PHARMACEUTICAL COMPOSITIONS, METHOD OF MAKING AND METHOD OF USING THEREOF

RELATED APPLICATIONS

This application claims priority of Chinese Application No. 2020102271770, filed on March 27, 2020, and American Application No.17/212,623, filed on March 25, 2021. The entirety of the aforementioned application is incorporated herein by reference.

FIELD

The invention belongs to the field of pharmaceutical preparations, and particularly relates to a cyclic phosphonate pharmaceutical composition suitable for storage at room temperature and a preparation method thereof.

BACKGROUND

The storage conditions of a drug product are a reflection of the stability of the drug in the drug product. Drugs or crystal forms with lower melting points are generally relatively less stable and need to be stored at lower temperatures, while drugs or crystal forms with higher melting points have better stability and can generally be stored at room temperature. The reasonable processing temperature of the preparation should also be reasonably determined according to the thermal stability of the drug. Thermal degradation of drugs is usually closely related to their melting point, and after 20°C beyond the melting point, degradation reactions occur rapidly.

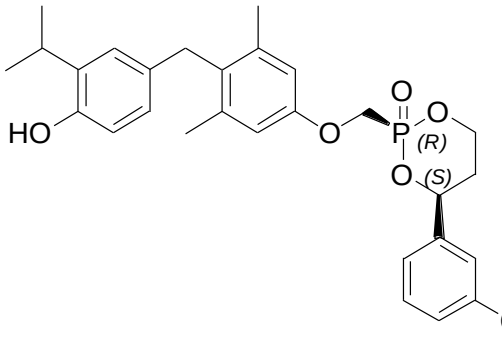
Steatohepatitis is a chronic inflammatory disease, thus long term medication is preferred. The requirement for low temperature storage will add many inconveniences to the long-term medication of patients, and may result missed administration or improper storage, which may affect the therapeutic effect, and may lead to delay or recurrent of the disease. In addition, the low-temperature refrigeration conditions also need to be equipped with special cold chain transportation vehicles and long-term use refrigerator, which bring additional costs to the commercial development of the product.

Therefore, in order to better meet clinical and commercial needs, it is

CLAIMS

1. A pharmaceutical composition, comprising the following components in weight portions:

(a) 1 part of the compound of formula (I)



(I); and

(b) 15 to 45 parts of copovidone with a glass transition temperature of 90 °C to 130 °C, wherein components (a) and (b) are mixed and undergo hot melt extrusion.

2. The pharmaceutical composition of claim 1, wherein components (a) and (b) are mixed and undergo hot melt extrusion at a temperature in the range of 80 °C -135 °C.

3. The pharmaceutical composition of claim 1, comprising 20 to 40 parts of copovidone.

4. The pharmaceutical composition of claim 1, comprising 22 to 33 parts of copovidone.

5. The pharmaceutical composition of claim 1, further comprising:

(c) 0.1 to 3.0 parts of one or more pharmaceutically acceptable excipients selected from the group consisting of non-volatile weak acids, neutral or weakly acidic inorganic substances, and pharmaceutically acceptable excipients with melting point lower than 80 °C, wherein components (a), (b) and (c) are mixed and undergo hot melt extrusion at a temperature in the range of 80 °C -135 °C.

6. The pharmaceutical composition of claim 5, wherein the one or more

Pharmaceutically acceptable excipients comprise anhydrous citric acid, citric acid monohydrate, or a mixture thereof.

7. The pharmaceutical composition of claim 5, wherein the one or more pharmaceutically acceptable excipients comprise one or more neutral or weakly acidic inorganic substances selected from the group consisting of mannitol, lactose monohydrate, lactose anhydrous, sorbitol, calcium hydrogen phosphate anhydrous and colloidal silicon dioxide.

8. The pharmaceutical composition of claim 5, wherein the one or more pharmaceutically acceptable excipients comprise one or more excipients selected from the group consisting of polyethylene glycol, such as polyethylene glycol 4000, polyethylene glycol 6000; lipidic materials, such as triethyl citrate, polyethylene glycol succinate; antioxidants, such as 2,6-di-tert-butyl-p-cresol, vitamin E; surfactants, such as Poloxamer 188, Tween 80.

9. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is formulated in a tablet or capsule form.

10. A method for preparing the pharmaceutical composition of any one of claims 1 to 9, comprising the steps of:

extruding a mixture of components (a) and (b) by hot melt extrusion at hot melt extrusion temperature between 80 ^{o}C and 135 ^{o}C to form an extrusion product;

cooling the extrusion product; and

breaking the cooled extrusion product into granules, particles or powders by cutting, crushing or grinding.

11. The method of claim 10, further comprising the step of:

processing the granules, particles or powders obtained in the breaking step into tablets, capsules.

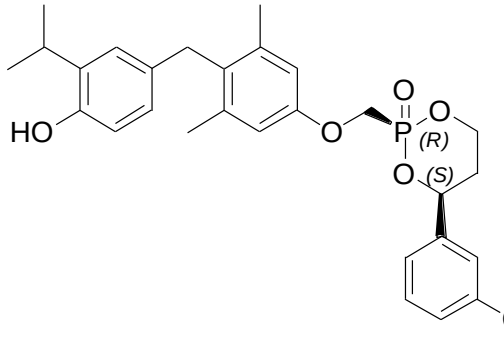
12. The method of claim 10, wherein the mixture of components (a) and (b)

is extruded with a twin screw hot melt extrusion device; wherein the screw diameter of the twin screw hot melt extrusion device is between 8 mm and 50 mm, and the extrusion speed is between 10 rpm and 300 rpm, wherein retention time of the hot melt extrusion is less than 30 min.

13. A pharmaceutical composition of any one of claims 1 to 9, for use in the treatment of steatohepatitis.

14. A pharmaceutical composition, comprising the following components in weight portions:

(a) 1 part of the compound shown in Formula (I);



(I); and

(b) 6 to 20 parts of hydroxypropyl methylcellulose with a glass transition temperature of 90 ºC to 130 ºC,

wherein components (a) and (b) are mixed and undergo hot melt extrusion.

15. The pharmaceutical composition of claim 14, wherein components (a) and (b) are mixed and undergo hot melt extrusion at a temperature in the range of 80 ºC -135 ºC.

16. The pharmaceutical composition of claim 14, further comprising:

(c) 0.1 to 3.0 parts of one or more pharmaceutically acceptable excipients selected from the group consisting of non-volatile weak acids, neutral or weakly acidic inorganic substances, and pharmaceutically acceptable excipients with melting point lower than 80 ºC, wherein components (a), (b) and (c) are mixed and undergo hot melt extrusion at a temperature in the range of 80 ºC -135 ºC.

17. The pharmaceutical composition of claim 16, comprising 0.2 to 2.0 parts of one or more pharmaceutically acceptable excipients.

18. The pharmaceutical composition of claim 14, wherein the pharmaceutical composition is formulated in a tablet or capsule form.

19. A method for preparing the pharmaceutical composition of any one of claims 14 to 18, comprising the steps of:

extruding a mixture of components (a) and (b) by hot melt extrusion at hot melt extrusion temperature is between 80 ^{o}C and 135 ^{o}C to form an extrusion product;

cooling the extrusion product; and

breaking the cooled extrusion product into granules, particles or powders by cutting, crushing or grinding.

20. A pharmaceutical composition of any one of claims 14 to 18, for use in the treatment of steatohepatitis.