Improved Synthesis of Paroxetine Hydrochloride Propan-2-ol Solvate through One of Metabolites in Humans, and Characterization of the Solvate Crystals

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Paroxetine, a potent and selective inhibitor of 5-hydroxytryptamine (serotonin) uptake, was prepared through a piperidine derivative, which was reported to be one of the paroxetine metabolites in humans.

Thus, the piperidine derivative was converted to its *N*-*tert*-butoxycarbonyl (*N*-Boc) derivative, which was then converted to *N*-Boc paroxetine. Paroxetine hydrochloride propan-2-ol (isopropyl alcohol (IPA)) solvate crystals were directly obtained from the *N*-Boc paroxetine by adding hydrogen chloride to the *N*-Boc paroxetine IPA solution. The amount of IPA content in the crystals was reduced by drying with a continuous change of powder X-ray diffraction patterns. Other characterizations of the solvate crystals were also conducted.

Key words paroxetine; paroxetine hydrochloride

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (serotonin) uptake, with a reduced propensity to cause the side-effects usually associated with a tricyclic antidepressant.[1)] The metabolic pathway of paroxetine in animals and man was studied using [^{14}C]-labeled paroxetine and one of the metabolites was revealed to be (3*S*,4*R*)-*trans*-4-(4-fluorophenyl)-3-hydroxymethylpiperidine (**6**),[2)] which seems to be an attractive intermediate for the preparation of paroxetine.

Conventionally, a paroxetine base has been synthesized in several steps, including deprotection of the *N*-alkyl group,[3)] whereas recently published journals and a patent report the preparation of enantiomeric paroxetine and paroxetine through an enantiomer of compound **6**[4a)] and compound **6** itself,[4b,c)] respectively. Paroxetine has been used as an active ingredient in anti-depressant drugs in the form of paroxetine hydrochloride (paroxetine HCl) crystals.[3b)] Paroxetine HCl was reported to exist in two solid state forms, hemihydrate (form-I) and anhydrate containing bound propan-2-ol (isopropyl alcohol (IPA)) (form-II).[5)] The report also describes the following: Form-I is thermodynamically more stable and form-II converts to form-I, if seed crystals of form-I are present, when exposed to humid conditions. There is a higher solubility for form-II at all temperatures, and the effect that such solubility differences between crystal forms have on absorption is therefore relevent.[5)] This description implies that form-II is pharmaceutically the more desirable ingredient if form-II can be steadily produced.

Recently, two independent crystal forms (form-I, form-II) of paroxetine HCl were analyzed by X-ray. The form-II crystal was reported to contain IPA molecules in the channel formed by paroxeine molecules and chloride anions, and was reported to be easily decomposed in open air at room temperature because the IPA molecules are easily released through the channels.[6)]

In this paper, first, we wish to report the convenient synthesis of *N*-*tert*-butoxy (*N*-Boc) paroxetine (**9**) through compound **6** and the direct conversion of compound **9** to paroxetine HCl crystals incorporating IPA (form-II).[4b)] Next, we wish to report the particular physical properties of form-II on drying, which are exemplified by a continuous change in analytical data such as IR spectroscopy, thermal analysis profile and powder X-ray diffraction (XRD) patterns. Other physical properties of IPA solvate crystals are also reported.

Preparation of One of the Paroxetine Metabolites (6) Methyl *p*-fluorocinnamate (**1**) was prepared from *p*-fluorobenzaldehyde and methyl acetate (MeOAc) in the presence of sodium methoxide (NaOMe). Methyl cyanoacetate was successively added to the reaction mixture to afford dimethyl 2-cyano-3-(4-fluorophenyl)glutarate (**2**) in 79% yield from *p*-fluorobenzaldehyde. Compound **2** was hydrogenated using Raney-cobalt to give (±)-*cis*,*trans*-4-(4-fluorophenyl)-5-methoxycarbonylpiperidin-2-one (**3**) as a mixture of crystals in 90% yield, which was then treated with sodium methoxide to give (±)-*trans* isomer (**4**) crystals. The defluorinated analog of compound **3** is a known compound.[7)] The crystals (**4**) were reduced with lithium aluminum hydride to give (3*SR*,4*RS*)-*trans*-4-(4-fluorophenyl)-3-hydroxymethylpiperidine (**5**) in 83% yield from compound **3**.[3d-i)] The racemic amino alcohol (**5**) was optically resolved using L-*o*-chlorotartranilic acid[8)] to give salt crystals of (3*S*,4*R*)-*trans*-4-(4-fluorophenyl)-3-hydroxymethylpiperidine (**6**). The optically active amino alcohol (**6**), a paroxetine metabolite, was obtained by decomposition of the salt.

Preparation of Paroxetine HCl IPA Solvate Crystals The *N*-Boc derivative (**7**) was obtained by adding aqueous sodium hydroxide to a mixture of the L-*o*-chlorotartranilic acid salt of the amino alcohol (**6**), $(Boc)_2O$, toluene and water. The alcohol moiety of the *N*-Boc derivative (**7**) was mesylated and reacted with sesamol to give *N*-Boc paroxetine (**9**). The *N*-Boc paroxetine (**9**) was dissolved in IPA, and hydrogen chloride was introduced to the solution. In this reaction, Boc deprotection and HCl salt formation were achieved and paroxetine HCl IPA solvate crystals were obtained.[4b)] The preparation pathway for proxetine HCl IPA solvate is shown in Chart 1.

Physical Properties of Paroxetine HCl IPA Solvate Crystals Two crystal forms of paroxetine HCl hemihydrate

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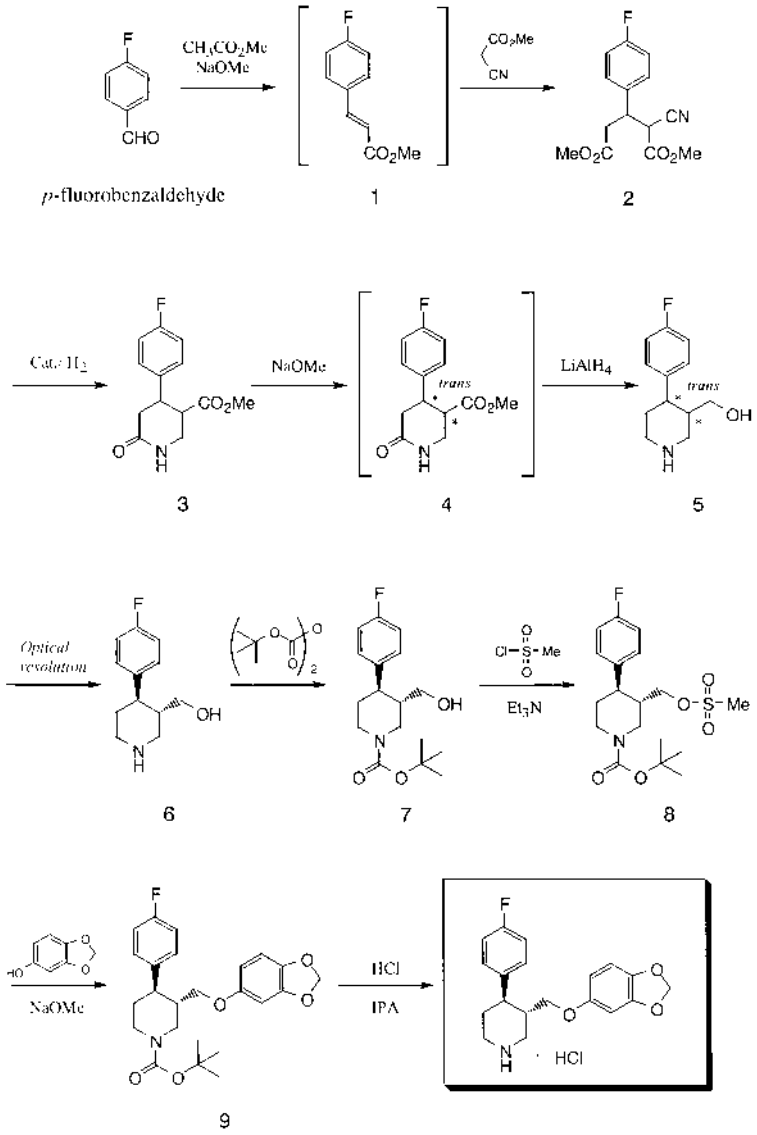

Chart 1. Synthesis of Paroxetine Hydrochloride Propan-2-ol Solvate

(form-I) and IPA solvate crystals (form-II) were reported to show distinct differences in IR spectra, in XRD patterns, in differential scanning calorimetry (DSC) curves and thermogravimetry (TG) experiments.[5] The form-II crystals used in the above experiments were reported to lose around 3% weight in TG analysis.[5] This means that the form-II crystals used in the experiments had approximately 3% of bound IPA in the crystals.

A patent published afterwards describes that paroxetine HCl IPA solvate crystals initially contain 13.0% of IPA, that the solvate crystals release IPA while being washed with water, and that the amount of IPA content in the crystals is measured to be 0.05% after subsequent drying, claiming that the IPA solvate crystals do not lose bound IPA up to this amount under conventional vacuum oven drying conditions.[9] These foregoing descriptions prompted us to ascertain the properties of paroxetine HCl IPA solvate crystals obtained by our improved preparation process.

Preparation of Form-II Crystals with Various IPA Contents and Their Behavior Related to Atmospheric Moisture: Figure 1 shows photographs of paroxetine HCl IPA solvate crystals (form-II) obtained by our improved preparation process, as well as conventional hemihydrate crystals (form-I). Form-II crystals are distinctly different from form-I crystals in shape. Form-II crystals initially contained around 14% weight of IPA, *i.e*. IPA molecules are incorporated into paroxetine HCl crystals in a 1-to-1 molar ratio, being consistent with the reported crystallographic analysis.[6]

Table 1 shows the relationship between drying conditions for these two forms of crystals, and the solvate (water, IPA) contents of the dried crystals. Figure 2 depicts the IPA releasing behavior of form-II crystals under various drying conditions. These data also show that these two crystal forms are different and that form-II crystals release IPA depending on the intensities of drying conditions. Figure 3 shows moisture absorption and desorption behavior of dried form-I and form-II crystals. Dried form-I crystals absorbed water rapidly up to around 2.5% weight, and the crystals with 2.5% water did not lose the water easily in a dry atmosphere; meanwhile, dried form-II crystals absorbed water slowly and the crystals with absorbed water released the water easily in a dry atmosphere. From these observations, we assumed that

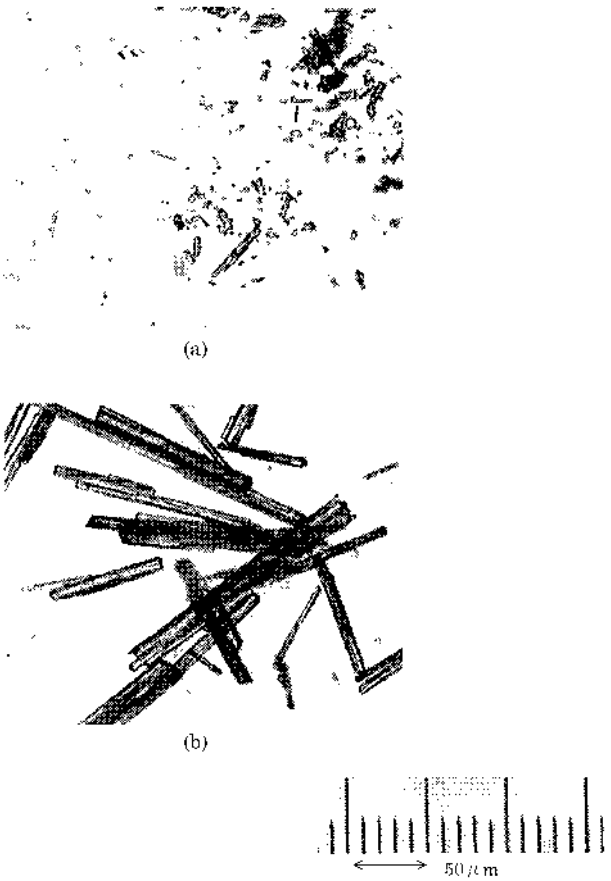

Fig. 1. Photographs of Paroxetine Hydrochroride

(a) Hemihydrate crystals (form-I), (b) IPA solvate crystals (form-II dried, IPA content 2—3%).

Table 1. Paroxetine HCl Solvates under Vacuum Drying Conditions

Sample	Solvate	
Form-I	H_2O	2.36%
Form-I-dry (Dry 100 °C, 12 h)	H_2O	0.25%
Form-II-1 (Dry 50 °C, 4 h)	IPA	13.75%
Form-II-2 (Dry 50 °C, 12 h)	IPA	9.17%
Form-II-3 (Dry 75 °C, 14 h)	IPA	5.79%
Form-II-4 (Dry 85 °C, 21 h)	IPA	2.82%
Form-II-5 (Dry 100 °C, 14 h)	IPA	0.48%

form-I crystals recaptured water as bound water in crystals but form-II crystals absorbed water not as bound water.

Thermal Analysis: Figure 4 and 5 show DSC and TG profiles of form-II crystals with various IPA contents, as well as those of form-I crystals, in open pans. Both form-I and dried form-I crystals showed similar DSC profiles, with the endothermic peak of dried form-I crystals being 1.5 °C below that of form-I crystals. DSC profiles of variously dried form-II crystals showed continuous changes in DSC patterns owing to a decrease in IPA content in the crystals, *i.e.* an endothermic peak at around 105 °C gradually diminished and a peak at around 125—131 °C emerged and finally form-II

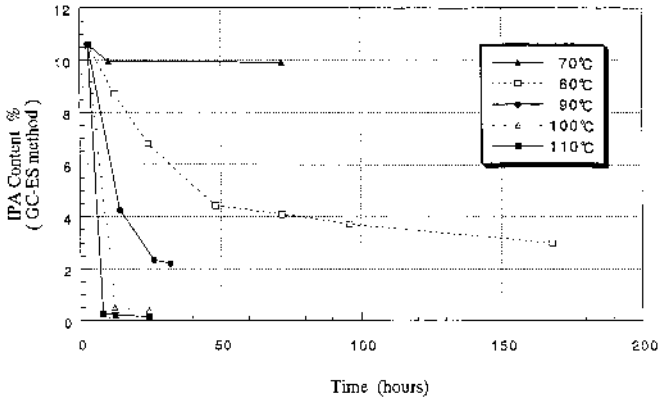

Fig. 2. IPA Releasing Behavior of Paroxetine HCl Form-II Crystals under Vacuum Drying Conditions

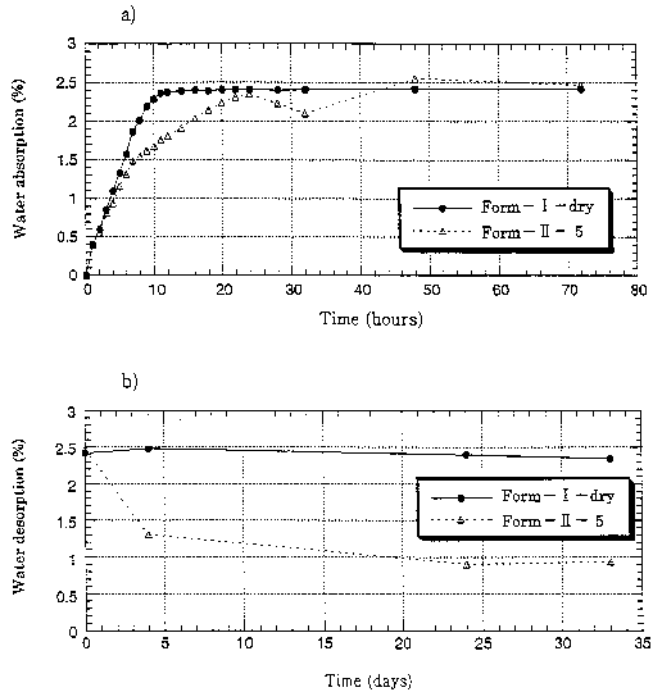

Fig. 3. Water Absorption and Desorption Curves of Dried Paroxetine HCl Solvates

a) Crystals were left open at ambient condition for 72 h. b) Then, crystals were replaced and dried for 24 d in a desiccator with silica gel in it.

crystals with 0.48% of IPA content showed almost a single peak at 131 °C. TG profiles showed that all form-II crystals lost weight between 50 °C and around 140 °C, indicating that the endothermic peaks at around 105 °C are due to the vaporization of IPA. These observation may be interpreted as follows: Form-II crystals with high IPA contents melt while losing IPA, but form-II crystals with low IPA contents only partly melt while losing IPA, and the remaining micro crystalline parts melt at a higher temperature of 125—131 °C.

IR Spectroscopy: Figure 6 shows OH IR absorption bands of variously dried form-II crystals as well as form-I crystals at between 4000 and 1800 cm^{-1}. Form-I crystals and dried ones showed almost the same IR patterns, and the IR patterns are consistent with that shown in the literature.[5] Meanwhile, form-II crystals showed a continuous change in IR absorption patterns with a decrease in IPA content. Form-II crystals

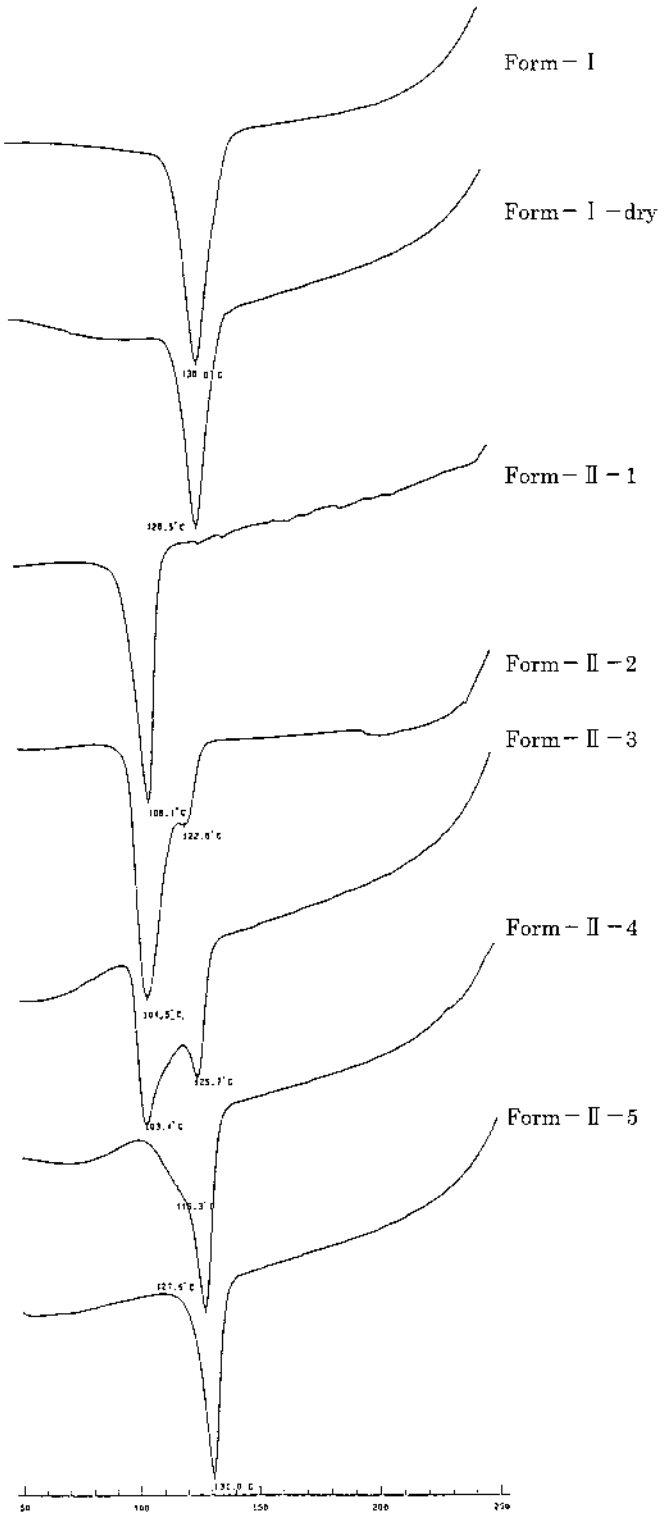

Fig. 4. Effect of Drying on DSC Curves of Paroxetine HCl Solvates

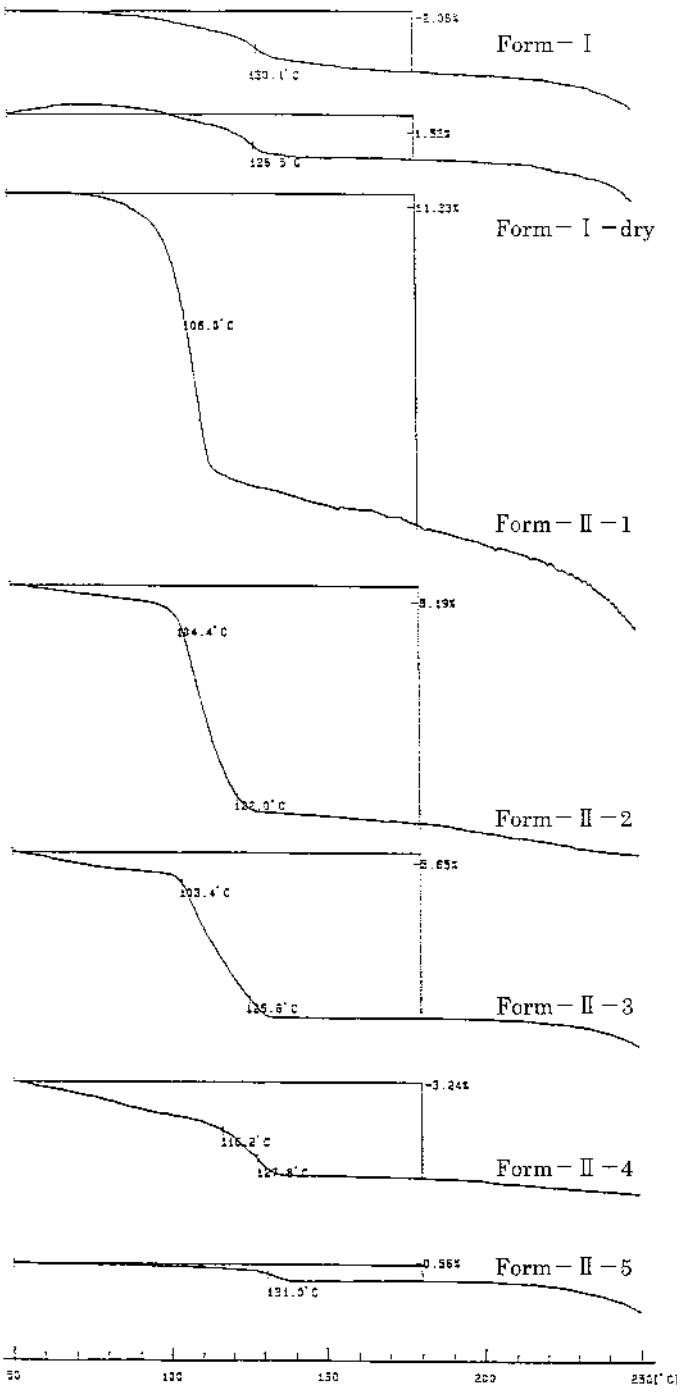

Fig. 5. Effect of Drying on TG Curves of Paroxetine HCl Solvates

with relatively high IPA contents showed relatively strong absorption at around 3400 cm^{-1} compared with an absorption band at around 3632 cm^{-1}, and an absorption intensity at around 3400 cm^{-1} gradually diminished. Finally, the form-II crystals with 0.48% of IPA content showed weak absorption at both 3400 cm^{-1} and 3632 cm^{-1}.

Powder XRD: Figure 7 shows XRD patterns of variously dried form-I and form-II crystals. Both form-I and anhydrous form-I crystals showed almost the same XRD patterns, and the XRD patterns of these form-I crystals were distinctly different from those of all variously dried form-II crystals. The XRD patterns of variously dried form-II crystals showed continuous changes with a decrease in IPA content in the crystals.

Form-II-1 crystals showed rather sharp XRD peaks which may suggest rather high crystallinity. Form-II-2, -3 and -4 crystals showed similar and rather vague XRD patterns. Form-II-5 crystals showed a rather sharp XRD pattern again. These phenomena may be interpreted as follows: Form-II-1 crystals containing IPA molecules in a 1-to-1 ratio have high crystallinity and the crystallinity is easily diminished with the release of IPA to give form-II-2, -3 and -4 crystals. From

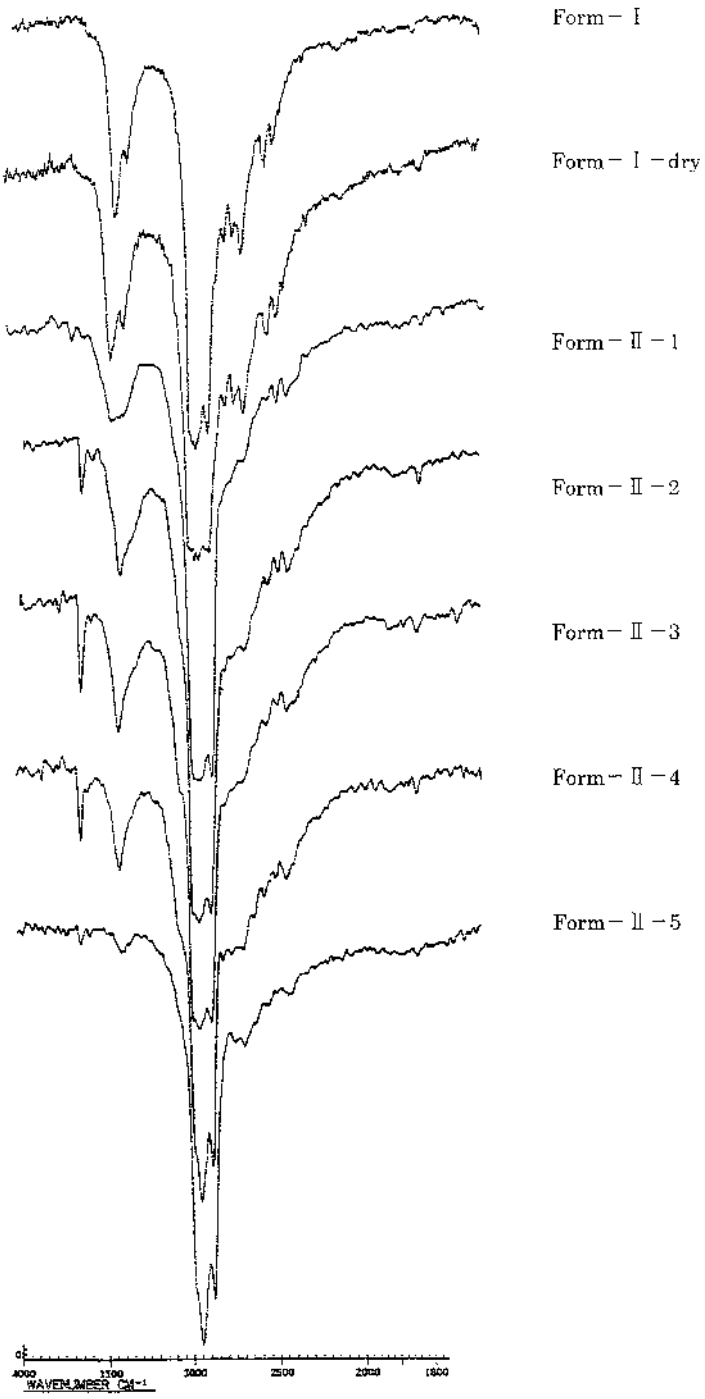

Fig. 6. Effect of Drying on IR Spectra of Paroxetine HCl Solvates

the similarity of all XRD patterns of variously dried form-II crystals, it is presumed that the original lattice of the form-II-1 crystals is not changed drastically by drying, but is partly closely packed together to make newly formed micro crystalline parts and these micro crystalline parts finally become dominant in form-II-5 crystals.

Resolvation and Re-desolvation of Dried Form-II Crystals with IPA: Table 2 shows the IPA contents of the crystals after resolvation and re-desolvation, as well as comparable IPA contents of dried form-II crystals as a reference. Figure 8 shows the XRD patterns of these crystals. These data showed that dried form-II crystals were resolvated with IPA up to about 14% of the weight of IPA content, and were re-desol-

Table 2. Resolvation and Re-desolvation of Dried Paroxetine HCl Form-I Crystals

Resolvated sample	Solvate	Reference dried form-II	Solvate
Form-II-7 (Dry r.t., 1 h)	IPA 14.0%	Form-II-1 (Dry 50 °C, 4 h)	IPA 13.8%
Form-II-8 (Dry 50 °C, 14 h)	IPA 4.37%	Form-II-3 (Dry 75 °C, 14 h)	IPA 5.79%
Form-II-9 (Dry 90 °C, 6 h)	IPA 1.83%	Form-II-4 (Dry 85 °C, 21 h)	IPA 2.82%

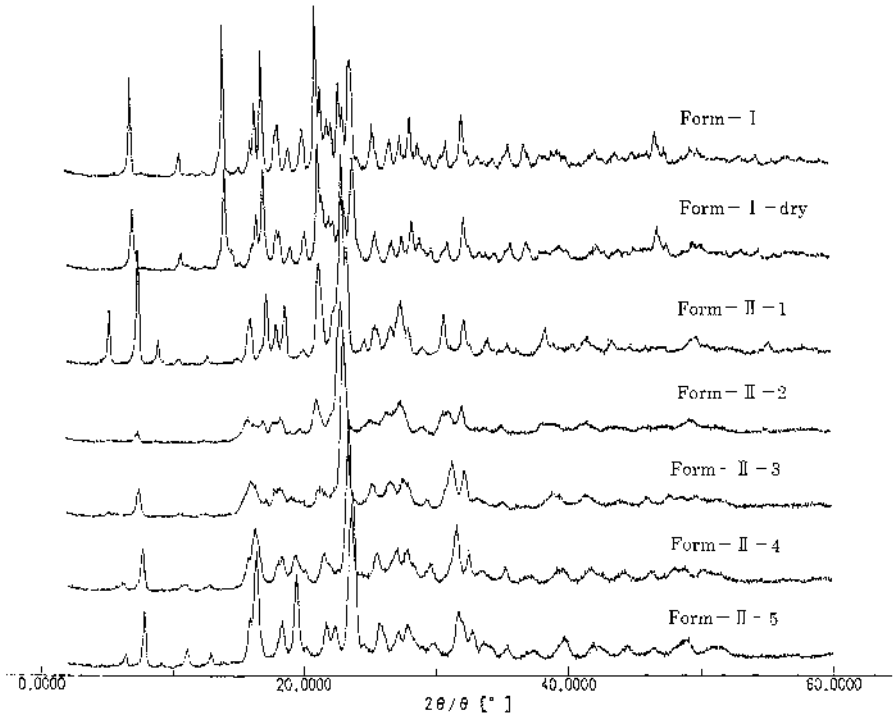

Fig. 7. Effect of Drying on XRD Patterns of Paroxetine HCl Solvates

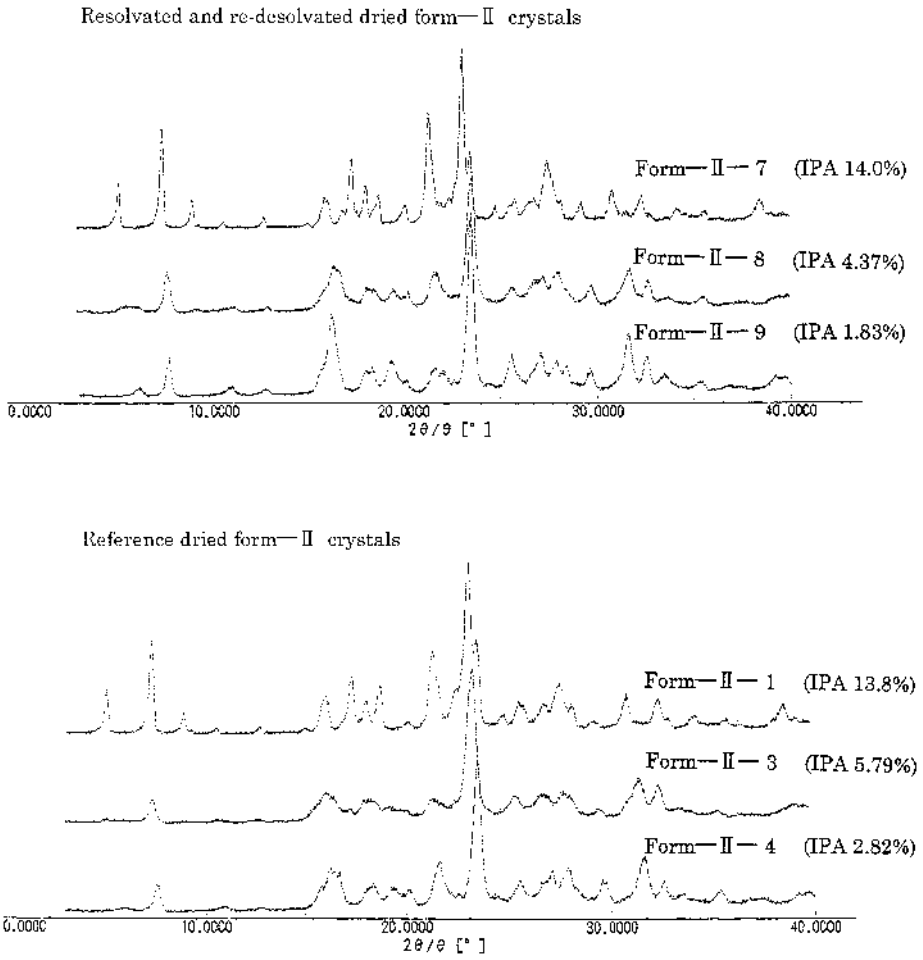

Fig. 8. Effect of Drying on XRD Patterns of Paroxetine HCl Solvates

vated again by drying. The XRD patterns of these crystals were almost the same as those of dried form-II crystals of comparable IPA content. These data show that form-II crystals can contain and release IPA reversibly.

Conclusion

An improved process for the preparation of paroxetine HCl IPA solvate crystals was developed. IPA in the solvate crystals was revealed to be loosely bound and was removed from the crystals by drying to give variously dried form-II crystals with a continuous change in IR spectroscopy, thermal analysis profile and XRD patterns.

Experimental

All melting and boiling points are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 1000 or on a Hitachi 270-30 IR Spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer, operating at 270 MHz. Chemical shifts were given in δ (ppm) values using tetramethylsilane as an internal standard. Differential scanning calorimeter and thermogravimetric analyzer were Shimadzu DSC-50 and Shimadzu TGA-50, respectively. The operating conditions were: sample weight about 5 mg, open pan, heating rate 10 °C per minute from 30 to 300 °C under nitrogen. Water contents were determined by a Karl-Fischer moisture meter, and IPA contents were determined by the GC method. For powder XRD, a Rigaku Denki Diffractometer (Min Flex) was used. The measurement condition was as follows: target, Cu; filter, Kβ filter; voltage, 30 kV; current, 15 mA; scanning speed, 2.00 degree/min.

Dimethyl 2-Cyano-3-(4-fluorophenyl)glutarate (2) To a mixture of MeOAc (222.2 g) and NaOMe (32.41 g) in toluene (240 ml) was added *p*-fluorobenzaldehyde (49.64 g, 0.40 mol) at 5—20 °C. After being stirred at 10—20 °C for 2 h, methyl cyanoacetate (47.56 g), 28% NaOMe (77.1 g) and MeOH (120 ml) were successively added to the mixture, and the mixture was warmed to 63—66 °C and kept at that temperature for 3 h. After being cooled to 10—20 °C, the reaction mixture was poured into diluted HCl and pH was adjusted to 8.6 and extracted with toluene. The organic layer was washed with water and evaporated *in vacuo* to remove remaining toluene. To the residue was added methanol (72 ml), and the solvent was evaporated *in vacuo*. To the residue was added methanol (560 ml) and water (240 ml) at 50—65 °C, and the mixture was kept at 40—45 °C for 30 min for crystallization, then gradually cooled to 0—5 °C. Crystals of **2** (88.04 g, yield 78.8% from *p*-fluorobenzaldehyde) were obtained by filtration and washed with 70% aqueous methanol and dried. The crude crystals were used in the subsequent reaction.

Analytical Sample: mp 81.0—83.8 °C. IR (KBr) cm^{-1}: 2523, 1740, 1605, 1513, 1446, 1341, 1264, 1225, 1177, 1161, 1107, 1062, 1015, 859, 711, 541. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (s, 0.33H), 2.80—3.07 (m, 2H), 3.61 (s, 1H), 3.67 (s, 2H), 3.68 (s, 2H), 3.74 (s, 1H), 3.80—3.94 (m, 1H), 4.21 (d, 0.67H, J=5.6 Hz), 7.00—7.07 (m, 2H), 7.27—7.33 (m, 2H).

(±)-*cis*,*trans*-4-(4-Fluorophenyl)-5-methoxycarbonylpiperidin-2-one (3) One liter autoclave was charged with toluene (100 ml), MeOH (25 ml), Raney-cobalt (2.1 ml) and H_2 (16—18 atm), then compound **2** (41.9 g, 0.15 mol) in a mixed solvent of toluene (100 ml) and MeOH (25 ml) was introduced to the autoclave at 90—100 °C and at 13—16 atm of H_2 over a period of 3 h. The reaction mixture was kept under a hydrogenating condition for an additional 1 h. The catalyst was removed by filtration and the solvent was partially distilled. The residue was gradually cooled and the crystals were obtained by filtration and washed with toluene to give a mixture of *cis* and *trans* isomers of 4-(4-fluorophenyl)-5-methoxycarbonylpiperidin-2-one (**3**) (33.8 g, yield 89.7%).

(±)-*trans*-4-(4-Fluorophenyl)-5-methoxycarbonylpiperidin-2-one (4) A mixture of compound **3** (25.13 g, 0.10 mol), 28% NaOMe (1.93 g) and toluene (126 ml) was warmed to 70—80 °C for 30 min, gradually cooled to 0—5 °C, and stirred for 1 h for crystallization and neutralized with HCl in MeOH. The solvent was partially distilled to remove MeOH. Crude crystals of compound **4** in toluene were used in the next reaction.

Analytical Sample: mp 151.0—151.9 °C. IR (KBr) cm^{-1}: 3185, 3052, 1732, 1675, 1604, 1514, 1504, 1443, 1376, 1320, 1222, 1210, 1182, 1172, 843. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (dd, 1H, J=10.6, 17.8 Hz), 2.72 (dd, 1H, J=5.9, 17.8 Hz), 2.97 (m, 1H), 3.41 (dt, 1H, J=5.9, 10.2 Hz), 3.47—3.66 (m, 2H), 3.50 (s, 3H), 6.85 (bs, 1H), 6.99—7.06 (m, 2H), 7.15—7.21 (m, 2H).

(3*SR*,4*RS*)-*trans*-4-(4-Fluorophenyl)-3-hydroxymethylpiperidine (5) Crude crystals of compound **4** in toluene (from 0.1 mol of **3**) were added to $LiAlH_4$ (7.02 g) in tetrahydrofuran (THF) (126 ml) and warmed to 73—75 °C for 2 h. To 12.8% NaOH (576.7 g) was added the reaction mixture at 25—35 °C and the organic layer was separated, then the lower layer was discarded. The organic layer was filtered to remove insoluble material. The solvent was partially distilled and the residue was gradually cooled to give crystals of compound **5** (17.4 g, yield 83.1%).

Analytical Sample: mp 124.8—125.9 °C. IR (KBr) cm^{-1} : 3276, 3245, 3118, 1602, 1508, 1218, 1159, 1129, 1070, 1046, 1027, 833. ^{1}H-NMR ($CDCl_3$) δ: 1.56—1.86 (m, 3H), 2.36—2.71 (m, 5H), 3.07—3.19 (m, 2H), 3.32—3.39 (m, 2H), 6.94—7.00 (m, 2H), 7.12—7.18 (m, 2H).

(3*S*,4*R*)-4-(4-Fluorophenyl)-3-hydroxymethylpiperidine (6) A mixture of compound **5** (20.0 g, 0.096 mol), 26.06 g of L-*o*-chlorotartranilic acid and Celite (0.4 g) in water was warmed to 83—87 °C and filtered to remove insoluble material, then acetone (50 ml) was added at 45—55 °C and gradually cooled to 30 °C to give 18.25 g of crystals of the L-*o*-chlorotartranilic acid salt of the compound **6** as a monohydrate (39.2% yield). Pure compound **6** was obtained by decomposition of the salt with aqueous NaOH.

Analytical Sample: The salt; mp 119.4—133.9 °C. IR (KBr) cm^{-1}: 3336, 3120, 1694, 1597, 1525, 1511, 1442, 1303, 1220, 1143, 1083, 834, 755. $[\alpha]_D^{25}$=+42.6° (c=0.5, EtOH(95)). Compound **6** (1 H_2O); mp 86.8—91.9 °C. IR (KBr) cm^{-1}: 3413, 3288, 3168, 1602, 1511, 1222, 1163, 1136, 1075, 1026, 915, 834. ^{1}H-NMR ($(CD_3)_2SO$) δ: 1.60—1.86 (m, 3H), 2.40—2.69 (m, 4H), 3.03—3.39 (m, 7H), 7.21—7.27 (m, 2H), 7.34—7.40 (m, 2H). $[\alpha]_D^{25}$=−38.1° (c=0.5, EtOH (95)).

Paroxetine HCl IPA Solvate To a mixture of the L-*o*-chlorotartranilic acid salt of compound **6** (monohydrate, 24.35 g, 0.05 mol), $(Boc)_2O$ (11.46 g, 0.315 mol), toluene (61 ml) and water (49 ml), was added dropwise 25% aqueous NaOH (8.4 g) at 25—30 °C, then the mixture was gradually warmed and stirred at 45—55 °C for 2 h. The organic layer was separated and washed with water. The solvent was partially distilled to remove water azeotropically, and the same amount of toluene was added to give a solution of compound **7** in toluene. To the solution was added triethylamine (6.58 g, 0.39 mol), and then methanesulfonyl chloride (6.87 g) was added dropwise at 10—35 °C. The reaction mixture was stirred at 22—25 °C for 75 min and water (56 ml) was added, then the organic layer was separated and washed with aqueous 25% NaOH (8.0 g). The toluene solution of compound **8** thus obtained was added to a mixture of sesamol (7.60 g), 28% NaOMe (10.13 g) and toluene (68 ml) and heated at reflux for 5.5 h. The reflux temperature was raised to 110 °C by the removal of methanol and kept at the temperature for 1.5 h. After cooling, the reaction mixture was washed with aqueous 25% NaOH and with water to give a solution of *N*-Boc paroxetine (**9**) in toluene. Toluene was removed by distillation, and IPA (19 ml) was added and distilled off. Again, IPA (19 ml) was added to the residue, and to the solution was added 20% HCl IPA solution (13.67 g) at 71—75 °C over a period of 1 h followed by stirring for 2.5 h. The solution was decolorized with active carbon (1.07 g) and filtered. The filtrate was gradually cooled to 3 °C to give crystals of paroxetine HCl IPA solvate. The crystals were dried under a vacuum at 50 °C for 3 h and at 85 °C for 12 h to give crystals of paroxetine HCl containing IPA (2.58%) and water (0.49%) (15.94 g, yield 87.14% from compound **6**).

Analytical Sample: Compound **9**: mp 72.1—74.1 °C. IR (KBr) cm^{-1}: 1688, 1628, 1606, 1506, 1491, 1473, 1404, 1391, 1279, 1243, 1223, 1188, 1164, 1125, 1037, 1020, 937, 838. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (s, 9H), 1.67—1.77 (m, 3H), 2.01 (br s, 1H), 2.68—2.80 (m, 3H), 3.41—3.47 (m, 1H), 3.58—3.61 (m, 1H), 4.32 (br d, 2H, J=52.8 Hz), 5.88 (s, 2H), 6.13 (dd, 1H, J=2.3, 8.6 Hz), 6.35 (d, 1H, J=2.3 Hz), 6.62 (d, 1H, J=8.6 Hz), 6.94—7.01 (m, 2H), 7.11—7.16 (m, 2H). $[\alpha]_D^{25}$=−27.9° (c=0.5, EtOH(95)).

Typical Sample of Dried Paroxetine HCl Form-II Crystals with around 2.6% Weight of Bound IPA: mp 114.4—119.4 °C. IR (Nujol) cm^{-1}: 3632, 3390, 1603, 1512, 1467, 1378, 1340, 1286, 1220, 1195, 1132, 1090, 1034, 923, 888, 831, 805. ^{1}H-NMR ($(CD_3)_2SO$) δ: 1.94 (br d, 1H, J=12.2 Hz), 2.18 (dd, 1H, J=22.6, 12.7 Hz), 2.59 (m, 1H), 2.91—3.09 (m, 3H), 3.45—3.68 (m, 4H), 6.01 (s, 2H), 6.27 (dd, 2H, J=8.6, 2.3 Hz), 6.58 (d, 1H, J=2.3 Hz), 6.82 (d, 1H, J=8.6 Hz), 7.24 (t, 2H, J=8.6 Hz), 7.70—7.35 (m, 2H). [For bound IPA in the crystals: 1.06 (d, 6H/6, J=6.3 Hz), 3.85 (m, 1H/6), 4.46 (d, 1H/6)]. $[\alpha]_D^{25}$=−88.0° (c=0.5, EtOH(95)).

Desolvation of Form-II Crystals A 100 ml flask was charged with 3.8 g of paroxetine HCl form-II crystals. The flask was connected with a vacuum line (2—3 mmHg) and placed in an oven. The temperature of the oven was gradually raised, then kept at a fixed temperature for a fixed number of hours. The IPA content and water content of the crystals were determined by appropriate analysis methods.

Resolvation and Re-desolvation of Dried Form-II Crystals A 100 ml

flask was charged with 3.8 g of paroxetine HCl form-II crystals and finally dried under a vacuum at 110 °C for 13 h. The flask was cooled to room temperature and 38 ml of IPA was added to the flask. The dried crystals were immersed in IPA and gently stirred for 1 h and filtered. For the re-desolvation experiment, the crystals thus obtained were treated as described in the desolvation experiment above.

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