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(57) Abstract

The invention relates to the stabilization of poly–ene macrolides and to a particular macrolide obtained in crystalline form.

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MACROLIDES

The present invention relates to the stabilization of a pharmaceutically active ingredient sensitive to oxidation, e.g. a poly-ene macrolide, preferably a poly-ene macrolide having immunosuppressant properties, particularly rapamycins.

The handling and storage particularly in the bulk form of pharmaceutically active ingredients which are sensitive to oxidation is difficult. Special handling is necessary and often the oxidation-sensitive ingredient is stored in air-tight packaging under protective gas. Substantial amounts of stabilizers are added during the formulating process of such pharmaceutically active ingredients.

Poly-ene macrolides have satisfactory stability properties. However, it has now been found that their stability to oxygen may substantially be improved by the addition of a stabilizer, e.g. an antioxidant, during their isolation step.

According to the invention, there is provided

1. A process for stabilizing a poly-ene macrolide comprising adding an antioxidant to the purified macrolide, preferably at the commencement of its isolation step.

   This process is particularly useful for the production of a stabilized poly-ene macrolide in bulk. The amount of antioxidant may conveniently be up to 1%, more preferably from 0.01 to 0.5 % (based on the weight of the macrolide). Such a small amount is referred to hereinafter as a catalytic amount.

As alternatives to the above the present invention also provides:

2. A mixture, e.g. a bulk mixture, comprising a poly-ene macrolide and an anti-oxidant, preferably a catalytic amount thereof, preferably in solid form.

   The mixture may be in particulate form e.g. cristallized or amorphous form. It may be in a sterile or substantially sterile condition, e.g. in a condition suitable for pharmaceutical use.

3. Use of a mixture as defined above in 2. in the manufacture of a pharmaceutical composition.

Examples of poly-enes macrolides are e.g. molecules comprising double bonds, preferably conjugated double bonds, for example such having antibiotic and/or immunosuppressant properties, e.g. macrolides comprising a lactam or lactone bond and their derivatives, e.g. compounds which have a biological activity qualitatively similar to that of the natural macrolide, e.g. chemically substituted macrolides. Suitable examples include e.g. rapamycins and ascomycins. A preferred poly-ene macrolide is a macrolide comprising at least 2 conjugated double bonds, e.g. 3 conjugated double bonds.

Rapamycin is a known lactam macrolide produceable, for example by Streptomyces hygroscopicus. The structure of rapamycin is given in Kessler, H. et al.; 1993; Helv. Chim. Acta, 76 : 117. Rapamycin has antibiotic and immunosuppressant properties. Derivatives of rapamycin are known, e.g. 16-O-substituted rapamycins, for example as disclosed in WO 94/02136 and WO 96/41807, 40-O-substituted rapamycins, for example as disclosed in WO 94/09010, WO 92/05179, WO 95/14023, 94/02136, WO 94/02385 and WO 96/13273, all of which being incorporated herein by reference. Preferred rapamycin derivatives are e.g. rapamycins wherein the hydroxy in position 40 of formula A illustrated at page 1 of WO 94/09010 is replaced by -OR wherein R is hydroxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl or aminoalkyl, e.g. 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, and 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin.

Ascomycins, of which FK-506 and ascomycin are the best known, form another class of lactam macrolides, many of which have potent immunosuppressive and anti-inflammatory activity. FK506 is a lactam macrolide produced by Streptomyces tsukubaensis. The structure of FK506 is given in the Appendix to the Merck Index, 11th ed. (1989) as item A5. Ascomycin is described e.g. in USP 3,244,592. Ascomycin, FK506, other naturally occurring macrolides having a similar biological activity and their derivatives, e.g. synthetic analogues and derivatives are termed collectively "Ascomycins". Examples of synthetic analogues or derivatives are e.g. halogenated ascomycins, e.g. 33-epi-chloro-33-desoxy-ascomycin such as disclosed in EP-A-427,680, tetrahydropyran derivatives, e.g. as disclosed in EP-A-626,385.

Particularly preferred macrolides are rapamycin and 40-O-(2-hydroxy)ethyl-rapamycin.

Preferred antioxidants are for example 2,6-di-tert.-butyl-4-methylphenol (hereinafter BHT), vitamin E or C, BHT being particularly preferred.

A particularly preferred mixture of the invention is a mixture of rapamycin or 40-O-(2-hydroxy)ethyl-rapamycin and 0.2% (based on the weight of the macrolide) of antioxidant, preferably BHT.

The antioxidant may be added to the poly-ene macrolide at the commencement of the isolation steps, preferably the final isolation step, more preferably just prior to the final precipitation step. The macrolide is preferably in a purified state. It may be dissolved in an inert solvent and the antioxidant is added to the resulting solution, followed by a precipitation step of the stabilized macrolide, e.g. in an amorphous form or in the form of crystals. Preferably the mixture of the invention is in amorphous form.

The resulting stabilized macrolide exhibits surprisingly an improved stability to oxidation and its handling and storage, e.g. in bulk form prior to its further processing for example into a galenic composition, become much easier. It is particularly interesting for macrolides in amorphous form.

The macrolide stabilized according to the invention may be used as such for the production of the desired galenic formulation. Such formulations may be prepared according to methods known in the art, comprising the addition of one or more pharmaceutically acceptable diluent or carrier, including the addition of further stabilizer if required.

Accordingly there is further provided:

4. A pharmaceutical composition comprising, as active ingredient, a stabilized mixture as disclosed above, together with one or more pharmaceutically acceptable diluent or carrier.

   The composition of the invention may be adapted for oral, parenteral, topical (e.g. on the skin), occular, nasal or inhalation (e.g. pulmonary) administration. A preferred

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