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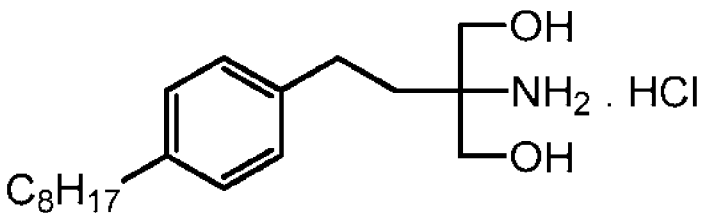
(54) Title: PROCESS FOR MAKING FINGOLIMOD HYDROCHLORIDE CRYSTALS



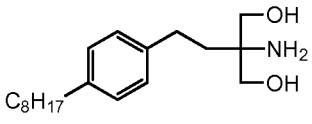
(1a)

(57) Abstract: The invention relates to a process of making crystalline fingolimod hydrochloride of Formula (1a), comprising a step of contacting a solution of fingolimod hydrochloride in a solvent with an antisolvent at an enhanced temperature, and cooling such solution whereby crystalline fingolimod hydrochloride precipitates, and isolating crystalline fingolimod hydrochloride from the liquid medium.

PROCESS FOR MAKING FINGOLIMOD HYDROCHLORIDE CRYSTALS

BACKGROUND OF THE INVENTION

[0001] Fingolimod (often coded as FTY 720), chemically 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol of the formula (1)



(1)

is a pharmaceutically active compound currently tested as an immunosuppressive drug and as an active agent in treatment of multiple sclerosis. It may form stable acid addition salts, of which fingolimod hydrochloride is the most common one.

[0002] Fingolimod has been first disclosed in EP 627406 of Yoshitomi, where also two basic routes for making it have been described.

[0003] Fingolimod hydrochloride exists in a stable crystalline form. Such crystalline product was first obtained in the above EP 627406 by recrystallization of fingolimod hydrochloride from a solution thereof in ethanol. In Example 5 of WO 2000/027798, crystals of fingolimod hydrochloride were obtained by crystallization from a mixture of ethyl acetate and ethanol. In Example 3 thereof, crystals were obtained by precipitation after concentration of the ethanolic solution.

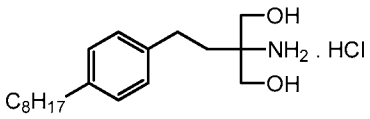
[0004] It was found by the present inventor after repeating the crystallization processes of the prior art that fingolimod hydrochloride is obtainable only as a waxy- or a cotton-like solid with poor filterability and flowability. Because of these properties, such crystal habit is inconvenient for large scale processing and for subsequent formulation into pharmaceutical compositions.

[0005] Thus, while processes for making crystalline fingolimod hydrochloride are known in the art, an improvement in the matter is still desirable.

SUMMARY OF THE INVENTION

[0006] The present invention is based on a discovery of an improved process for making crystalline fingolimod hydrochloride.

[0007] In a first aspect, the present invention provides for a process of making crystalline fingolimod hydrochloride of formula (1a),



(1a)

comprising a sequence of steps of

a] contacting a solution of finglimod hydrochloride in a solvent, which preferably is an aliphatic alcohol solvent, with an antisolvent at a temperature of at least 50°C,

b] cooling the obtained solution to a temperature of below 40°C , whereby crystalline fingolimod hydrochloride precipitates,

and

c] isolating crystalline fingolimod hydrochloride from the mixture.

[0008] In a preferred aspect, the temperature of the antisolvent before and during contacting it with the solution of fingolimod in the solvent is substantially the same and is not lower than 40°C.

[0009] In yet a preferred aspect, the antisolvent is an aliphatic, cyclic and/or aromatic hydrocarbon.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 XRPD pattern of "Form I" fingolimod hydrochloride

Fig.2 DSC scan of "Form I" fingolimod hydrochloride

Fig.3 IR spectrum of Form I" fingolimod hydrochloride

DETAILED DESCRIPTION OF THE INVENTION

[0010] The crystalline fingolimod hydrochloride obtainable by processes of the prior art documents disclosed above is characterized by a distinctive XRPD pattern and IR spectrum, which allow to conclude that each of these processes provides a stable crystalline form, which is denoted for purpose of the present invention as Form I.

[0011] The process of our invention provides the same crystalline form, however in a better habit which results in better filterability and flowability. In particular, the population of crystals obtainable by the process of the present invention is characterised by small regular crystals with low tendency to adhere together and to adsorb solvent on the surface of the crystals.

[0012] The general feature characterizing the process of the present invention is in that the crystalline fingolimod hydrochloride does not crystallize from an oversaturated solution in a solvent. Instead, crystals of fingolimod hydrochloride are obtained by crystallization from a solution in a mixture of a solvent and an antisolvent (as defined later). Careful selection of the nature of both these liquids as well as of their mutual ratio and of the concentration of fingolimod hydrochloride in the mixture is performed with the goal to obtain a system, which allows to dissolve fingolimod hydrochloride in the mixture at temperatures of at least 50°C, whereby, simultaneously, the same system allows to precipitate fingolimod hydrochloride at temperatures of 40°C and lower. Such a precipitation provides small regular crystals, which exhibit good filterability and flowability after drying. As a result, isolation and elaboration procedures of the solid fingolimod hydrochloride are short, which is advantageous, in particular, at a large scale production process.

[0013] The second advantageous feature of the process of the present invention is in that it provides the crystalline Form I defined above with no contamination with other crystalline forms. Careful study of solid state properties of the crystalline fingolimod hydrochloride confirmed the teaching recently disclosed in WO 2010/055028 shown that fingolimod hydrochloride may form metastable crystalline forms upon heating. At least two crystalline forms, hereby denoted as Form II and Form III, respectively, are formed after heating the Form I at 40-60°C or 80°C, resp. Each of the metastable forms converts to the stable Form I after cooling, however, at least in case of the Form II, such conversion is very slow. Thus, precipitating fingolimod hydrochloride at temperatures higher than about 40°C,

which is the typical feature of the prior art crystallization procedures, may produce fingolimod hydrochloride as a mixture of crystalline forms, which is undesirable.

The second production possibility known in the art, namely crystallization from a solution that has been concentrated by evaporation, has yet another disadvantage that solvated crystals and/or liquid crystals might be formed in case of too high degree of concentration (such forms have been detected after thorough concentration of solutions of fingolimod hydrochloride in water or in methanol) . Such lyotropic crystal forms are metastable, they however might impurify the desired Form I (and thus alter the physical properties thereof) in case of incomplete removal of the solvent.

[0014] In the first technological step of the process of the present invention, a solution of fingolimod hydrochloride in a solvent is provided. The starting fingolimod hydrochloride may preferably be an isolated solid material obtained after separation of the solid from a reaction mixture comprising it. Alternatively, a reaction mixture comprising fingolimod hydrochloride and the solvent (as defined hereinafter) may be used as well. Yet alternatively, fingolimod hydrochloride may be produced directly in the solvent by treatment of fingolimod base with hydrogen chloride.

[0015] The "solvent" as used throughout the present invention, is a liquid, in which fingolimod hydrochloride is sufficiently soluble, at least at enhanced temperature. Preferably, the concentration of fingolimod hydrochloride in the solvent at such temperature is higher than 2.5 g/100 ml, advantageously higher than 10g/100 ml.

[0016] The solvent of the present invention is preferably an aliphatic alcohol of 1 to 6 carbon atoms, both straight or branched, such as methanol, ethanol, n-propanol, isopropanol, and/or n-butanol, and mixtures thereof with water.

[0017] To the obtained solution, which is kept at the temperature of at least 50°C, the antisolvent is added in such a way that the temperature of the mixture during the mixing step does not drop below 40°C.

[0018] The "antisolvent" is an organic liquid, in which fingolimod hydrochloride is essentially insoluble, at least at ambient temperature. Furthermore, the antisolvent is miscible with the solvent. Typical antisolvent is a C_5-C_{10} straight or branched aliphatic, cyclic or aromatic hydrocarbon, e.g. n-hexane, n-heptane, cyclohexane, benzene, toluene etc., or C_4-C_{10} aliphatic ether, e.g. diethyl ether or di-isopropyl ether.

Advantageously, the temperature of the antisolvent before and during mixing with the solvent is the same is the solution of fingolimod hydrochloride in the solvent, and should not be lower than 40°C. The final amount of the antisolvent is such that the fingolimod hydrochloride is still dissolved in the obtained final mixture. If this is not the case, the temperature of the system must be increased or the mixture must be diluted with the solvent. Useful ratio between the solvent and antisolvent is from 1:2 to 1:20 (v/v), typically about 1:4 to 1:10 (v/v).

After the solution of fingolimod hydrochloride in the solvent/antisolvent mixture is obtained, it is cooled to a temperature of below 40°C and stirred at this temperature, whereby crystals of fingolimod hydrochloride separate from the solution. As shown above, the temperature of 40°C is the critical temperature, above which the crystallization should not occur for to obtain the proper crystalline Form I. The cooled solution may be advantageously seeded with seed crystals of the Form I of fingolimod hydrochloride. In an advantageous mode, the formed suspension of fingolimod hydrochloride in the solvent/antisolvent mixture is stirred for some time, typically from 30 minutes to 2 hours, preferably at ambient or lower than ambient temperature. Further prolongation of stirring has essentially no improving effect (only a decent growth of the originally formed crystals has been sometimes observed).

[0019] In the third technological step, the formed crystalline fingolimod hydrochloride is separated from the mother liquor, e.g. by filtration or centrifugation, is washed, advantageously by the antisolvent, and dried until volatile residues, if any, are removed. Further treatment, e.g. milling, is essentially not necessary, but not excluded.

[0020] The produced crystalline fingolimod hydrochloride may be used as a pharmaceutically active compound for making pharmaceutical compositions for treatment various diseases, as known in the art.

[0021] The present invention is illustrated by following non-limiting examples.

EXAMPLES

Comparative example 1 (example 29 of EP 0627406 B1)

1.0 g of fingolimod hydrochloride was dissolved in 3 ml of ethanol at reflux. The solution was allowed to cool to room temperature and stirred at room temperature for about 1 hour. As a result, a solid was formed (thick cake). The solid was isolated by filtration over a

P3-glass filter (reduced pressure) and air-dried overnight at R.T. An off-white, greasy to sticky solid with lumps was obtained. The yield was 0.70 g (70%).

DSC: solid-solid transitions below 75°C and melting around 107-110°C.

Comparative example 2 (example 5 of WO 2000/27798)

1.0 g of fingolimod hydrochloride was dissolved in 4 ml of ethanol/ethyl acetate (1:1 V/V) at reflux. The solution was stirred and allowed to cool to room temperature. As a result, a solid was formed (thick cake, sudden crystallization). The solid was isolated by filtration over a P3-glass filter (reduced pressure) and air-dried overnight at R.T. An off-white, greasy to sticky solid with lumps was obtained. The yield was 0.86 g (86%).

DSC: Similar to the DSC scan of Comparative example 1.

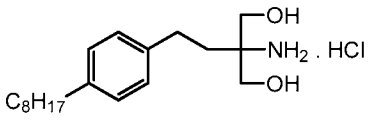
Example 1: Precipitation of fingolimod hydrochloride Form I crystals

Fingolimod (5 g, 16.1 mmol) was stirred with 2-propanol (30 ml). Into the heterogenic mixture, hydrogen chloride solution in 2-propanol (21%) (3.7 ml) was dropwise added. The heterogeneous mixture was warmed to 50°C. Into resulting clear solution, pre-heated n-heptane (120 ml) was added slowly, while the homogeneity of the reaction mixture was maintained. Clear reaction mixture was stirred at a temperature of 50°C for 10 min. The solution was cooled to 0°C during 15 min. The resulted suspension was stirred at 0-3°C for 40 min, filtered off, washed with 2 x 15 ml n-heptane. The yield of fingolimod hydrochloride was 5.1 g (91%) of off-white crystals.

[0022] The invention having been described, it will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts and embodiments described herein can easily be made or may be learned by practice of the invention, without departing from the scope of the invention as defined by the following claims.

CLAIMS

1. A process of making crystalline fingolimod hydrochloride of formula (1a),



(1a)

comprising a sequence of steps of

a] contacting a solution of fingolimod hydrochloride in a solvent with an antisolvent at a temperature of at least 50°C,

b] cooling the obtained solution to a temperature of below 40°C, whereby crystalline fingolimod hydrochloride precipitates, and

c] isolating crystalline fingolimod hydrochloride from the mixture.

2. The process according to claim 1, wherein the solvent is C_1-C_6 aliphatic alcohol.

3. The process according to claims 1-2, wherein the solvent is selected from the group comprising methanol, ethanol, n-propanol, isopropanol, and/or n-butanol, and mixtures thereof with water.

4. The process according to claims 1-3, wherein the concentration of fingolimod hydrochloride in the solvent is higher than 2.5 g/100 ml, preferably higher than 10 g/100 ml.

5. The process according to claims 1-4, wherein the antisolvent is a C_5-C_{10} aliphatic, cyclic or aromatic hydrocarbon, preferably n-hexane, n-heptane, cyclohexane, benzene, toluene, or C_4-C_{10} aliphatic ether, preferably diethyl ether or di-isopropyl ether.

6. The process according to claims 1-5, wherein the temperature of the antisolvent before and during contacting it with the solvent is at least 40°C.

7. The process according to claims 1-6, wherein the ratio between the solvent and antisolvent is from about 1:2 to 1:20 (v/v), preferably from about 1:4 to 1:10 (v/v).

8. The process according to claims 1-7, wherein the formed suspension in the solvent/antisolvent mixture is stirred after completing the precipitation process for 30 minutes to 2 hours and , preferably, at ambient or lower than ambient temperature.

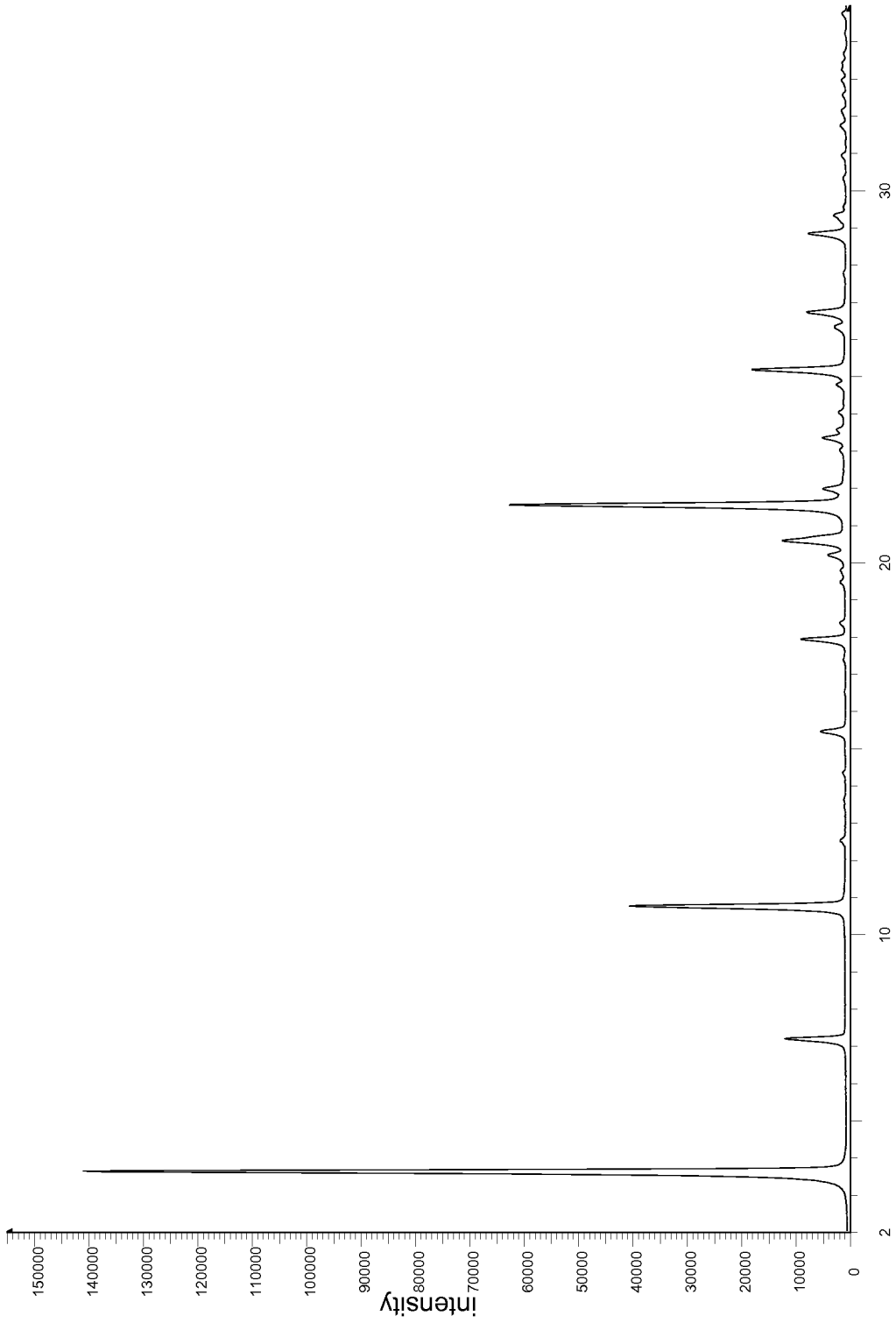


FIGURE 1: XRPD SPECTRUM OF FINGOLIMOD HYDROCHLORIDE FORM I

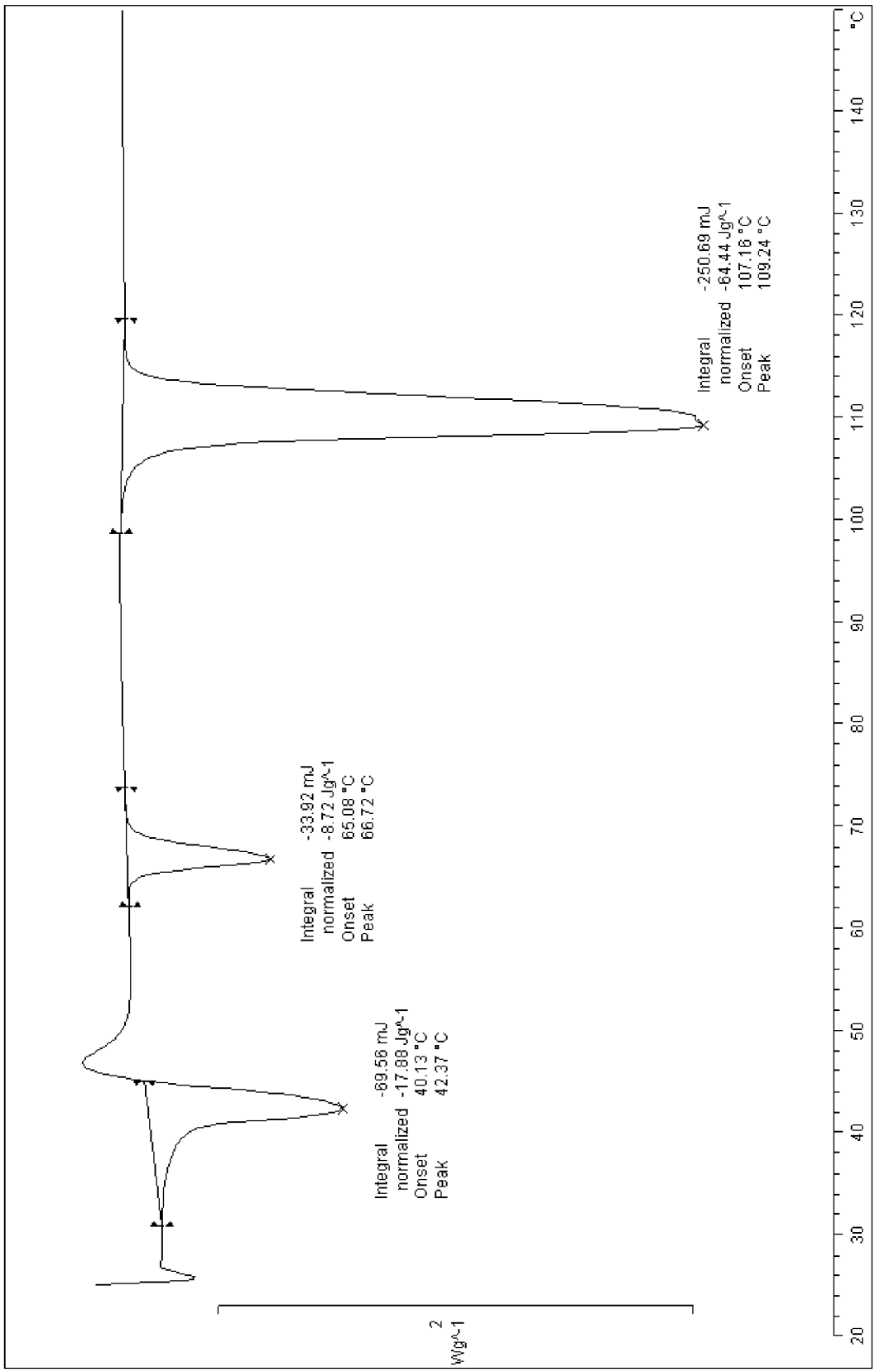


FIGURE 2: DSC SCAN OF FINGOLIMOD HYDROCHLORIDE FORM I RECORDED WITH 10°C/MIN

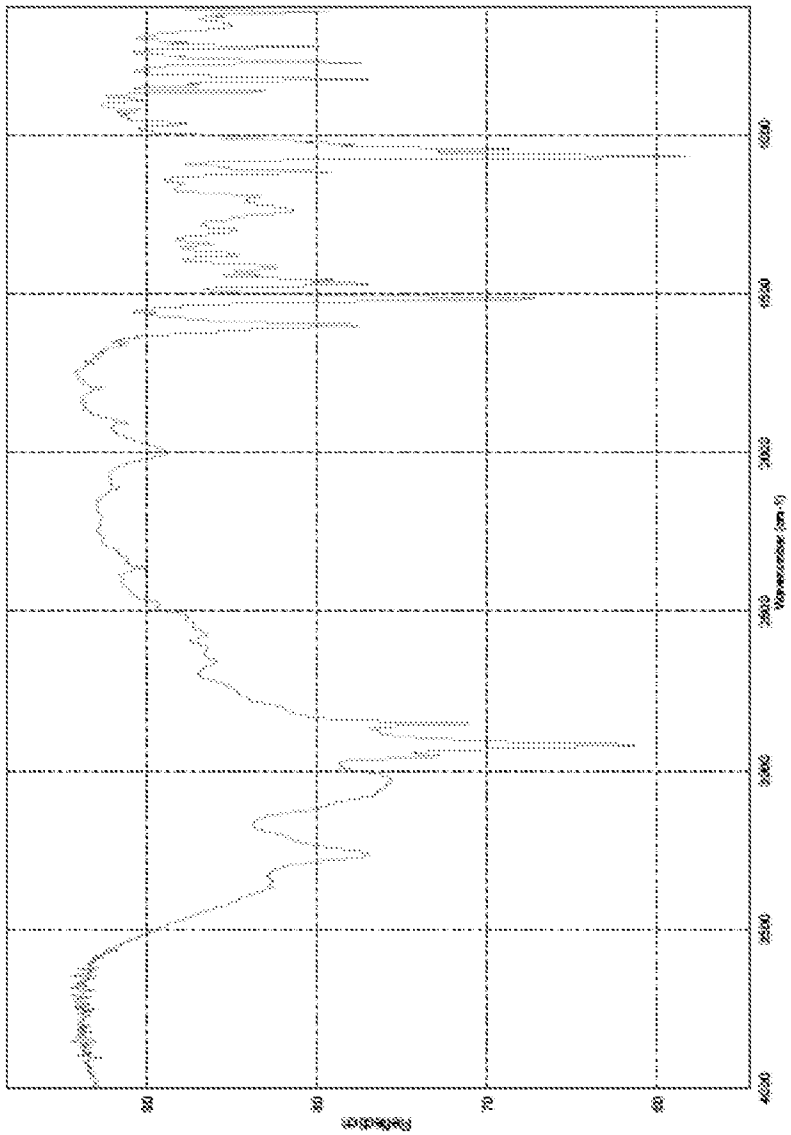


FIGURE 3: IR SPECTRUM OF FINGOLIMOD HYDROCHLORIDE FORM I

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/070780

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C213/10 C07C215/28
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)
C07C

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/055028 A2 (NOVARTIS AG [CH]; MUTZ MICHAEL [CH]; JORDINE GUIDO [CH]) 20 May 2010 (2010-05-20) cited in the application page 1, paragraph 3 -----	1-8
Y	WO 00/27798 A1 (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; TAITO CO [JP]; YO) 18 May 2000 (2000-05-18) cited in the application page 12; example 5 -----	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2011	14/10/2011

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/070780

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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