Structural Study of Polymorphs and Solvates of Finasteride

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ABSTRACT: NMR and XRD data are reported for several new forms of finasteride, including the results of complete structure determinations for three solvates. Form III of finasteride, hitherto only mentioned in the patent literature, and a new anhydrous form designated Form X, have been found in mixtures of polymorphs and their ^{13}C NMR chemical shifts obtained. The results demonstrate that the crystallographic asymmetric units contain three molecules and one molecule, respectively. Attempts to reproduce "Form H1", as described in a patent, resulted in a new IPA solvate hydrate. The previously-reported acetic acid, dioxane, and ethyl acetate solvates have been further characterised, and new THF and diethyl ether solvates prepared and characterised. The crystal structures of the dioxane, IPA, and THF solvates have been determined by single-crystal X-ray diffraction. All the solvates (except the acetic acid case) are found to be hemihydrates, to have a finasteride: solvent molar ratio of 2:1 and to have a common structure. The solvate molecules are highly disordered and sited in channels in the structure. The powder XRD patterns are characteristic of the common structure. These solvates may be distinguished by the characteristic CPMAS ^{13}C signals from the solvent molecules, but the resonances of the host finasteride structures differ only marginally, and powder XRD patterns are almost indistinguishable. Magic-angle spinning (MAS) proton spectra give sharp lines for the solvent peaks, confirming their high degree of mobility. This is further shown in one case by direct polarisation ^{13}C spectra. Mobility of the *tert*-butyl group is also implied. Thermal characteristics have been studied and TGA used (in conjunction with solution-state proton NMR) to estimate molar ratios.
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INTRODUCTION

Structural studies of solid pharmaceutical materials have traditionally relied on single-crystal diffraction experiments, with further characterisation involving, *inter alia*, thermal methods and vibrational spectroscopy. High-resolution NMR spectroscopy using cross polarisation (CP) and magic-angle spinning (MAS) was first applied[1] to organic and pharmaceutical compounds soon after the CPMAS combination of techniques was introduced[2] in 1976. For a number of years such applications were relatively rare and most CPMAS studies involved either zeolites or synthetic polymers.[3] However, since the mid 1990s NMR has come to the fore in studies of pharmaceutical systems [Ref. 4 (Chapter 4), Ref. 5 (Chapter 4), Ref. 6 (Chapter 6) and Ref. 7]. This

Dedicated to the late Professor David J. W. Grant in tribute to his scientific achievements and in recognition of his great interest in the characterization of solid pharmaceutical compounds.

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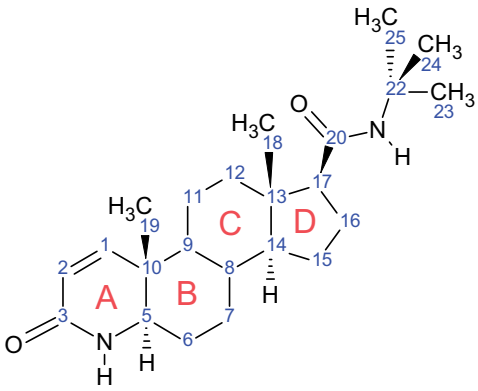
is especially true for investigations of polymorphs and solvates, since the existence of such forms can pose major problems for pharmaceutical industry in procedures such as scale-up, processing, formulation and storage.[4,5] Moreover, polymorphism and solvate issues are frequently encountered in patent establishment and litigation.[5,8] The strengths of NMR in solid-state characterisation are many and varied. It can be used for most solid systems, including amorphous and heterogeneous materials as well as pure crystalline compounds. Its applications to organic polymorphs and solvates have recently been reviewed[7] In many ways, high-resolution NMR of solids is complementary to the longer-established diffraction techniques. It can provide much information on matters of crystal structure and there is increasing recognition for the emerging discipline of NMR crystallography.[9,10] It has even been reported that complete crystal structures can be derived essentially by NMR alone.[11] Nevertheless, NMR is at its most powerful when used in combination with diffraction methods, particularly in view of the development of new techniques within the diffraction manifold (especially for powder diffraction,[12] which can be reinforced by combination with solid-state NMR information).[13–16] The present paper uses CPMAS NMR, X-ray diffraction and thermal methods to examine a number of polymorphs and solvates of the aza-steroid finasteride (**1**), 17-β-(N-*t*-butyl carbamoyl)-4-aza-5-α-androst-1-ene-3-one.



(**1**)

The replacement of one or more carbon atoms in a steroid molecule by nitrogen affects the chemical properties and changes its biological activity,[17] leading to pharmaceutically useful systems. In particular, steroids which are 4-aza lactams act as 5α-reductase inhibitors. Finasteride is the most potent drug molecule of this class and is used for the treatment of benign prostatic hypertrophy. There are several known forms and solvates, but the literature contains some confusion regarding their nature. There are three known anhydrous modifications. Forms I° and II were patented in the late 1990s[18,19] and in 2005[20] (the superscript zero indicates the form stable under ambient conditions, as suggested by Professor U. Griesser, private communication). They have also been the subject of articles in the research literature.[21–24] Their crystal structures appear in the Cambridge Crystal Structure Database (CSD) under the codes WOLXOK01 and WOLXOK02 for Form I° and WOLXOK03 for Form II. Form I° is orthorhombic, whilst Form II is monoclinic. The system is enantiotropic, with transition from Form I° to Form II observed[22] to occur between 200 and 230°C (depending on the heating rate). Differential scanning calorimetry (DSC) experiments in our work (with a heating rate of 1°C min^{-1}) showed a transformation event at 217°C. Wenslow et al.[22] calculate the true transition temperature to be 129°C. Some minor confusion in respect of the two reported crystal structures of Form II, which appeared to differ, has been cleared up by Karami et al.[25] It was concluded that the structures were actually the same. Form III has only been described in the patent literature to date[26] and the crystal structure has not been described, though 2θ values for powder diffraction data are given in the patent application. Solid-state (CPMAS) ^{13}C spectra of Forms I° and II have been published.[2122] Two solvates (with guest molecules acetic acid and ethyl acetate) have been reported[23] and their crystal structures appear in the CSD under the codes WOLXEA and WOLXIE, respectively. The acetic acid solvate has a monoclinic space group, with a 1:1 molecular ratio of finasteride to solvent molecule, whereas the ethyl acetate solvate is orthorhombic. The latter has a 2:1 molecular ratio of finasteride to ethyl acetate and it also contains water in a finasteride to water ratio of 2:1. It is described as a bis(finasteride) monosolvate monohydrate[23] (and was also denoted as a clathrate), but it could equally well be named a finasteride hemisolvate hemihydrate. We will use the former notation to be consistent with the literature, but will frequently use the term finasteride solvate hydrate as a shorthand. The ethyl acetate molecules were found to be "disordered in channels."[23] A dioxane solvate has also been described and its ^{13}C CPMAS

spectrum illustrated[21], but its crystal structure has not been published nor was its powder XRD reported.

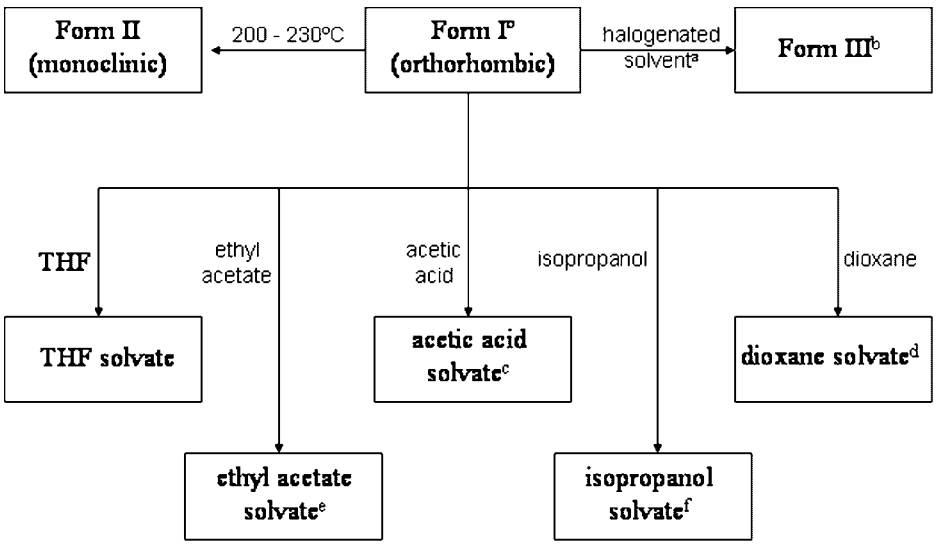
However, there is some confusion in the patent literature. Parthasaradhi et al.[24] describe the preparation of two "novel crystalline" Forms, H1, and H2, but they do not properly characterize them, though they do list powder XRD data. The Form H1 is obtained by use of "methanol or ethanol or isopropyl alcohol; or mixture (*sic*!) thereof", whilst Form H2 has dioxane as the solvent. The patent reported some powder XRD data for Form H2 but did not attempt to study the structure further and they did not identify the product as the dioxane solvate of Morzycki et al. Reddy et al.[26] claim to produce "Form IV and Form V", by the use of an ethyl acetate/tetrahydrofuran/water mixture for the former and aqueous acetic acid for the latter. They comment that the XRD and thermal characteristics of the two forms "reasonably match with those" of the ethyl acetate and acetic acid solvates, respectively, known previously.[23] Reddy et al. also make cryptic reference to a "Form-E" and a "Form-M", but close reading of the patent suggest that both these terms are typographical errors for Form III. Figure 1 shows the relationships between the various forms of finasteride, both as described in the literature and as revealed by our work.

EXPERIMENTAL

Samples

Form I° was obtained from Hikma Pharmaceuticals, Jordan, and was used without further purification. It was originally produced by Hunan Steroids Chemicals Co., Ltd., China. Form II was prepared by dissolving about 1 g of Form I° in a solution of ethyl acetate containing water with a concentration of 24 mg/mL. The solution was then maintained at ambient temperature under stirring for an hour. The solution was left to evaporate overnight and then the solid was dried in a vacuum oven for 6 h at 80°C. This method is as described by McCauley et al.[18] Another sample, ostensibly of Form I°, was provided by Hikma Pharmaceuticals after storage at room temperature for several years. Powder XRD showed it to also contain a little Form II together with an unknown form, which we designate as Form X. Values of 2θ found for this form are very similar to those of Form III (see below). NMR showed, however, that Form X differs significantly from Form III.

A number of attempts were made to produce Form III by the various methods described in the relevant patents.[26,27] Use of dichloromethane/petroleum ether as the solvent resulted in



[a] Inter alia; [b] ≡ Form E ≡ Form M[26]; [c] ≡ Form V[26]; [d] ≡ Form H2?[24]; [e] ≡ Form IV[26]; [f] ≡ Form H1?[24]

Figure 1. Relationships between the polymorphs and solvates of finasteride as given in the literature,[18–24] modified and expanded by the research described in the present article.

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a mixture of Forms I° and II. However, with chloroform/petroleum ether as the solvent a third form was obtained, together with Form I° and a little Form II. Specifically, the method used was as follows: 0.5 g of finasteride Form I° was dissolved in 1.5 mL of chloroform. 60–70% of the chloroform was distilled off at 60–70°C. The resulting solution was saturated with about 5 mL of petroleum ether at 60–65°C under stirring. The solution was concentrated at 60–65°C for about 15 min. The sample was kept overnight for further solvent to evaporate, dried under vacuum at 65°C for 30 min, and finally further dried at 80°C for 12 h. The presence of Forms I° and II was detected by powder XRD. The 2θ peaks not accounted for by these two modifications are listed in Table 1, together with the values reported for Form III. These peaks are not in the characteristic positions found for many solvates, though that does not prove that the sample is unsolvated. A TGA thermogram showed a minor (2.2%) mass loss at about 70°C. It is clear that Form III is present in this sample but we were unable to further characterise it. Unfortunately, repetition of the above preparation method yielded a sample which contained no Form III. A further repetition, but without the final drying step, gave an XRPD pattern now known to be characteristic of a hydrated solvate, presumably arising from either chloroform or petroleum ether, with adventitious moisture. It is clear that, at least in our hands, the preparation of Form III described in the patent literature is not robust and that optimum operation of the drying steps is crucial.

Because the ^{13}C CPMAS NMR spectrum of the sample purportedly containing Form III showed an anomalous peak, thought to arise from a solvent molecule, attempts were carried out to see if chloroform or diethyl ether solvates could be made. The former experiment produced a mixture of Forms I° and II, as shown by powder XRD. In the latter case, a sample was prepared by mixing Form I° and a 1:1 solution of diethyl ether (replacing petroleum ether) and chloroform at 60°C. The resultant slurry solution was evaporated to dryness under ambient conditions overnight. The sample was a microcrystalline powder, unsuitable for single-crystal XRD. This was found to be a diethyl ether hydrated solvate, again as shown by powder XRD and solid-state NMR (see also the Results and Discussion). Further drying under vacuum at 65°C for 30 min of this material produced Form II.

Table 1. Powder XRD 2θ Values from Our Finasteride Sample Compared with the Reported Form III Values

Peak Number	2θ Values for Our Sample	Corresponding 2θ Values of Form III[26,27]
1	5.4	5.3
2	10.7	10.7
3	13.7	13.6
4	16.2	16.1
5	18.3	18.2

Attempts were also made to reproduce Forms H1 and H2, as described in the patent literature. In the former case,[24] when ethanol was used as a solvent, Form I° was obtained, identified by powder XRD. When the solvent was methanol, Form II was produced, again as shown by powder XRD. However, the result of using isopropanol was a sample whose powder XRD was distinct from those of Forms I° and II. The pattern was also different from that claimed for Form H1. We show below that it is an isopropanol solvate hydrate. Form H2 was successfully prepared by the patent method, the product giving a powder XRD pattern which matched the data reported by Parthasaradhi et al.[24] We have fully characterised this form, which is a dioxane solvate hydrate.

The acetic acid solvate was also successfully prepared by literature methods.[23,26,27] However, gummy solids were first obtained. Further drying of the product in an oven at 50°C for an hour produced a highly crystalline solid.

The ethyl acetate solvate hydrate was obtained by the literature method.[23] An attempt was made to prepare an anhydrous ethyl acetate solvate. By omitting the addition of water as specified in the published method, however, a mixture of Forms I° and II alongside the major fraction (ca. 65%), which was shown to be an ethyl acetate hydrate by powder XRD, was obtained. Water was obviously picked up either from adventitious amounts present in the solution prior to crystallization or from the atmosphere during overnight drying. It would seem that water stabilizes the solvate and is both necessary to obtain the structure and readily incorporated. An attempt to prepare the ethyl acetate solvate hydrate by the patent method[26,27] produced a sample which is essentially a THF solvate hydrate, but which also contained a little ethyl acetate. In fact, a pure THF solvate hydrate was produced by the following method: 0.5 g of finasteride Form I° was dissolved in THF. The resulting solution was heated to a temperature of 55°C for about 20 min and then was cooled to RT

Table 2. Crystallographic Details for Bis(Finasteride) Monosolvate Monohydrates

Composition	Dioxane Solvate Hydrate	IPA Solvate Hydrate	THF Solvate Hydrate	Ethyl Acetate Solvate Hydrate[a]
Empirical formula	2 $C_{23}H_{36}N_2O_2$· H_2O·$C_4H_8O_2$	2 $C_{23}H_{36}N_2O_2$· H_2O·$C_3H_8O_1$	2 $C_{23}H_{36}N_2O_2$· H_2O·$C_4H_8O_1$	2 $C_{23}H_{36}N_2O_2$· H_2O·$C_4H_8O_2$
Gross formula	$C_{50}H_{82}N_2O_7$	$C_{49}H_{82}N_2O_6$	$C_{50}H_{82}N_2O_6$	$C_{50}H_{82}N_2O_7$
Molecular mass (amu)[b]	823.2	795.2	807.2	851.20
Crystal dimensions/mm^3	$0.12 \times 0.16 \times 0.28$	$0.16 \times 0.20 \times 0.20$	$0.20 \times 0.20 \times 0.20$	$0.2 \times 0.25 \times 0.6$
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	8.1110 (7)	8.1132 (3)	8.1317 (3)	8.173 (3)
b (Å)	18.0856 (16)	17.9012 (8)	17.7767 (7)	18.364 (6)
c (Å)	35.512 (3)	35.6948 (15)	35.7349 (15)	35.65 (2)
V (Å^3)	5209.4 (8)	5184.2 (4)	5165.7 (4)	5350.67
Z[b]	4	4	4	4
Z'[b]	1	1	1	1
T/K	120	120	120	Ambient
Calculated density (g cm^{-3})	1.141	1.101	1.105	1.057
μ (mm^{-1})	0.07	0.07	0.07	0.551
Number of observed reflections	6405	5135	6887	7554
Number of parameters refined	595	568	568	Not given
R_{int} (%)	3.5	2.2	1.5	Not given
R (%) for I > 1σ	9.90	8.87	9.58	7.65[c]
wR (%)	21.47	20.52	21.75	17.43

[a]Ref. 23.
[b]Based on bis(finasteride) monosolvate monohydrate as the molecular entity.
[c]For I > 2σ.

and kept to evaporate overnight. Large crystals suitable for single-crystal XRD examination were produced. For the IPA solvate, 0.5 g of finasteride Form I° was dissolved in 2 mL IPA, heated to 60°C and maintained at this temperature for 1 h. The solution was cooled in a refrigerator overnight and was then left to evaporate at room temperature for 24 h. A highly crystalline sample was produced (suitable for single-crystal XRD studies).

Nuclear Magnetic Resonance

The solid-state NMR spectra and relaxation times were measured at ambient probe temperatures (and in one case at various high temperatures) using a Varian InfinityPlus spectrometer, which operates at 125.65 MHz for ^{13}C and 499.70 MHz for ^{1}H. Samples for ^{13}C CPMAS spectra were packed, with light grinding, into 5.0 mm o.d. rotors (except for the acetic acid solvate, for which a 2.5 mm rotor was used). Contact times were in the range 1–5 ms, with spin rates 8.5 kHz, recycle delays of 4 s and acquisition times of 40 ms. The duration of the proton 90° pulse was 4.4 μs. Proton decoupling was carried out with the TPPM[28] method (except for the acetic acid solvate, for which SPINAL[29] was used). Good quality spectra could be obtained with accumulation of 150–220 transients for the 5 mm probe, though 10000 transients were considered desirable for the 2.5 mm probe (acetic acid solvate). Proton MAS spectra were also obtained using 5.0 or 2.5 mm rotors, spinning at 8.5 and 20.0 kHz, respectively. Pulse angles of 90° were used, with recycle delays of 1 s and 5 s and numbers of transients 4 and 10–20 for the two probes, respectively.

Chemical shifts for ^{13}C and ^{1}H are reported relative to the relevant signals for tetramethylsilane but were recorded by replacement with respect to the adamantane signals at $\delta_C = 38.4$ ppm (high-frequency peak) and $\delta_H = 1.9$ ppm (unresolved).

Proton spin-lattice relaxation times were obtained by the saturation-recovery method at ambient temperature using the 5 mm probe under MAS conditions. Saturation was obtained by 100, 90° pulses separated by 10 μs. Plots were derived using 10 (THF, acetic acid, and ethyl acetate cases) or 20 (Form II, IPA, and dioxane cases) points, with 1 s recycle delays.

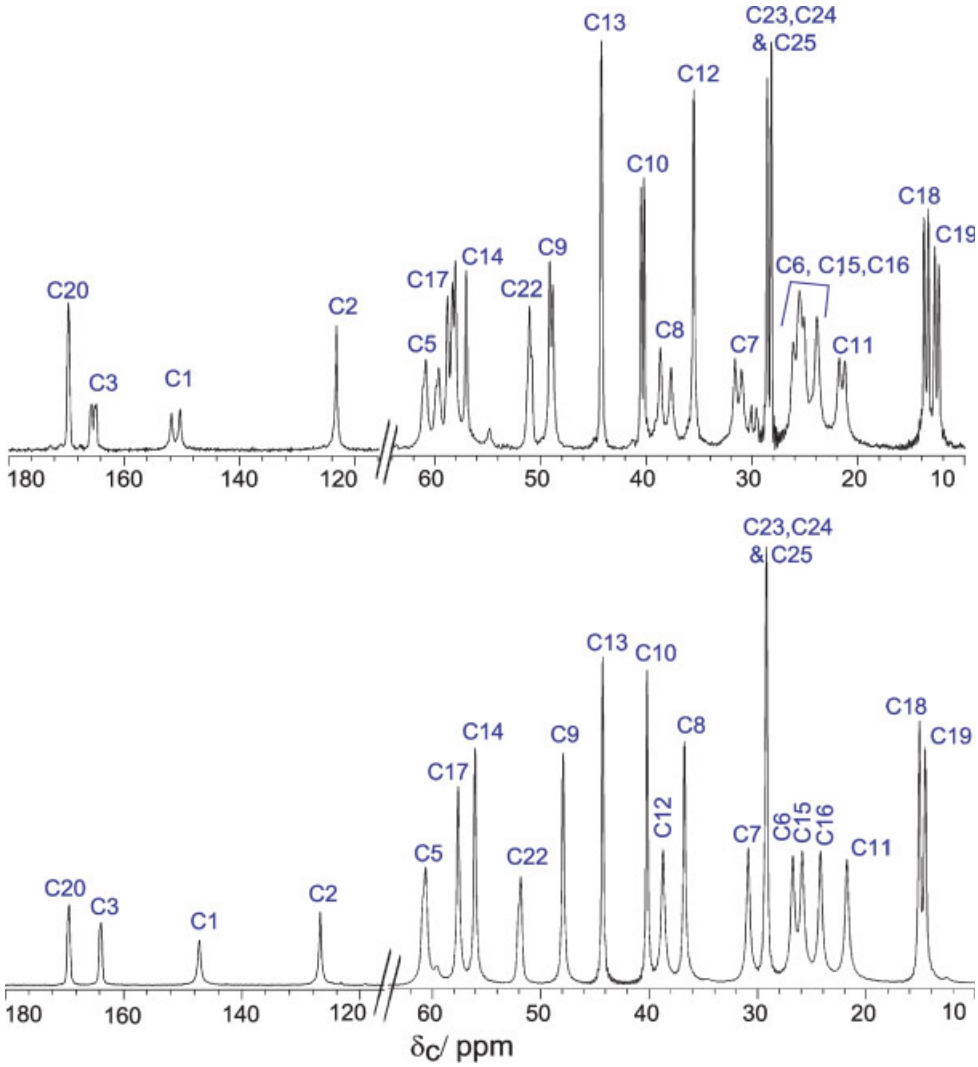

Figure 2. Carbon-13 CPMAS spectra of finasteride Form I (below) and Form II (above). The signals of some quaternary carbons show evidence of truncation of the FID, arising from limitation of the acquisition time in order to avoid probe damage from extended proton high-power decoupling.

A Varian Inova spectrometer was employed for solution-state ^{13}C and ^{1}H NMR spectra (at 125.68 and 499.77 MHz, respectively. For ^{13}C, recycle delays of 3 s, acquisition times of 1.4 s, a pulse angle of 45° and 3000 transients were used. The corresponding values for ^{1}H were 30 s, 4.1 s, 45° and 32, respectively. Proton decoupling for ^{13}C spectra was achieved by the WALTZ-16 pulse sequence.

Thermal Methods

DSC was carried out on a TA Instruments system. All samples were run from 25 to 300 °C. Nitrogen was used as purge gas in ambient mode. The heating rate was kept constant at $1^{\circ}C\,min^{-1}$. Aluminium sample pans were used for all samples. A single point calibration was carried out using indium (melting point 156.60°C) as a standard sample. A Perkin-Elmer Pyris 1 instrument was used for all TGA samples. Nitrogen was used as the purge gas and the heating rate was kept constant at $2^{\circ}C\,min^{-1}$.

X-Ray Diffraction

Two diffractometers (Siemens D5000 and Bruker D8 Advance) were used for powder work. They utilised CuK$\alpha_{1,2}$ radiation. All sample scans were in the range of 2θ 5–70 or 5–50, with a 20 mm

Table 3. Carbon-13 Chemical Shifts (δ_C/ppm) for Finasteride Forms I, II and X, and also for the Solution State

Carbon Number and Type		Solution[a]	Form I°	Form II	Form X	Shift Change[b]
1	CH	151.11	146.9	150.4/151.9	148.6	−4.2
2	CH	123.25	126.9	123.3	126.1	3.6
3[c]	Q[d]	166.89[e]	164.3[f]	164.9/165.7[g]	166.4[g]	−2.6
5[c]	CH	59.88	60.6	59.6/60.9	60.3	0.7
6	CH_2	26.12	26.8	26.6	25.2/25.8	0.7
7	CH_2	29.66	30.6	31.1/31.7	31.2	0.9
8	CH	35.54	36.8	35.6	36.2	1.3
9	CH	47.82	48.0	48.9/49.2	48.9	0.2
10	Q[d]	39.62	40.2	40.3/40.6	40.3	0.6
11	CH_2	21.48	21.9	21.3/21.9	21.7	0.4
12	CH_2	38.66	38.8	37.7/38.7	39.7	0.1
13	Q[d]	44.16	44.3	44.3	44.5	0.1
14	CH	55.87	56.1	57.1/58.1	55.8	0.2
15	CH_2	25.51	26.0	25.6	25.2/25.8	0.5
16	CH_2	24.46	24.3	24.0/25.2	25.2/25.8	−0.2
17	CH	57.67	57.6	58.3/58.8	57.3	−0.1
18	CH_3	13.53	15.2	13.5/13.9	14.8	1.7
19	CH_3	12.24	14.7	12.5/12.9	12.5	2.5
20[c]	Q[d]	171.84	169.3[f]	169.7[g]	171.1[g]	−2.5
22[c]	Q[d]	51.33	51.9	50.9	51.2	0.6
23, 24, 25	CH_3	29.28	29.3	28.3/28.7	30.1	0.0

[a] In deuterochloroform.
[b] From the solution state to Form I.
[c] Showing broadening arising from second-order effects[42] of coupling to quadrupolar ^{14}N—a lesser effect than observed by Wenslow et al.[22] because we operated at a higher magnetic field.
[d] Quaternary carbon, as shown by dipolar dephasing experiments.
[e] Assignments confirmed by two-dimensional gHMBC spectra.
[f] Assignments confirmed by a two-dimensional experiment.
[g] Assuming assignments for C3 and C20 the same way round as for Form I.

variable-divergence slit and a step time of 1 s. Highly crystalline samples were subjected to grinding under liquid nitrogen before examination in order to minimise preferred orientation effects.

All single-crystal X-ray data collections were performed on a Bruker SMART 6000 diffractometer, equipped with a CCD detector, MoKα source and an Oxford Cryostream N_2 cooling system. In each case, a full sphere of data was collected and a multiscan absorption correction[30] was applied to the raw data. Frames were integrated using the program SAINT.[31] The crystal structure was solved by direct methods using the SIR92 software[32] and refined using the Oxford Crystals suite.[33] The positions and anisotropic atomic displacement parameters of all non-hydrogen atoms were refined. Hydrogen atoms could be located in the Fourier difference maps, but they were placed geometrically and treated using a riding model. All crystallographic information, including experimental and structural details and the agreement factors obtained in the refinements, is given in Table 2.

RESULTS AND DISCUSSION

Solid-State NMR of Forms I° and II, Together with Some Information for Two Further Forms

Figure 2 shows the ^{13}C CPMAS NMR spectra of Forms I° and II of finasteride. As is usually the case with steroids, the quality of the spectra is high. The resolution is generally excellent because high-quality crystallites are readily obtained. Wenslow et al.[22] reported some linewidths as low as 5 Hz in halfwidth. However, CH_2 resonances are usually relatively broad for steroids[34,35] (as in the present case) unless proton decoupling is especially efficient.[36] The spectra of the two forms are consistent with those published previously[21,22] but appear to be of better quality. The chemical shifts are reported in Table 3. Our values are consistently ca. 0.3–0.4 ppm. higher

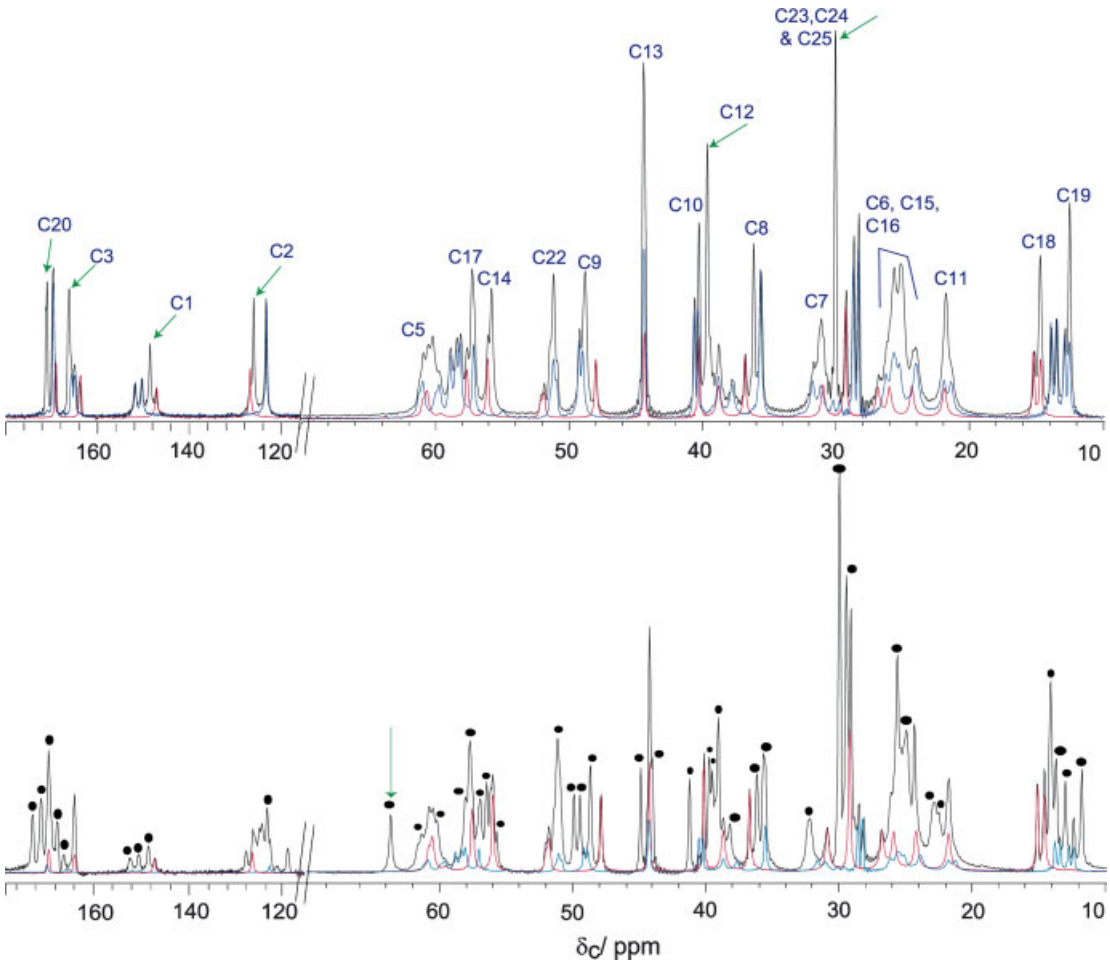

Figure 3. Carbon-13 CPMAS NMR spectra of samples of finasteride with mixtures of forms containing (bottom) Form III, (top) Form X. Green arrows are used for the former to show some of the distinct peaks due to Form X. The red traces are for Form I and the blue plots for Form II. The resonances identified as arising from Form III are indicated by black spots in the lower spectrum and are numbered from right to left for the purposes of Table 4, whereas carbon atom numbers are shown for Form X.

than those of Wenslow et al.,[22] but we are unable to advance any reason for this. We have adopted the assignments of Ref. 22. Those of the later Ref. 21 are identical except for an interchange of the peaks assigned to C3 and C20. The original assignments were assisted by dipolar dephasing experiments to identify signals from quaternary carbons and by observation of line splitting or broadening of resonances for carbons bonded to nitrogen. However, such considerations cannot distinguish between the signals for C3 and C20. We have now established, by INADEQUATE experiments at 176 MHz, that the C20 resonance is at 169.3 ppm since there is a correlation peak with the signal for C17 at 57.6 ppm. Thus the original assignments of Wenslow et al. are confirmed. Assignments in the region 22–32 ppm were said to be tentative and remain so.[21]

Table 3 also contains our chemical shift results for a solution in deuterochloroform. The values are consistent with those given by Wenslow et al.[22] and by Morzycki et al.[21] We have confirmed the solution-state assignment of the signals to C3 and C20 by recording a two-dimensional HETCOR (gHMBC) spectrum. Morzycki et al.[21] briefly compared solution-state and solid-state chemical shifts for finasteride. Using their assignments for C3 and C20, they state that high-frequency shifts in the solid-state for C3 are caused by greater hydrogen bonding in the solid than in solution, whilst the very large low-frequency shift for C20 in Form I° is dismissed as confirming "that this

Table 4. Carbon-13 Chemical Shifts (δ_C/ppm) for the Purported Form III of Finasteride

Peak Number[a]	Chemical Shift		Peak Number	Chemical Shift	
1	11.8	Methyl groups	21	48.7	C9
2	13.0		22	49.5	
3	13.7		23	50.0	
4	14.1		24	51.2	C22
5	22.6	C6,C11,C15, and C16	25	55.7	C14
6	22.9		26	56.5	
7	25.0		27	57.0	
8	25.6		28	57.7	C17
9	29.5	*t*-Butyl group	29	58.1	
10	29.9		30	60.3	C5
11	32.2	C7	31	61.4	
12	35.7	C8	32	63.7	Solvent
13	36.2		33	124.0	C2
14	38.2	C10, C12, and C13	34	148.6	C1
15	39.1		35	150.6	
16	39.5		36	152.5	
17	39.8		37	166.3	C3 and C20
18	41.2		38	167.4	
19	44.0	C13	39	169.4	
20	44.9		40	171.0	
			41	172.6	

[a]See Figure 2 (bottom).

carbonyl group is not involved in hydrogen bonding!" However, these arguments fail, in view of our INADEQUATE experiments, since the true assignments show that both C3 and C20 experience a low-frequency shift (of 2–3 ppm) in going from solution to the Form I solid state. Currently, we have no explanation for such shifts, but we hope that ongoing first principles shielding computations will help to understand them. We note that C1, C2, C8, C18, and C19 also have solution to solid shifts greater than 1 ppm in magnitude. Comparisons with the literature for other steroids[35–38] show that variability is marked and cannot be accounted for in a simple manner. In fact, solid-state shifts are affected by both intra- and intermolecular interactions, and it is extremely difficult to disentangle these effects empirically. The former are influenced by both conformation and geometry (bond distances and angles), whilst the latter include both electronic interactions (primarily hydrogen bonding) and relative geometry (such as the position of neighboring carbonyl groups). Hope is offered by shielding computations based on the repetition inherent in crystal structures,[7,39,40] but much work will be needed for a variety of solid steroid systems before understanding can be gained. Similar considerations apply, with additional force, for comparisons of chemical shifts between different polymorphs or solvates.

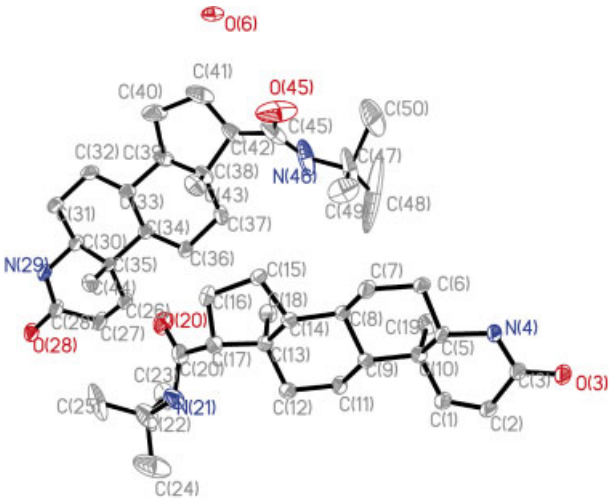

Figure 4. Molecular structure and atom numbering scheme for finasteride dioxane solvate hydrate. Atomic displacement parameters are drawn at 50% probability. Disordered solvent and hydrogen atoms have been omitted from the picture for clarity. The same numbering scheme is used for the isomorphous IPA and THF solvates.

Figure 3(bottom) illustrates the ^{13}C CPMAS NMR spectrum of the mixture containing another form which is presumably to be identified as Form

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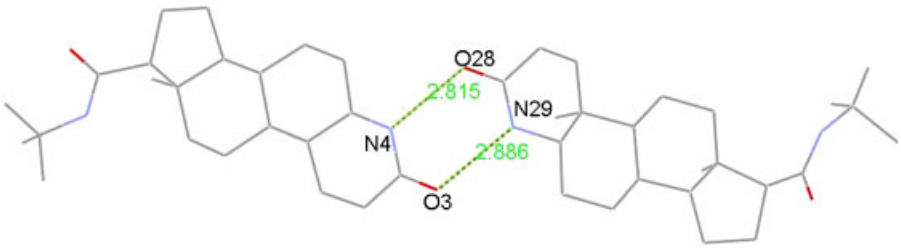

Figure 5. Dimers formed between crystallographically independent finasteride molecules through N–H...O hydrogen bonding in the bis(finasteride) monosolvate monohydrates.

III (see the Experimental section), together with the spectra of Forms I° and II at appropriate intensity levels. By a procedure of subtraction, we were able to identify most of the resonances of the additional form and the chemical shifts are given in Table 4. It is evident, in particular from the number of peaks in the carbonyl and methyl regions, that Form III (assuming the mixture only contains a single form in addition to Forms I° and II) probably has three molecules in the asymmetric unit. However, the spectrum also contains a signal at $\delta_C = 63.7$ ppm, indicated by an arrow in Figure 3 (bottom), which cannot be ascribed to finasteride but presumably arises from solvent. Such a peak also appears (at 62.8 ppm) for a solution in deuterated THF. A TGA experiment reveals a weight loss between 55 and 110°C, but only in minor amount (2.2%). We conclude that the sample (i.e. Form III) contains some (unidentified) solvent, possibly in Form III, or, perhaps, that there is more than one additional form, one of which contains solvent.

Figure 3(top) shows the ^{13}C NMR spectrum for the unknown Form X and Table 3 also gives the chemical shifts. Evidently this form has only one molecule in the asymmetric unit and seems to have no carbon-containing solvent molecules (as shown by solution-state ^{13}C NMR), though we cannot rule out the presence of water.

Single-Crystal X-Ray Diffraction of the Solvate Hydrates

The crystal structures of the three finasteride solvates studied in detail in the present work are found to be isomorphous, and they are also isomorphous with the ethyl acetate solvate reported in the literature.[18] The cif files have been deposited in the CSD (CCDC deposition numbers 638162-4). In all of these cases, crystallographic asymmetric units contain two finasteride molecules, together with (probably) one water molecule and one highly disordered solvent molecule, though the X-ray work cannot ascertain that the systems are stoichiometric in solvent. Moreover, whilst water molecules are at well-defined positions, giving a 2:1 finasteride:water ratio, there is some extra electron density (corresponding to approximately one-third of a water molecule) in all three systems we studied at fractional coordinates of $x \sim 0.50$, $y \sim 0.80$ and $z \sim 0.04$ which may imply additional water content.

Bis-finasteride monosolvate monohydrates crystallize in orthorhombic space group $P2_12_12_1$. Two unique finasteride molecules (referred to as molecule 1 and molecule 2, containing carbon atoms 1–25 and 26–50, respectively) and the crystallized water molecule in the dioxane

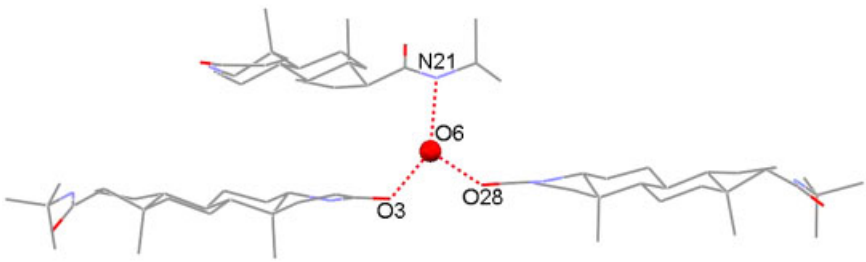

Figure 6. Hydrogen bonding between water and finasteride molecules in bis(finasteride) monosolvate monohydrates.

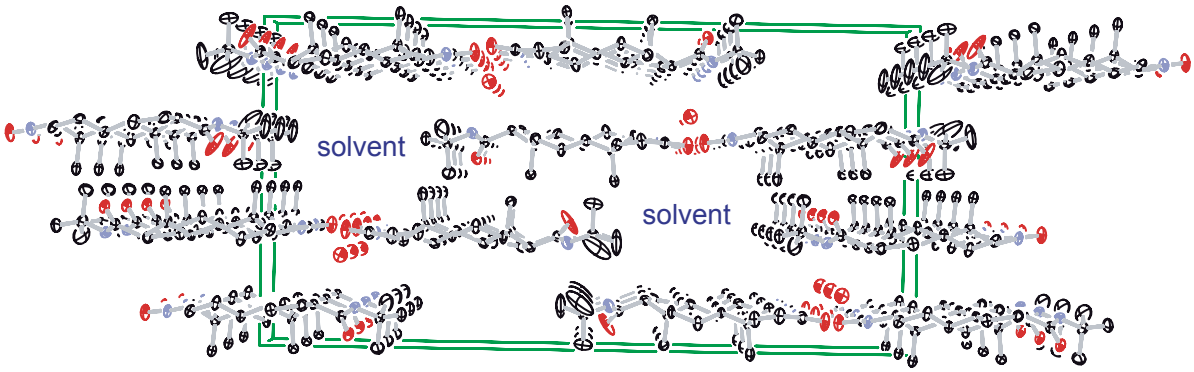

Figure 7. The packing in bis(finasteride) monosolvate monohydrates viewed down the *a* axis.

complex, together with the atom numbering scheme (which is consistent with that shown in (**1**)), are shown in Figure 4, which is also representative of the IPA and THF solvates. The two central six-membered rings B and C adopt a chair conformation, whilst ring A and the five-membered ring D adopt distorted half-chair conformations, as is normal for steroids. The appearance of the anisotropic atomic displacement parameters shown in Figure 4 suggests a degree of (dynamic) disorder in the tail *tert*-butylamide group in molecule 2, as reported by Wenslow et al.[22]

Two crystallographically independent finasteride molecules are approximately related by a pseudo twofold rotation axis and they form dimers around this axis through a pair of N–H...O hydrogen bonds, with the N...O separations in the participating lactam groups in the three solvates ranging from 2.82 to 2.89 Å (Fig. 5). Water molecules in finasteride monohydrate solvates are involved in hydrogen bonding, which provides bridging contacts between finasteride molecule dimers. Each water molecule acts as a hydrogen bond donor to lactam group O atoms on two finasteride molecules below, and a hydrogen bond acceptor from the peptide N atom from the finasteride molecule above (Fig. 6).

A packing diagram for bis-finasteride monosolvate monohydrates viewed down the *a* crystallographic axis is shown in Figure 7. Finasteride molecules are arranged into staggered layers, leaving cavities in the structure, which are occupied by disordered solvent molecules. It should be pointed out that the solvent disorder is severe, and that dioxane, IPA, and THF could not in fact be located as recognizable molecular entities in the Fourier difference maps, though the general molecular positions are reasonably well-defined. This is in agreement with solid-state NMR results (see below), which suggest the existence of a substantial amount of molecular motion. A similar degree of solvent disorder was found in the isomorphous ethyl acetate solvate.[23] Nonetheless, the host and guest systems are commensurate, with the guests occupying defined translational positions in the channels, that is the disorder appears to be rotational rather than translational.

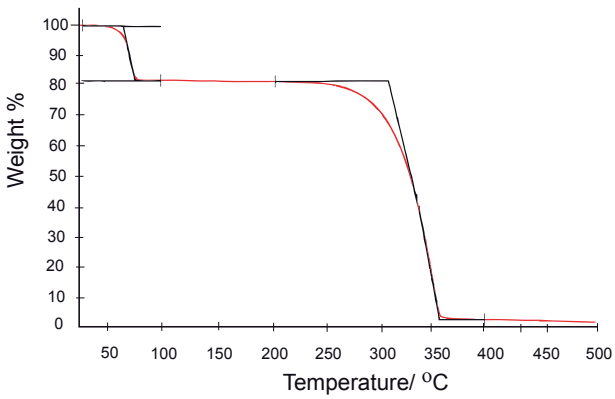

Figure 8. TGA plot for the finasteride diethyl ether hydrate.

Characterisation of the Solvates by Thermal Methods and Powder XRD

A DSC plot for the IPA solvate hydrate showed endothermic processes at ca. 69 and 102°C, indicating two desolvation processes, presumably associated with IPA and water. Correspondingly, the TGA experiment reveals weight loss of a total of 9.8% in two steps over the range 40–110°C. On

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Table 5. TGA Data Comparisons for the Prepared Finasteride Solvate Hydrates

Sample	Observed Weight Loss/%	Expected Weight Loss/% as per 0.5 Ratios of Solvent and Water to Finasteride
Diethyl ether solvate	17.9	10.9
Ethyl acetate solvate	10.3	12.5
IPA solvate	9.8	9.5
Dioxane solvate	13.2	12.5
THF solvate	13.0	10.8

the other hand, the dioxane solvate hydrate shows only a single broad thermal event peaking at 77°C and loss of 13.2% by weight (as measured by TGA) over a small temperature range around 59°C. The sample of the ethyl acetate hydrate showed only a single thermal event by DSC, with weight loss over a narrow range by TGA. The DSC event occurs at ca. 46°C. The TGA weight loss was 10.3% and was seen at 45°C. The THF solvate hydrate gave a DSC event peaking at 76°C and weight loss of 13.0% over the range 50–65°C. The DSC traces of all four solvates indicate melting points of 257.8–258.0°C, which is that of Form II. No thermal events intervene between solvent loss and melting. The diethyl ether solvate hydrate was examined by TGA (only). A weight loss of 17.9% occurred at a single event with an inflection point of 73°C (Fig. 8).

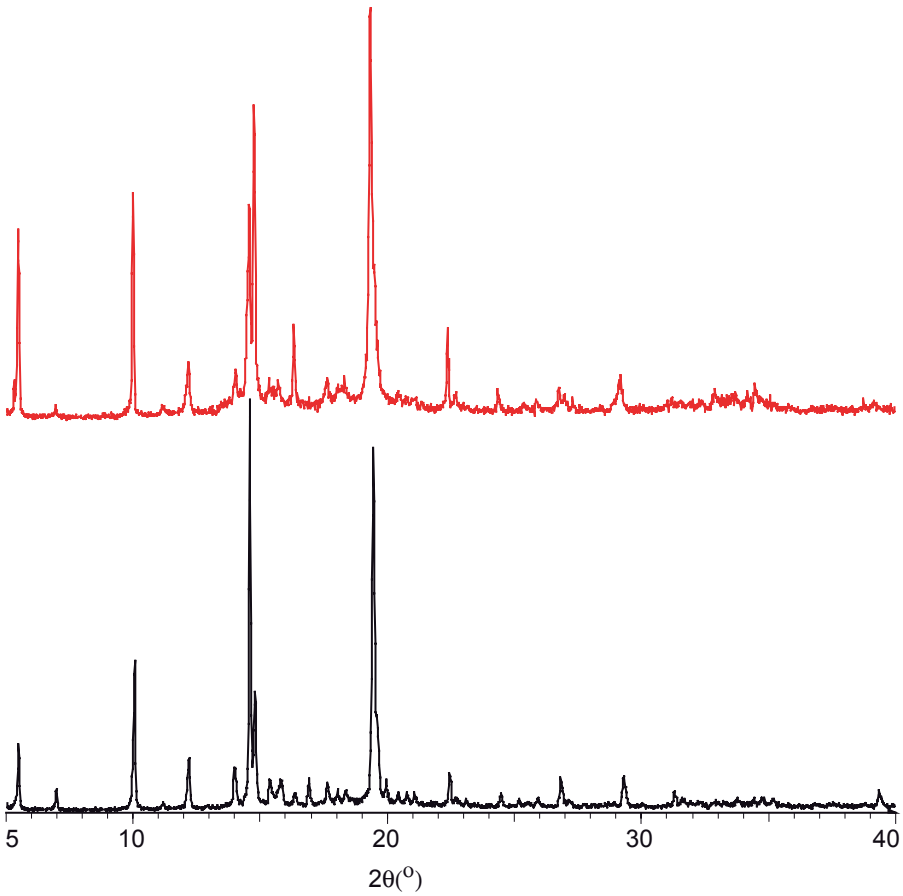

Figure 9. X-ray powder pattern for the (top) dioxane and (bottom) IPA solvate hydrates of finasteride. The similarities between the patterns clearly indicate the isomorphous nature of the structures. The differences arise mainly from preferred orientation effects.

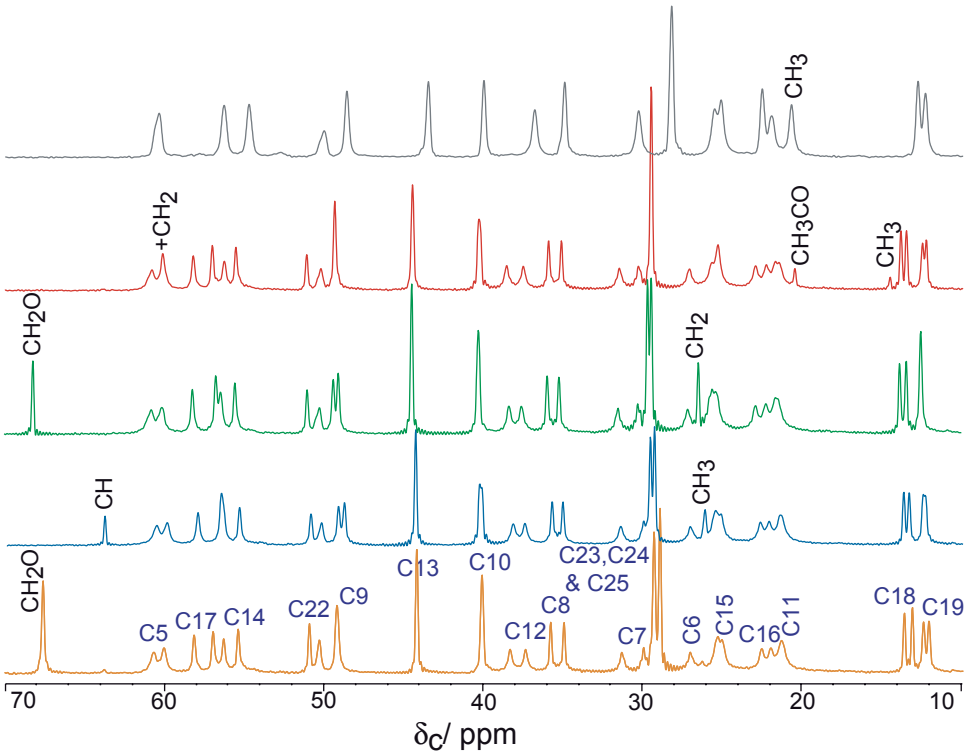

Figure 10. Carbon-13 CPMAS spectra of five solvates of finasteride (excluding the high-frequency part). Top to bottom: acetic acid; ethyl acetate hydrate; THF solvate hydrate; isopropanol solvate hydrate; dioxane solvate hydrate. Assignments are indicated for the solvent peaks.

Calculated total weight losses of solvent and water for 2:1:1 molecular compositions are listed and compared to the experimental values in Table 5. With the exception of the ethyl acetate solvate hydrate, the observed weight losses are more than expected, possibly indicating the presence of additional solvent and/or water. It is difficult to estimate the accuracy of the experimental weight losses, but ±1% is a reasonable value. The ethyl acetate result may be low since this is, as shown by both DSC and TGA, the least stable of the solvate hydrates.

The powder X-ray diffractograms for the four solvate hydrates are very similar, as expected given the close relationship between the structures, the small range of solvent molecular masses and the disorder. The diffractograms for the dioxane and IPA solvate hydrates are illustrated in Figure 9, displaying their very strong similarity (arising from their isomorphous natures), deviations in relative intensities being probably accounted for by some preferred orientation.

Solid-State NMR Spectra of the Solvates

The low-frequency part of the ^{13}C CPMAS spectra of five solvates are shown in Figure 10. The number of peaks observed clearly establishes that for each of the solvate hydrates the crystallographic asymmetric unit contains two molecules of finasteride, in agreement with the diffraction results, that is $Z' = 1$ for a bis(finasteride) monosolvate monohydrate, whereas for the acetic acid solvate a single molecule constitutes the asymmetric unit (as found previously[23]). In all cases, singlets are observed for the solvent molecules. The chemical shifts for finasteride in the solvates are given in Table 6 (we assume that the assignments for C3 and C20 are the same way round as for Form I) and those for the solvent molecules in Table 7. In each case, only one peak is observed for the three methyl carbons of each independent *tert*-butyl group, suggesting rapid internal rotation about the N–C bond, as noted by Wenslow et al.[22] and supported by the appearance of atomic displacement parameters from single-crystal

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Table 6. Carbon-13 Chemical Shifts (δ_C/ppm) for the Finasteride Solvates

Carbon Number	Dioxane Solvate Hydrate	IPA Solvate Hydrate[a]	THF Solvate Hydrate	Ethyl Acetate Solvate Hydrate	Acetic Acid Solvate
1	152.5/153.5	154.0[b]	153.5[b]	152.8/153.7	153.0[b]
2	122.1/122.7	122.0/122.6	122.1/122.8	122.3/122.87	120.9[b]
3[c]	168.6,169.0	169.4[b]	169.0[b]	168.8[b]	166.7
5	59.9/60.6	59.9/60.5	60.1/60.8	60.1[d]/60.8	60.4
6	27.0	27.1	27.2	27.1	25.6
7	29.9/31.3	30.0/31.5	30.3/31.5	30.3/31.5	30.3
8	34.9/35.7	35.1/35.8	35.2/35.9	35.1/35.9	35.0
9	49.1	48.8/49.2	49.1/49.4	49.3	48.6
10	40.0	40.3	40.3	40.3	40.0
11	21.4[b]	21.4	21.6	21.5/21.7	22.0
12	37.3/38.4	37.5/38.2	37.5/38.5	37.5/38.6	36.8
13	44.1	44.3	44.4	44.5	43.5
14	55.3/56.2	55.4/56.5	55.5/56.4	55.5/56.2	54.7
15	25.1/25.3	25.2/25.5	25.7[b]	25.3/25.7	25.2
16	22.0/22.6	22.1/22.7	22.3/22.9	22.3/23.0	22.6
17	56.9/58.2	56.5/58.0	56.7/58.1	57.0/58.2	56.3
18	13.2/13.6	13.7/13.4	13.4/13.9	13.5/13.9	12.8
19	12.1/12.3	12.4[e]	12.5[f]	12.3/12.5	12.4
20[c]	170.5	170.9	171.0	171.0	170.1
22	50.2/50.9	50.2/50.9	50.3/50.9	50.2/51.1	50.0
23, 24, 25	28.9/29.2	29.3/29.6	29.4/29.7	29.5	28.3

[a]Underlined chemical shifts correspond to the resonances assigned for two carbons.
[b]Broad peak.
[c]The assignments for C3 and C20 assume $\delta(C3) < \delta(C20)$ in all cases, as proved for Form I, but there is no proof for this statement.
[d]Overlapped by the CH_2 resonance of the ethyl acetate.
[e]Small splitting.
[f]Double intensity peak.

XRD. As expected, the finasteride peaks for the solvate hydrates are at closely similar chemical shifts, though there are some distinct differences—for example, the signal for C9 is clearly a doublet for the IPA and THF solvates whereas it is a singlet for the other two cases. In this respect, NMR is more informative than powder XRD for these samples. Moreover, peaks assigned to the solvent molecules are clearly seen and are at characteristic chemical shifts. The solvate hydrates can therefore be clearly distinguished and the fact that they are solvates established unequivocally by solid-state NMR. The presence of solvent molecules can be and has been confirmed by solution-state NMR (both ^{13}C and ^{1}H), which affords higher resolution than solid-state spectra.

Table 7. Carbon-13 NMR Chemical Shifts Corresponding to the Solvent Molecules in the Examined Finasteride Solvate Hydrates

Sample	Chemical Shift δ_C/ppm	Assignment
IPA solvate hydrate	26.2	CH_3
	63.8	CH
Dioxane solvate hydrate	67.5	CH_2
Acetic acid solvate	20.7	CH_3
	174.6	C=O
THF solvate hydrate	26.5	CH_2
	68.1	CH_2O
Ethyl acetate solvate hydrate	14.5	CH_3
	20.5	CH_3CO
	60.1	CH_2
	169.2	C=O

A direct polarization ^{13}C spectrum was obtained for the THF solvate (Fig. 11). This clearly reveals the signals for the solvent molecule and for methyl carbons in finasteride, showing the considerable mobility occurring in both cases. Other signals were basically absent, but those for the quaternary carbons (C10, C13, and C22) did appear—presumably because their ^{13}C spin-lattice relaxation times are reduced by proximity to the mobile methyl groups.

Proton spectra of the solvates have been obtained by rapid MAS. Figure 12 shows the case of the dioxane solvate hydrate. In each spectrum

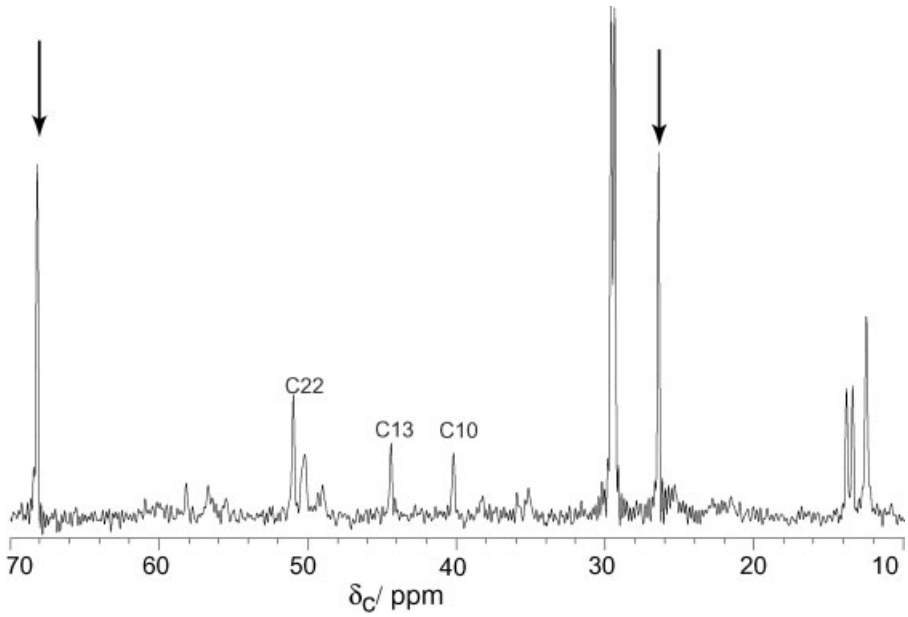

Figure 11. Carbon-13 direct-polarisation spectrum of finasteride THF solvate hydrate. The THF resonances are prominent (indicated by arrows), as are the CH_3 signals of finasteride. Quaternary finasteride peaks (assigned by their carbon numbers) also appear, though more weakly.

there is a relatively broad band for the finasteride protons. In addition, there are sharper peaks which can be assigned to the solvent molecules, which are thereby identified as relatively mobile. The shifts and linewidths of the solvent peaks are given in Table 8. The carboxylic OH of the acetic acid solvate hydrate is rather broad. The widths of the finasteride main band (given where this is unaffected by overlap with solvent peaks) are 730, 473, and 868 Hz at chemical shifts 1.0, 1.1, and 1.2 ppm for the dioxane solvate hydrate, the acetic acid solvate and Form II, respectively. In most cases (including that of the anhydrous acetic acid solvate) there is a broad shoulder at ca. $\delta_H = 8$ ppm which may arise from protons bonded to sp^2 carbons or to NH protons or (in the case of the hydrates) to water protons. However, neither resolved peaks assignable to water protons nor any signals at high frequency attributable to strong hydrogen bonding were seen. The acetic acid solvate showed a resonance at $\delta_H = -0.1$ ppm, presumably from the methyl protons. This represents a considerable change from the shift for a solution of acetic acid.

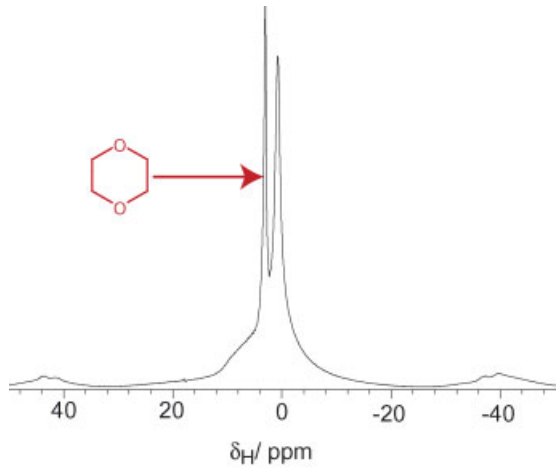

Figure 12. MAS proton spectrum of finasteride dioxane solvate hydrate.

Solution-state proton spectra were recorded in order to quantify the molecular proportions of solvate and water present. Table 9 gives the results. The data for the solvent: finasteride ratios lie in the narrow range 0.63–0.65, with the exception of that for the ethyl acetate case, where the value may be low because of prior loss of solvate, The water: finasteride ratios are more difficult to measure but are found to be between 0.43 and 0.67. It is difficult to estimate likely errors, but ±0.1 might be anticipated. Morzycki et al.[21] claimed that their dioxane solvate hydrate had a finasteride:dioxane ratio of 1:1 (on the basis

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Table 8. Proton NMR Chemical Shifts for the Solvent Resonances of Finasteride Solvate Hydrates[a]

Sample	Chemical Shift δ_H/ppm	Assignment	Linewidth at Half Height/Hz[b]
IPA solvate hydrate	1.4	CH_3	(279)
	3.4	CH	203
	4.2	OH	160
Dioxane solvate hydrate	3.2	CH_2	342
Acetic acid solvate	−0.1	CH_3	126
	13.3	OH	502
THF solvate hydrate	1.8	CH_2	(310)
	3.7	CH_2O	170
Ethyl acetate solvate hydrate	1.2	CH_3	(299)
	2.0	CH_3COO	110
	4.2	CH_2	204

[a]MAS rate 20 kHz/2.5 mm rotor for the first three cases; MAS rate 8.5 kHz/5 mm rotor for the next two.
[b]Values in brackets are for resonances overlapping the finasteride peak.
With a shoulder at ~1.2 ppm.

of ^{1}H solution-state NMR measurements), but we believe this to be unlikely. Our ^{1}H NMR results are consistent with observations based on TGA measurements (see Table 5) and suggest that some departures may occur from 2:1:1 stoichiometry, which is not totally unexpected (at least for the solvents) given the nature of the channels and the disorder of the guest molecules. However, the TGA weight losses expected on the basis of the NMR-derived molar ratios are generally closer to those observed, than to those calculated on the basis of 2:1:1 stoichiometry. For a channel structure with disordered guest molecules, gain and loss of solvent might be expected to be relatively easy. However, a variable-temperature ^{13}C NMR experiment on the dioxane solvate hydrate showed stability of the structure up to ca. 100°C, above which transformation to Form I° occurred. In this experiment, spectra were obtained at ten degree intervals from 50 to 110°C and then at 115 and 125 °C, with ca. 45 min spent at each temperature. It is evident that the solvate hydrate structure is stabilized by the water molecules such that the host structure is unstable in their absence (and the existence of such an anhydrous asolvate has not been proved to date). This is analogous to other cases where host structures are unstable in the absence of guest molecules (e.g. urea host-guest clathrates—see Ref. 41, page 23)

In order to investigate molecular mobility, preliminary proton spin-lattice relaxation measurements were made on the solvates and on Form II (anhydrous) under MAS conditions. The relaxation parameters (T_1) obtained are similar for the various solvates (1.38, 1.10, 1.15, 1.22, and 1.02 ms for the dioxane, IPA, THF, ethyl acetate, and acetic acid cases, respectively) and are within experimental error (±0.5 ms) the same for both solvent and "host." The value for anhydrous Form II is 0.92 ms, a little shorter than those for the solvated forms. These observations suggest that the relaxation is driven by reorientation of the methyl groups of the finasteride molecules rather than by solvent dynamics.

Table 9. Quantitative Analysis Results From Solution-State NMR Experiments

Solvate Hydrate	Chemical Shift, δ_H/ppm	Assignment	Molar Ratio Solvent:Finasteride	Chemical Shift, δ_H/ppm	Molar Ratio Water:Finasteride
Ethyl acetate	4.12	CH_2O	0.46	1.96	0.45[a]
IPA	4.04	CH	0.63	~1.91[a]	0.43
Dioxane	3.70	CH_2	0.65	1.96	0.54
THF	1.85	CH_2	0.64	1.95	0.67
	3.74	CH_2O	0.63		

[a]The signal includes an ethyl acetate CH_2 resonance. The result assumes the molar ratio in column 4.
Broad; the signal includes the IPA OH resonance. The result assumes the molar ratio in column 4.

CONCLUSIONS

We have shown that finasteride exists in at least four polymorphic forms, though two of them have not yet been fully characterised. Two new solvate hydrates have been obtained and their structures, along with that of the dioxane solvate hydrate, determined by single-crystal X-ray methods. The four known solvate hydrates are isomorphous, with the solvate molecules residing in channels but in disordered fashion. Solid-state NMR is able to distinguish these forms though powder XRD is not. Evidence of the mobility of the solvent guests is provided by several NMR observations. Figure 1 collates the relationships between the various forms of finasteride, as brought up to date by the present research.

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