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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 April 2014 (24.04.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/060445 A1

(51) International Patent Classification:
C07D 305/12 (2006.01)

(21) International Application Number:
PCT/EP2013/071569

(22) International Filing Date:
16 October 2013 (16.10.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12189193.1 19 October 2012 (19.10.2012) 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, LT, 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, 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 2014/060445 A1

(54) Title: METHOD FOR PREPARING HIGH PURITY ORLISTAT

(57) Abstract: The present invention relates to a method of purifying Orlistat comprising the steps of: a) providing an injection solution comprising crude Orlistat; b) injecting said injection solution into a reverse phase high performance liquid chromatography preparative column; c) eluting said Orlistat with an eluent comprising water, C_1-C_4 alcohol and C_1-C_6 ester; and d) collecting Orlistat. The present invention also relates to a method of preparing high-purity Orlistat by reverse phase high performance liquid chromatography, comprising the steps of: a) providing an injection solution comprising an organic solvent and/or water, and crude Orlistat; b) injecting said injection solution obtained in step (a) into a reverse phase high performance liquid chromatography preparative column; c) eluting said Orlistat with an eluent comprising water and a C_1-C_4 alcohol and a C_1-C_6 ester; d) collecting purified Orlistat having a higher purity than crude Orlistat.

METHOD FOR PREPARING HIGH PURITY ORLISTAT

Field of the Invention

The present invention relates to the field of medical technology and, more specifically, to a method for preparing high-purity Orlistat by reverse phase high performance liquid chromatography.

Background of the Invention

Orlistat is a derivative obtained by the catalytic hydrogenation of lipstatin, a secondary metabolite of *Streptomyces toxytricini* fermentation. Orlistat is a specific gastrointestinal lipase inhibitor, cf. U.S. Pat. No. 4,598,089. It has been observed that Orlistat can reduce the absorption of fat in food by around 30%, and Orlistat is being used as a pharmaceutical for treating overweight and obese patients. When used as a pharmaceutical, it is essential to provide high purity Orlistat.

CN 102070567 discloses the use of reverse phase high performance liquid chromatography (RP-HPLC) to purify Orlistat. This method, however, gives a low loadability of samples and takes a long time to perform.

Accordingly, there is still a need for a simple and efficient method for purifying Orlistat. There is also a need for a simple and efficient method for preparing high purity Orlistat.

Summary of the Invention

It is an object of the present invention to provide a method for preparing or purifying Orlistat which is simple and efficient, allows a high loadability, can be carried out in small and simple equipment, provides improved purity and quality of the Orlistat product, and results in increased yield and productivity of Orlistat.

The present invention makes it possible to separate impurities from Orlistat, or a composition comprising Orlistat. More specifically, the enhanced displacement effect of the invention makes it possible to elute impurities before the Orlistat product, which results in a higher yield at a given purity level of the crude Orlistat starting material.

Accordingly, in one aspect, the present invention relates to a method of purifying Orlistat comprising the steps of:

a) providing an injection solution comprising crude Orlistat;
b) injecting said injection solution into a reverse phase high performance liquid chromatography preparative column;
c) eluting Orlistat with an eluent comprising water, C_1-C_4 alcohol and C_1-C_6 ester; and
d) collecting Orlistat.

In another aspect, the present invention relates to a method of purifying Orlistat, and a method of preparing high-purity Orlistat, by reverse phase high performance liquid chromatography, comprising the steps of:

a) providing an injection solution comprising an organic solvent and/or water, and crude Orlistat;
b) injecting said injection solution obtained in step (a) into a reverse phase high performance liquid chromatography preparative column;
c) eluting said Orlistat with an eluent comprising water and a C_1-C_4 alcohol and a C_1-C_6 ester; and
d) collecting purified Orlistat having a higher purity than crude Orlistat.

These and other objects, aspects and advantages of the invention will be described in further detail hereinafter.

Detailed Description of the Invention

Orlistat is also known as tetrahydrolipstatin (THL, CAS 96829-58-2). The term “crude Orlistat”, as used herein, refers to a composition which comprises Orlistat and any impurity. The terms “pure Orlistat” and “purified Orlistat”, as used herein, mean a composition which comprises Orlistat and which may also comprise one or more impurities, whereby the amount of said one or more impurities is lower in pure Orlistat and purified Orlistat compared to the amount present in crude Orlistat.

Crude Orlistat is commercially available and usually comprises Orlistat in an amount of, or has purity, from 40 to 90 % by weight, the remainder being one or more impurities. Accordingly, crude Orlistat usually contains from 10 to 60 % by weight of impurities.

The Orlistat product, or purified Orlistat, obtained according to the invention has a higher purity than crude Orlistat. According to the invention, purified Orlistat may comprise Orlistat in an amount of, or has purity, above 95 % by weight, suitably above 99 % by weight, preferably above 99.5 % by weight, and each individual impurity is suitably present in an amount of less than 0.1 % by weight.

In the injection solution, crude Orlistat may be dissolved in an organic solvent, water, or a mixture of an organic solvent and water. The composition of the injection solution may vary as long as Orlistat remains soluble. Preferably, crude Orlistat is dissolved in a mixture of an organic solvent and water. The organic solvent is preferably a C_1-C_4 alcohol, C_3-C_4 ketone, ethyl acetate, acetonitrile, propionitrile or tetrahydrofuran. Most preferably, crude Orlistat is dissolved in the eluent used for eluting Orlistat.

The load concentration of crude Orlistat may be from 0.5 to 10 % mass/volume, meaning that each 100 ml of solution contains from 0.5 to 10 g of crude Orlistat, and preferably from 2 to 5 % mass/volume, meaning that each 100 ml of solution contains from 2 to 5 g of crude Orlistat.

The composition of the eluent may be varied as long as Orlistat remains soluble. The eluent may comprise from 5 to 30 % (volume/volume) water, preferably 10-20 % (volume/volume). The eluent may comprise from 65 to 95 % (volume/volume) of a C_1-C_4 alcohol, preferably 75-85 % (volume/volume). The C_1-C_4 alcohol may be methanol, ethanol, isopropanol or butanol, preferably methanol or ethanol. The eluent suitably comprises from 0.5 to 10 % (volume/volume) C_1-C_6 ester, preferably 1-5 % (volume/volume). The C_1-C_6 ester may be methyl acetate or ethyl acetate, or mixtures thereof. Preferably, the eluent comprises from 5 to 30 % (vol/vol) water, from 65 to 95 % (vol/vol) C_1-C_4 alcohol, and from 0.5 to 10 % (vol/vol) C_1-C_6 ester. Preferably, the eluent has a higher volume percentage of C_1-C_4 alcohol as compared to the injection solution. The composition of the eluent is preferably kept substantially constant during chromatography.

According to the invention, steps (b) to (d) may be repeated in order to further increase the purity. For example, if the crude Orlistat used contains a high amount of impurities, it may be preferable to repeat steps (b) to (d) to reach the desired purified Orlistat.

The present invention makes it possible to achieve an enhanced displacement effect which causes impurities to elute before the Orlistat, which will result in a higher yield of

Orlistat at a given purity level. This positive effect is called the compression effect. As a result of this effect, it is also possible to use more frequently stacked injections, i.e. to inject new samples of crude Orlistat before the previous sample of crude Orlistat has eluted entirely, as the impurities will not interfere with the next sample. This will also contribute to the efficiency of the present method. According to the invention, stacked injections may occur every 15 minutes.

According to the invention, the reverse phase high performance liquid chromatography preparative column may be a DAC (Dynamic Axial Compression) preparative column.

Appropriate column parameters may be selected according to the type and specification of the packing, for example, silica gel packing typically employs a column pressure of 3 MPa to 45 MPa, and a column bed height of between 20 cm and 35 cm; in polymeric reverse phase resin packing, the column pressure is typically selected from a range between 1 MPa and 10 MPa, depending on the packing height.

According to the invention, the reverse phase high performance liquid chromatography preparative column may be a stationary phase comprising a silica gel or a polymeric reverse phase resin functionalized with C_{18}-, C_8-, C_4-, or C_6H_5 groups, preferably C_{18}- and C_8- groups. The silica gel or polymeric reverse phase resin may have a particle size of from 5 to 250 µm, preferably from 10 to 20 µm, as measured by Coulter counter.

The stationary phase may have a pore size as measured by N_2-adsorption from 60 Å to 300 Å, preferably from 100 Å to 120 Å, and the shape of the packing may be irregular or spherical, where spherical is preferred.

According to the invention, the temperature during elution of Orlistat may be from 10 to 35 °C.

Examples

The invention is further illustrated in the following Examples which, however, are not intended to limit the same. Parts and % relate to parts by weight and % by volume, respectively, unless otherwise stated.

Example 1

25 mg crude commercial Orlistat with a purity of 92.9 % was dissolved in 1800 µl eluent of H_2O/MeOH/EtOAc 18/77/5 (volume/volume %). It was loaded onto a RP HPLC system (Agilent 1200) with a 4.6x250 mm Kromasil® 100 Å-10 µm-C8 stationary phase. Loading was 15.1 $mg_{crude}/(g_S x t_{cycle})$. The eluent flow was 0.7 ml/min, and the temperature was 25°C. The system pressure drop was 47.2 bar during elution. Detection was performed at a wavelength of UV determination of 230 nm. The target analytes were collected between 52.0 and 63.5 minutes. The samples analyzed by HPLC were found to have a purity of 99.7 %, and the yield was 72.4 %. The productivity was 10.6 $mg_{product}/(g_S x t_{cycle})$.

Comparative Example

The example above was followed, except that an eluent of H_2O/MeOH 15/85 (volume/volume %) was used. Loading was 9.9 $mg_{crude}/(g_S x t_{cycle})$. The purity was 99.7 %, but the yield was only 61 %. The productivity was 5.59 $mg_{product}/(g_S x t_{cycle})$.

Claims

1. A method of purifying Orlistat comprising the steps of:
   a) providing an injection solution comprising crude Orlistat;
   b) injecting said injection solution into a reverse phase high performance liquid chromatography preparative column;
   c) eluting Orlistat with an eluent comprising water, C_1-C_4 alcohol and C_1-C_6 ester; and
   d) collecting Orlistat.

2. A method of preparing high-purity Orlistat by reverse phase high performance liquid chromatography, comprising the steps of:
   a) providing an injection solution comprising an organic solvent and/or water, and crude Orlistat;
   b) injecting said injection solution obtained in step (a) into a reverse phase high performance liquid chromatography preparative column;
   c) eluting said Orlistat with an eluent comprising water and a C_1-C_4 alcohol and a C_1-C_6 ester;
   d) collecting purified Orlistat having a higher purity than crude Orlistat.

3. The method according to claim 1 or 2, wherein the Orlistat obtained in step d) has a purity over 99 % by weight and individual impurities below 0.5 % by weight, preferably the Orlistat obtained in step d) has a purity over 99.5 % by weight and individual impurities below 0.1 % by weight.

4. The method according to any one of the preceding claims, wherein said crude Orlistat has a purity above 40 % by weight, preferably above 60 % by weight.

5. The method according to any one of the preceding claims, wherein said injection solution comprises from 0.5 to 10 % (mass/volume) crude Orlistat.

6. The method according to any one of the preceding claims, wherein said injection solution comprises an organic solvent comprising a C_1-C_4 alcohol, C_3-C_4 ketone, ethyl acetate, acetonitrile, propionitrile or tetrahydrofuran.

7. The method according to any one of the preceding claims, wherein said eluent comprises from 5 to 30 % (volume/volume) water.

8. The method according to any one of the preceding claims, wherein said C_1-C_4 alcohol is methanol, ethanol or a mixture thereof.

9. The method according to any one of the preceding claims, wherein said eluent comprises from 0.5 to 10 % (volume/volume) of C_1-C_6 ester.

10. The method according to any one of the preceding claims, wherein said C_1-C_6 ester is methyl acetate, ethyl acetate or a mixture thereof.

11. The method according to any one of the preceding claims, wherein said eluent comprises from 5 to 30 % (vol/vol) water, from 65 to 95 % (vol/vol) C_1-C_4 alcohol, and from 0.5 to 10 % (vol/vol) C_1-C_6 ester.

12. The method according to any one of the preceding claims, wherein steps (b) to (d) are repeated to increase the purity of Orlistat, preferably repeated one or more times.

13. The method according to any one of the preceding claims, wherein the reverse phase high performance liquid chromatography preparative column is a DAC preparative column.

14. The method according to any one of the preceding claims, wherein the reverse phase high performance liquid chromatography preparative column comprises a stationary phase comprising a silica gel or a polymeric reverse phase resin functionalized with C_{18}-, C_8-, C_4-, or C_6H_5 groups.

15. The method according to claim 14, wherein said silica gel or polymeric reverse phase resin has a particle size from 5 to 250 µm.

16. The method according to claim 14 or 15, wherein the stationary phase has a pore size from 100 Å to 120 Å.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/071569

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D305/12
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)
C07D

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, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102 070 567 A (TIANJIN HAIDE ANKE PHARMACEUTICAL TECHNOLOGY DEV CO LTD) 25 May 2011 (2011-05-25) cited in the application the whole document -----	1-16
A	SOURI E ET AL: "HPLC Analysis of Orlistat and Its Application to Drug Quality Control Studies", CHEMICAL AND PHARMACEUTICAL BULLETIN,, vol. 55, no. 2, 1 January 2007 (2007-01-01), pages 251-254, XP007921435, ISSN: 0009-2363 the whole document -----	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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2013	12/11/2013

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/071569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 102070567 A	25-05-2011	NONE	