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Patent Department

Date
18 April 2008

Your reference

Your letter dated

Our reference

Our letter dated

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Patent Application No. 05 770 026.2 - 2103
Our reference: GRA 3111-EP / ST-PN / RS-KN

Reply to the communication according Article 96(2) EPC

In reply to the communication according Article 96(2) EPC an amended claim set is provided on a separate sheet. We are confident that the examiner's objections with respect to the formal issues 1.1, 1.2, 1.3. and 2 of the office action have been overcome by the amendments. Regarding the formal objections 1.1, we would like to emphasis that claim 2, 3 and 4 are dependent claims of claim 1 and that is stated in the description on page 2, line 19-25, that crystalline form A is best and sufficient described by the parameters recited in claim 1.

Regarding 3:
The subject matter of the present claims are regarded as being novel by the examination division.

Regarding 4:
The applicant provides with the enclosed "experiment 1" data that the novel crystalline form A is inventive over the prior art: The crystalline form B disclosed in D1 has the disadvantage that under the influence of pressure (which occurs e.g. in the manufacturing process for the drug tablet) polymorph B (crystalline form of D1) is transformed in a mixture of the crystalline forms A and B.

The underlined problems can be defined in view of D1 to find a crystalline form which can be used in a manufacturing process of drug tablets. Surprisingly and shown by the data enclosed in Table 1 the crystalline form A claimed in the pending application shows stability regarding high pressure. There can be no mixture of polymorphs A and B detected up to the limit of quantification (LOQ) with the starting material B. The experiment shows clear evidence for a change in the

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modification of all form B batches exposed to pressure of 2 tons within only 60 seconds. All form A batches remain unchanged.

In the case the amended claim set enclosed are considered to be not allowable by the examination division, a further official communication or, as an auxiliary request, oral proceedings are requested before any decision is taken other than the grant of the patent.

Furthermore the applicant asks to postpone the amendments of the description until the examination division agreed on the amended claim set.

Yours sincerely,
Grünenthal GmbH

ppa. Dr. Hellfeldt

i. V. Dr. Stowasser

Enclosures:

- Table 1 with experimental data
- amended claim set
- self-addressed envelope (by mail only)

Table 1 (Experiment)

There is clear evidence for a change in the modification of all form B batches exposed to a pressure of 2 tons within 60 seconds. All form A batches remain unchanged.

1 Method Description

1.1 Instruments and Material:

Analytics:

- STOE STADI P X-ray powder diffractometer system; transmission geometry, Cu-Kα_1 radiation at 50 kV and 30 mA, Ge (111) monochromator, position sensitive detector; omega-2-theta scan type, time/step 300s, preparation as flat sample, WinXpow software package.
- Balance for analytical quantification: Mettler Toledo MX5, Inv. Nr. 28523.00

Pressure Experiments:

- Intrinsic dissolution preparation devices according to Ph. Eur. 2.9.29 [1], purchased by Sotax AG, Basel, Switzerland
- Press: SPECAC, max. 5 tons.
- Balance for pressing experiments: Mettler Toledo AX205.

1.2 Experimental

Approx. 50 mg of the sample material was weighed accurately into the intrinsic dissolution preparation device for the pressing experiment [1]. A pressure of 2 tons was applied to the sample material for 60 seconds. The bottom plate of the intrinsic dissolution preparation device was removed. The pressed sample was carefully taken out of the pressing cylinder where it formed a compacted pellet. The sample was placed on the sample holder of the X-ray diffractometer and measured according to the above described method.

2 Results

Three batches of each of the two polymorphs were tested following the described experimental method and analysed accordingly. The batches were selected to cover a broad variety of batch types.

Table 2-1: Results of the Pressure experiments

No.	Batch	Material amount for polymorph ratio determination [mg]	Pressure/ time	Initial Polymorph	Polymorph ratio after pressure A : B
1	A	25,2	2 t/ 60 sec	B	70 : 30
2	B	24,7	2 t/ 60 sec	B	5 : 95
3	C	24,5	2 t/ 60 sec	B	96 : 4
4	D	25,5	2 t/ 60 sec	A	Form A only
5	E	24,8	2 t/ 60 sec	A	Form A only
6	F	25,5	2 t/ 60 sec	A	Form A only

The results clearly show the instability of form B during an exposure of pressure. After only 60 seconds a significant part of form B already changed its modification to form A. Ratios vary from 4 to 95% of form A in the originally form B batches.

All polymorph A batches however remain unchanged.

3 References

[1] European Pharmacopeia, Version 6.0, Chapter 2.09.29, Intrinsic Dissolution

amended claim set, 21.2.08
GRA 3111, EP 05770026.2 -2103

Claims

1. Crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride showing at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K_α radiation at 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2, 29.3±0.2 and 30.4±0.2.

2. Crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim 1 showing in addition at least X-ray lines (2-theta values) in a powder diffraction when measured using Cu K_α radiation at 14.5± 0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 25.5±0.2.

~~3. Crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim 1 showing a X-ray pattern (2-theta values) in a powder diffraction when measured using Cu K_α radiation essentially as in Fig. 1~~

3. Crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to claim 1 characterized in that the elemental cells has a monoclinic form.

4. Process for production of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A by dissolving the (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B in acetone, acetonitrile or isopropanol, leaving the solution to crystallize and isolating the crystals of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A.

according claim 1-3

5. Process for production of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A according to claim 4. characterized in that during the process the temperature is kept below + 40°C, preferably below + 25°C.

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