IN THE MATTER OF
The Patents Act, 1970 as amended by
Patents (Amendment) Act, 2005

AND

IN THE MATTER OF
The Patent Rules, 2003 as amended by
Patents (Amendment) Rules, 2005

AND

IN THE MATTER OF
An Application for the grant of a Patent
On Application No. 3176/KOLNP/07
Dated 29.8.2007 filed in the name of
MITSUBISHI TANABE PHARMA
CORPORATION, A Japanese Company of 2-
10, Dosho-machi, 3-chome,Chuo-ku, Osaka-
Shi, Osaka 541 8505, Japan

...Applicant

AND

IN THE MATTER OF
A Pre-grant Opposition to the grant of a
Patent on said Application under Section
25(1) of said Act filed by LUPIN LIMITED
Of 159 C.S.T. Road, Kalina, Santacruz
(East), Mumbai 400 098, Maharashtra, India

.... Opponent

REPLY STATEMENT

Referring to paragraphs 1 and 2, the contents have been noted.

Referring to paragraph 3, the Opponents have just reproduced certain Grounds of Opposition.

Referring to paragraphs 4.1 to 4.3, the Opponents have just mentioned certain points of the present invention in accordance to their own analysis.

Referring to paragraph 4.4, Opponents have just reproduced claims 1 to 33 of the present Patent application as originally filed. However, now to meet the requirements of the objections raised in the First Office Action, the entire set of claims has been duly amended. The amended set of claims is reproduced herein below :

1. 3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine 2.5 hydrobromide, or a hydrate thereof.

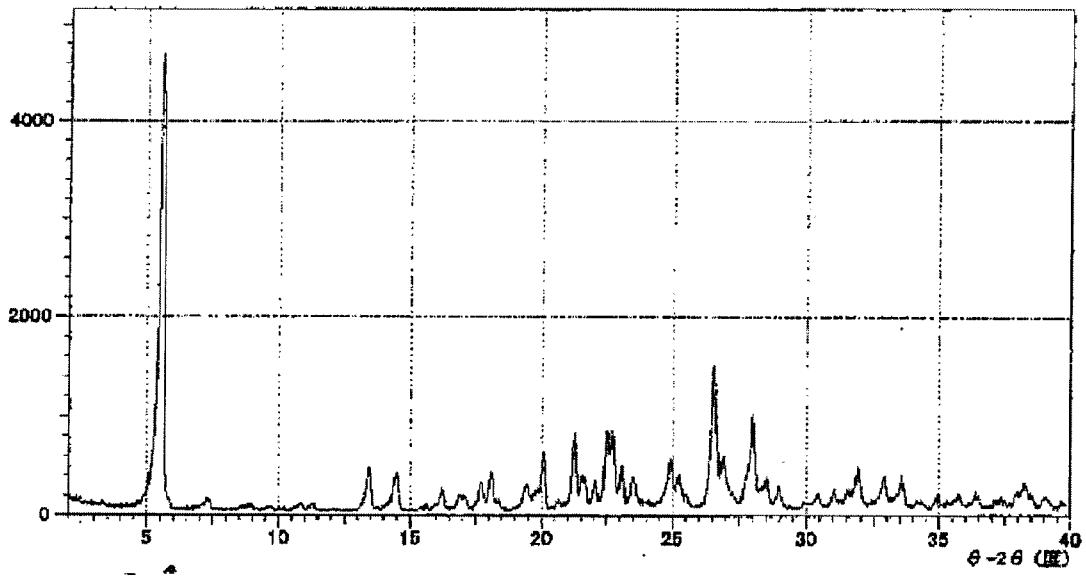
2. A crystal of 3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine 2.5 hydrobromide, or a hydrate.

3. The crystal of 3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine 2.5 hydrobromide 1.0 to 2.0 hydrate.

4. The crystal as claimed in claim 3, which has peaks at diffraction angles represented by 2θ of 5.4°, 13.4° and 14.4° (each ± 0.2°) in a powder X-ray diffraction pattern.

5. The crystal as claimed in claim 3, which has peaks at diffraction angles represented by 2θ of 5.4°, 13.4°, 14.4°, 22.6° and 26.5° (each ± 0.2°) in a powder X-ray diffraction pattern.

6. The crystal as claimed in claim **3**, which shows a powder X-ray diffraction pattern as illustrated in Fig. 1□.



wherein the axis of abscissa shows diffraction angle (2θ) (each of ±0.2°).

7. A method of producing 3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine 2.5 hydrobromide or a hydrate thereof, which comprises eliminating 1,1-dimethylethyloxycarbonyl from 3-{(2S,4S)-1-(1,1-dimethylethyloxycarbonyl)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine with hydrobromic acid, and simultaneously forming a salt.

8. A method of producing 3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine 2.5 hydrobromide or a hydrate thereof, which comprises crystallizing 3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine 2.5 hydrobromide from water and/or a solvent selected from ethanol, 1-propanol, 2-propanol, ethyl acetate and acetone.

9. The method as claimed in claim 8, wherein water and/or a solvent selected from ethanol, 1-propanol, 2-propanol, ethyl acetate and acetone is ethanol and/or water.

10. A 1.0 to 2.0 hydrate of 3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl} thiazolidine 2.5 hydrobromide.

Referring to paragraph 5, Opponents have cited three documents against the present invention but unfortunately such citations do not constitute prior art and thus are not pertinent to any of the Grounds of Opposition relied upon by the Opponents.

Referring to paragraph 6.1, claim 1 has been deleted.

Referring to paragraph 6.2, claim 7 has been deleted.

Referring to paragraph 6.3, claim 10 has also been deleted. Thus, the ground of anticipation is not a valid ground anymore in view of the revised set of claims as mentioned hereinbefore.

Referring to paragraph 7.1,claim 1 has been deleted. Thus, the Opponents' contention is not valid anymore.

Referring to paragraph 7.2. claims 1 to 13, 20 to 26 and 29-31 have been deleted and in view of the revised claims, the Opponents allegation is no more pertinent.

Referring to paragraphs 7.3 to 7.12,claims 1 to 13, 20-26 and 29-31 have been deleted and thus the revised set of claims do not lack inventive step.

Referring to paragraphs 7.13 and 7.14, 7.17, 7.18 and 7.20 we submit that in general, even if HCl salt of a compound can be obtained, it does not mean that HBr salt can also be obtained in the same manner. In addition, even if a salt can be obtained, it is difficult to predict that the salt can be crystallized. Therefore, it is not easy even for those of ordinary skill in the art to predict the best salt by referring to the list of salts provided by FDA or the contents of D3.

The compound of Ex. 222 of D1 is described as a 3HCl salt and a white solid (not as a crystal). Since the compound of Ex. 222 of D1 is not in the form of a crystal, the present inventors have tried crystallization of 3HCl salt of compound I. However, a crystal could not be obtained stably (see the above-mentioned Experimental Report).

The opponent argues by referring to the similarity in many properties between HCl and HBr that the artisan will try to convert the HCl salt disclosed in D1 to an HBr salt with a reasonable expectation of success. However, when crystallization of HCl salt is difficult as in Ex. 222, it is more reasonable for those of ordinary skill in

the art to try to obtain a salt having different properties than those of HCl, based on the contents of D3. In other words, given the problem with HCl salt, HBr salt presumably having similar properties will not be selected with a reasonable expectation of success.

In addition, the compounds used in D3, and the compounds of D1 and D2 seem to have no common structures and physical properties. D3 does not describe or suggest that the characteristic of a salt of a certain compound is applicable to any other compound. Therefore, the assertion of the opponent that that the 2.5 HBr salt of the present invention, which is chemically stable and superior in solubility and hygroscopicity to HCl salt, is obvious from the descriptions of D1, D2 and D3 is a hindsight.

Therefore, claim 14 (new claim 1) is not obvious and has an inventive step, and claims 15-19 and 27-28 and 32-33 (new claims 2-10) are also not obvious and have an inventive step.

Referring to paragraphs 7.15 and 7.16, 7.19, claims 20-26 and 29-31 have been deleted. Thus, the allegation of the Opponents are not correct.

Referring to paragraph 8, the Opponent alleges that the present invention is known to the public and in this connection the applicant states that claims that had been objected to under the ground of anticipation has been deleted. Thus, the revised set of claims are completely novel and thus are neither published and nor are used prior to the date of filing the instant application.

Referring to the 9th item (9.1 to 9.9), the applicants submit that the disclosure made in the specification is more than sufficient for the person skilled in the art to understand the invention. Moreover, the claims pointed out by the Opponents Agent as being not supported by the description are not present in the revised set of claims. Thus, the revised set of claims are well supported by the description and claims 7, 8, 10-13 and 29-30 have been deleted.

Referring to the 10th item, the Opponents alleges that claims are not patentable and also not an invention and such an allegation is not meant for the revised set of claims. The revised claims are both novel and are also not lacking in inventive step.l In this connection, please refer to the arguments given hereinbefore under paragraph 7. Additionally, we have also enclosed an Experimental Report (Attachment) which establishes the following points : (A) That crystallization of the compound of Example 222 in WO 02/14271 (3 hydrochloride of compound I) is difficult.

(B) That the present compound (2.5 hydrobromide of compound I) can be crystallized with a given level of reproducibility.

(C) That the present compound is superior in hygroscopicity, chemical stability and crystallinity, in a comparative test with the compound of Example 222 of WO 02/14271.

In other words, the compound of Example 222 of WO 02/14271 cannot be obtained as stable crystals by a general recrystallization method, and production thereof to meet the same standards with reproducibility is difficult. In contrast, the present compound can be obtained with given reproducibility, and shows more superior hygroscopicity, chemical stability and crystallinity than does the compound of Example 222 of WO 02/14271. Such superior effects of the compound of the present application cannot be predicted from WO 02/14271 even by those having ordinary skill in the art.

Accordingly, the revised set of claims neither attracts the provisions of Section 2(1)(j) nor 3(d).

Referring to the 10th item, Applicants have filed the particulars of corresponding foreign particulars at the Patent office vide their letter dated 21st February, 2008 and an updated list of particulars have again been filed at the Patent Office at the time of filing a response to the Office Action. Thus, such a Ground of Opposition is not a relevant ground for the Opponents to rely upon.

The Applicants further pray that (i) none of the relief sought for by the Opponents be granted, (ii) that the representation made by the Opponents be dismissed, (iii) any other relief that the Ld. Controller may deem appropriate.

The Applicants pray that a patent may be granted on their application No.3176/KOLNP/07.

Yours faithfully,

S BANERJEE
OF L S DAVAR & CO
APPLICANTS' AGENT

SB;EP

Experimental Report

In the Experimental Report, 3-{(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine is to be referred to as compound I.

Experimental Example A: Consideration of crystallization of 3 hydrochloride of compound I

[Object of experiment]

Consideration of crystallization, from various solvents, of 3 hydrochloride of compound I obtained in amorphous form.

[Sample]

A white solid of 3 hydrochloride of compound I obtained by the method of Example 222 of D1 (EP-A-1308439).

[Test method]

The sample (about 10 mg) was measured in a microtube, and dissolved in various kinds of solvents A (50 - 100 μL) in the following Table A-1. To these solutions was added dropwise solvent B in the following Table A-1 until white turbidity was developed. In the solvent systems that developed white turbidity, the white turbidity was dissolved by heating and the systems were left open-standing at room temperature. The results are shown in the following Table A-1.

Table A-1. Consideration of crystallization solvent for 3 hydrochloride of compound I

solvent A	solvent B	white turbidity	after left open-standing at room temperature
ethanol	-	none	no precipitation
	ethyl acetate	none	no precipitation
	THF	none	no precipitation
water	acetone	none	no precipitation
	ethanol	none	no precipitation
2-propanol	-	yes/dissolved by heating	solid precipitate
	heptane	yes/dissolved by heating	solid precipitate
	ethanol	yes/dissolved by heating	solid precipitate
	THF	yes/dissolved by heating	solid precipitate

The sample (600 mg) was measured, and crystallization was tried using the solvent system that afforded solid precipitate in the above-mentioned test. The results are shown in the following Table A-2.

Table A-2. Crystallization test of 3 hydrochloride of compound I

solvent A	solvent B	white turbidity	after left open-standing at room temperature
2-propanol	heptane	yes/dissolved by heating	oil out
	ethyl acetate	yes/dissolved by heating	oil out
	THF	yes/dissolved by heating	oil out

[Discussion]

From the above-mentioned test results, it has been found that 3 hydrochloride of compound I cannot be obtained as crystals easily by a conventional method.

Experimental Example B: Recrystallization test of 2.5 hydrobromide of compound I using 1-propanol or 2-propanol

[Content of test]

Crystals of 2.5 hydrobromide of compound I obtained by the method described in Example 4 of the present specification (crystallization from ethanol) characteristically have peaks at diffraction angles represented by 2θ of 5.4°, 13.4°, 14.4°, 22.6° and 26.5° (each ±0.2°) in a powder X-ray diffraction pattern (Example 4 of the present specification). In this test, the crystals were subjected to a recrystallization test from 1-propanol or 2-propanol, and the obtained solid was subjected to powder X-ray diffraction measurement, based on which whether the crystals are the same as those obtained by crystallization from ethanol was determined.

[Sample]

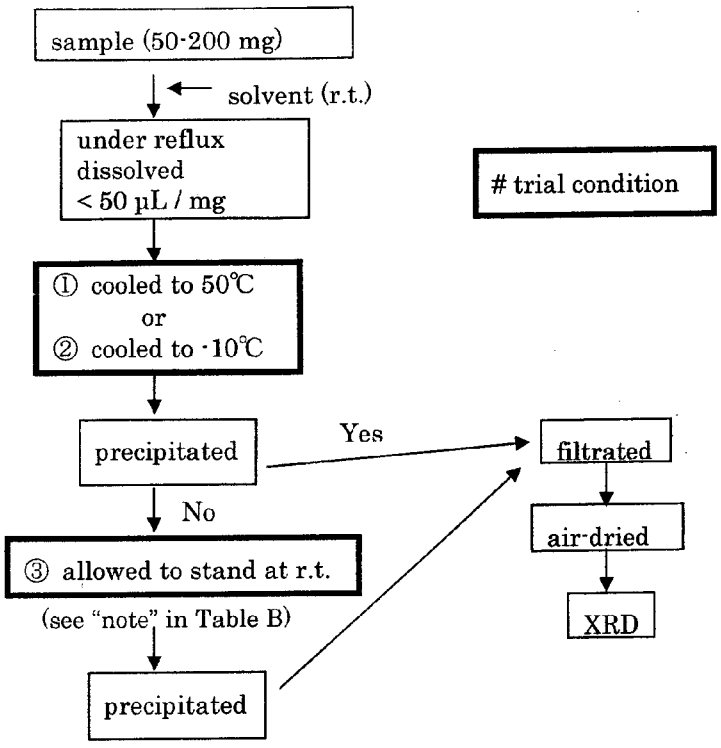
Crystals of 2.5 hydrobromide of compound I prepared by the method described in Example 4 of the present specification

[Test method]

(1) Recrystallization test

The sample was dissolved in 1-propanol or 2-propanol, a supersaturated solution was prepared by a heating/cooling method, and a recrystallization test of 2.5 hydrobromide of compound I was performed. Fig. B shows an operation flow chart of the heating/cooling method.

Fig. B.
operation flow chart of heating/cooling method using solvent



The sample (50-200 mg) was measured in a 10 mL test tube and a Dimroth condenser was set. Stirring with a stir bar, the mixture was refluxed while adding a solvent in an amount of not more than 50-fold volume (μL/mg) relative to the weight of the measured sample. Crystals were dissolved in the solvent, and the mixture was gradually cooled to 50°C (trial condition ①) or rapidly cooled to -10°C (trial condition ②). In the absence of crystal precipitation, the mixture was further left standing at room temperature (trial condition ③). The resultant precipitate was collected by filtration and air dried at room temperature for one day. The obtained solid was subjected to a powder X-ray diffraction measurement. The purity of the obtained solid was measured by HPLC system [Shimadzu; column oven: CTO-10AS vp (40°C)].

(2) Powder X-ray diffraction measurement of obtained solid

[Measurement conditions]

apparatus: RINT2200/Ultima+
X-ray: Cu (Kα)/40 kV/40 mA
goniometer: Ultima+ Horizontal Goniometer Type I
attachment: sample medium low temperature attachment
filter: none
counter monochromator: full automatic monochromator
divergence slit: 1 deg/scattering slit: 1 deg/receiving slit: 0.15 mm
scanning mode: continuous
scanning speed: 4°/min
scanning step: 0.02°
scanning axis: 2θ/θ
scanning range: 3-40°

[Results]

The results are shown in the following Table B.

Table B. Data of obtained solid

solvent	v/w (μL/mg)	trial condition[1]	yield (%)	XRD 2θ(±0.2°)[2] 5.4°	13.4°	14.4°	22.6°	26.5°	purity (%)	note
2-propanol	40	①	63	○	○	○	○	○	99	-
	40	②	69	○	○	○	○	○	99	-
1-propanol	4	①	90	○	○	○	○	○	-	-
	3.5	②→③	68	○	○	○	○	○	-	allowed to stand for 2 h

[1] trial condition shown in Fig B

[2] ○ shows presence of peak

[Discussion]

From the above-mentioned results, it has been found that the solid obtained by crystallization from 1-propanol or 2-propanol has peaks at diffraction angles represented by 2θ of 5.4°, 13.4°, 14.4°, 22.6° and 26.5° (each ±0.2°) in a powder X-ray diffraction pattern. Hence, the crystals obtained by crystallization from 1-propanol or 2-propanol are the same as those obtained by crystallization from ethanol.

Experimental Example C

[Object of experiment]

Comparison of the properties of the compound prepared according to the method described in Example 3 or 4 of the present specification (hereinafter to be referred to as compound A) and the compound of Example 222 of D1 (EP-A-1308439) (hereinafter to be referred to as compound B).

Experimental Example C-1: Measurement of powder X-ray diffraction

Using RINT2200/Ultima+ (RIGAKU), the powder X-ray diffraction of compound B was measured under the following measurement conditions. The sample was gently pulverized to give a powder, molded by filling in a small filling unit of a flat sample holder (Si non-reflective sample holder No.9292A1, RIGAKU) to give a measurement sample.

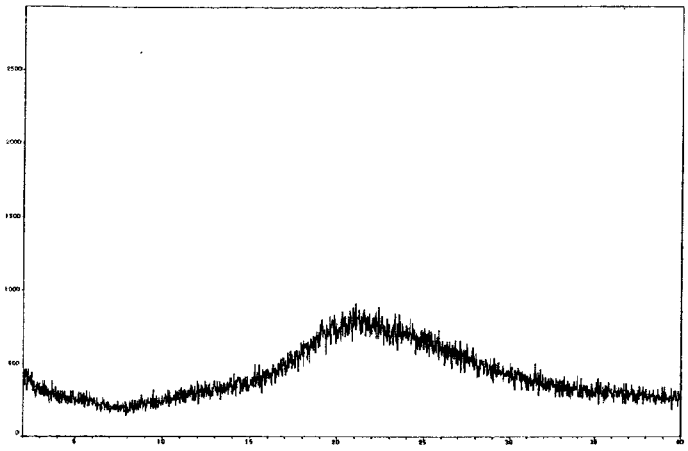
[Measurement conditions]
X-ray tube: Cu (Kα)
tube current: 40 mA
tube voltage: 40 kV
operating rate: 4°/min or 1°/min
Operating range: 2θ = 2-40°

[Results]

The powder X-ray diffraction measurement results of compound B are shown in Figure C-1.

It was found that Figure C-1 did not show a clear peak and compound B was amorphous.

Fig. C-1: XRPD pattern of compound B



Compound A is known to show good crystallinity (see Experimental Example 1 and Figure 1 of the present specification).

Experimental Example C-2: Measurement of hygroscopicity

Using a water adsorption testing apparatus (DVS-1 (SMS)) and thermohygrostat (PLATINOUS RAINBOW PR-2G, TABAI ESPEC Corp.), the hygroscopicity of compound B was measured under the following measurement conditions. Compound B (3-10 mg) was analyzed by DVS-1 at 25°C (in thermohygrostat). The program (DPP4 9.SAO) used for the measurement is shown in the following Table C-1.

Table C-1. Measurement conditions of dynamic water adsorption

Stage	Start RH(%	Stop RH(%	Sine RH(%	Freq(cyc..	DMDT	TIME(min)
1	50	0	1			120
2	0	0	1			600
3	10	0	1		0.002	
4	20	0	1		0.002	
5	30	0	1		0.002	
6	40	0	1		0.002	
7	50	0	1		0.002	
8	60	0	1		0.002	
9	70	0	1		0.002	
10	80	0	1		0.002	
11	90	0	1		0.002	
12	95	0	1			300
13	90	0	1		0.002	
14	80	0	1		0.002	
15	70	0	1		0.002	
16	60	0	1		0.002	
17	50	0	1		0.002	
18	40	0	1		0.002	
19	30	0	1		0.002	
20	20	0	1		0.002	
21	10	0	1		0.002	
22	0	0	1		0.002	
23	10	0	1		0.002	
24	20	0	1		0.002	
25	30	0	1		0.002	
26	40	0	1		0.002	
27	50	0	1		0.002	

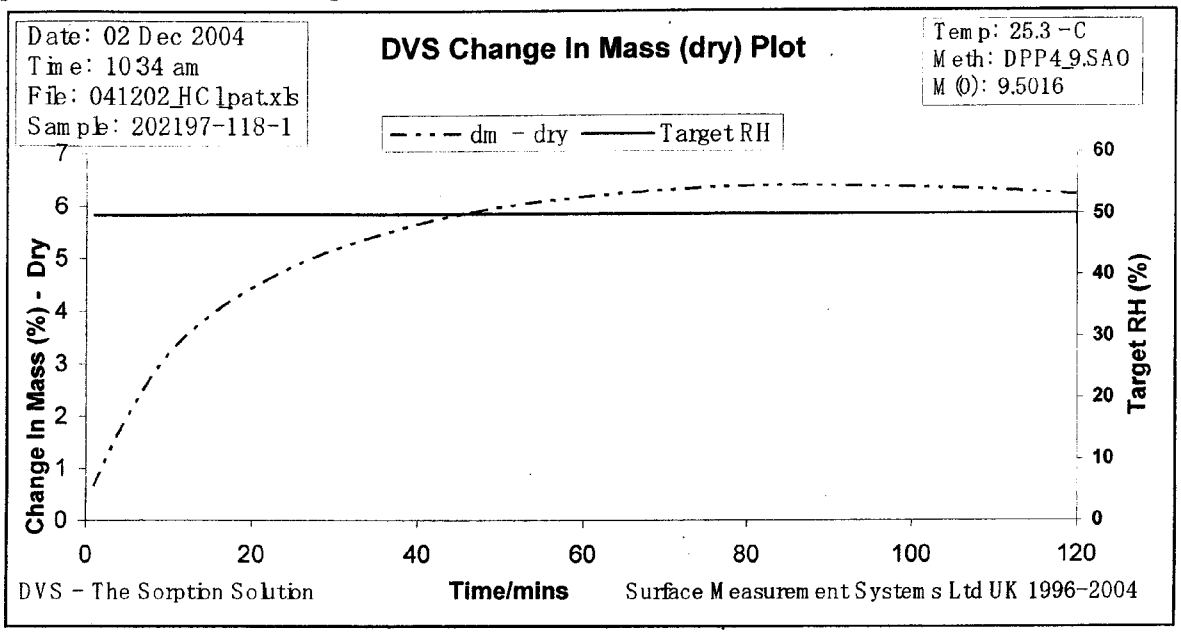
Mode: Half Cycle
DMDT Window (min.): 5
DMDT Min. Time (min.): 10
DMDT Max. Time (min.): 360
Total Flow(mL/min) = 200.000000

[Results]

The hygroscopicity measurement results of compound B are shown in Figure C-2.

Since compound B deliquesced within 2 hrs at 50%RH of measurement starting condition, the measurement was stopped.

Fig. C-2: Water adsorption of compound B



Compound A was known to show about 2% of hygroscopicity when measured at relative humidity of 5% to 90% at 25°C (see Experimental Example 2 and Figure 5 of the present specification).

Experimental Example C-3: Measurement of chemical stability

The pharmaceutical ingredients of compound B and compound A (prepared according to the method described in Example 3 in the present specification) were preserved at 40°C, 75%RH for 3 weeks, and the chemical stability was evaluated according to a related substances method.

Related substances method:

A sample (10 mg) was measured and a mixture of water/acetonitrile (1:1) was added to 10 mL, which was used as a sample solution. The test solution (10 µL) was subjected to a liquid chromatograph method (apparatus used: LC-solution high-performance liquid chromatography system, Shimadzu Corporation) under the following conditions, each peak area A_T and total peak area ΣA_T were measured, and each peak area (%) was calculated.

[Operating conditions]
detector: photodiode array (measurement wavelength 244 nm)
column: Inertsil ODS-3V 4.6 mmID×150 mm
column temperature: constant temperature around 40°C
mobile phase: solution A; 0.1 % TFA solution
solution B; 0.1% TFA acetonitrile solution
concentration gradient: B% 5→100% (60 min)
flow rate: 1.0 mL/min

[Results]

The chemical stability measurement results are shown in the following Table C-2.

Table C-2. Increase (%) of decomposed material under storage conditions

Compound B		Compound A	
Initial	40°C, 75% RH, 3 weeks	Initial	40°C, 75% RH, 1 month
3.34	13.81	0.22	0.22
	(10.47)		(0.00)

( ) shows increase or decrease (%) of decomposed material based on Initial.

Compound B showed an increase of 10.47% in the impurity after preservation at 40°C and 75% RH for 3 weeks. The sample was deliquesced under the storage conditions and became a red-colored solution.

Compound A did not show an increase in impurity even after preservation at 40°C and 75% RH for 1 month.

[Discussion]

From these results, the superiority of compound A to compound B was confirmed in hygroscopicity, chemical stability and crystallinity.