release tablet or capsule for oral administration. Such a tablet or capsule might contain pharmaceutically acceptable excipients of different functional categories, including, but not limited to, diluents, binders, disintegrants, lubricants, glidants, surfactants and polymeric film coatings.

In a further preferred example, the amorphous Vamorolone dispersion of the present disclosure is prepared by spray drying. Accordingly, the present disclosure provides a method for preparing a Vamorolone composition of the present disclosure, i.e. Vamorolone as a solid dispersion of amorphous Vamorolone in a polymer matrix, by spray drying. Spray drying is well known in the art. The method e.g. comprises atomizing a solution containing the drug substance Vamorolone and a polymer, optionally together with suitable excipients to generate fine droplets that are introduced into a chamber, where they are contacted with a hot drying gas and dried through solvent evaporation to form particles. The particles may subsequently be separated from the drying medium, e.g. using a cyclone or a bag filter. Hence, the spray drying process e.g. comprises: atomizing the feed liquid comprising Vamorolone and polymer or other suitable excipients, contacting the so obtained droplets with a hot drying medium, drying of the droplets into particles and separating the particles from the drying medium. The powder obtained may preferably undergo a secondary drying step to ensure the removal of residual solvents to acceptable levels.

It has been surprisingly found that other methods were largely unsuccessful in preparing the composition of the present disclosure. Experiments using hot melt extrusion failed to obtain stable amorphous solid dispersions of Vamorolone with suitable drug loads. E.g. drug loads of about 20 wt% Vamorlone in the dispersion or lower were necessary to obtain and stabilize the amorphous form of Vamorolone. Such drug loads are not compatible with a suitable tablet size that is convenient for the patient in terms of swallowability. Conditions required for higher drug loads, on the other hand, led to significant degradation of the drug substance.

One example of preparing the solid dispersion of the disclosure using spray drying comprises dissolving the drug and a polymer in an organic solvent or a mixture of organic solvents, and spraying the obtained solution into a stream of heated gas to remove the organic solvent. In another aspect of the present disclosure, there is provided a method of preparing the amorphous solid dispersion as disclosed herein by spray drying.

With spray drying, it is possible to co-precipitate a drug substance with a polymer into a stable amorphous solid dispersion thanks to the fast drying rate that enables the drug substance to be captured in amorphous form.

In another example of the disclosure, a pharmaceutical composition comprising the Vamorolone of the present disclosure is provided. More preferably, the present disclosure provides a solid dosage form, preferably a tablet or coated tablet. In another example, the solid dosage form is a capsule. The capsule may be filled with a powder, granules, pellets, multiparticulates or mini-tablets comprising the composition of the present disclosure.

Further provided is a solid oral pharmaceutical composition comprising a Vamorolone composition of the present disclosure, as an amorphous solid dispersion; and at least one filler, one disintegrant, binder glidant, wetting agent and/or one lubricant. In preferred examples, a film coating may be added. Also provided are methods for preparing such solid oral pharmaceutical composition.

In another example, the present disclosure provides Vamorolone compositions of the present disclosure for use in methods of treating of a disease selected from

a) asthma or chronic obstructive pulmonary disease,

b) a skin disease,

c) Sjogren's syndrome ,

d) arthritis, or

e) muscular wasting.

Preferably, the muscular wasting disease is muscular dystrophy In some examples, the muscular dystrophy is chosen from Duchenne muscular dystrophy, Becker muscular dystrophy, limb girdle muscular dystrophy, congenital muscular dystrophy, facioscapulohumeral muscular dystrophy, myotonic muscular dystrophy, oculopharyngeal muscular dystrophy, distal muscular dystrophy, and Emery Dreifuss muscular dystrophy.

Most preferred, the muscular dystrophy is Duchenne muscular dystrophy.

Further provided is the use of a polymer to improve the solubility of Vamorolone in an aqueous medium by dispersing Vamorolone in a solid amorphous form in the polymer. In a further aspect of the present disclosure, there is provided a use of a polymer for improving the solubility of Vamorolone in an aqueous medium by dispersing Vamorolone in amorphous form in the polymer. In this example of the disclosure, at least 50 wt% of the total Vamorolone amount shall be dispersed amorphous Vamorolone; more preferably at least 60 wt% of the total Vamorolone amount shall be dispersed amorphous Vamorolone; even more preferably at least 70 wt% of the total Vamorolone amount shall be dispersed amorphous Vamorolone; even more preferably at least 80 wt% of the total Vamorolone amount shall be dispersed amorphous Vamorolone; even more preferably at least 90 wt% of the total Vamorolone amount shall be dispersed amorphous Vamorolone, even more preferably at least 95 wt% of the total Vamorolone amount shall be dispersed amorphous Vamorolone; even more preferably at least 97 wt% of the total Vamorolone amount shall be dispersed amorphous Vamorolone; and most preferably at least 99 wt% of the total Vamorolone amount shall be dispersed amorphous Vamorolone. All amounts are amounts of amorphous Vamorolone per total Vamorolone. The Vamorolone dispersion is preferably obtained by spray drying. The Vamorolone is preferably the Vamorolone in a composition of the present disclosure as defined in any of the examples set forth above.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A and 1B depict X-ray diffractograms obtained for solid dispersion prototypes obtained by hot melt extrusion (1A) and spray drying (1B). Figure 1A shows a XRPD pattern of the HME prototype (40% Vamorolone in VA64). Figure 1B shows XRPD patterns of SDD prototypes: (1) Vamorolone : Kollidon VA 64 (1:2); (2) Vamorolone : HPMC E3 (1:2); (3) Vamorolone : HPMC E3 (1:1); (4) Vamorolone : HPMCAS M (1:2); (5) Vamorolone : HPMCAS M (1:1) ; (6) Vamorolone : HPMCAS M (2:1). For hot melt extrusion, the choice of the polymer (copovidone VA64) was based on the outcome of preformulation studies (miscibility experiments) employing differential scanning calorimetry (DSC) that evaluated the following polymers: copovidone VA64, mixtures of copovidone VA64/poloxamer, mixtures of copovidone VA64/HPMC E3, HPMCAS-L, and HPMCAS-M. The results of hot melt extrusion with the polymer that exhibited the best miscibility were unsatisfactory for a drug load of 40% or more, since signs of crystallinity were evident in the diffractograms. In addition, HPLC analysis of the samples revealed degradation of the drug substance.

For spray drying, however, XR patterns typical of amorphous materials were obtained for several polymers: HPMCAS-M (67%, 50% and 33% drug load), HPMC E3 (drug load 50% and