Identification, Preparation, and Characterization of Several Polymorphs and Solvates of Terazosin Hydrochloride

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ABSTRACT: The phenomenon of polymorphism is prevalent in pharmaceuticals, yet it is unusual to identify more than three or four forms for any particular drug. Terazosin hydrochloride has been found to exist at room temperature in four solvent-free forms that can be isolated directly, one solvent-free form that can be prepared by desolvation of a methanolate, a methanol solvate, and a dihydrate. This study presents characterization and methods for preparation of each of these forms. Data are also presented demonstrating the relative stability of these forms. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 95:917–928, 2006

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INTRODUCTION

Terazosin monohydrochloride or 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(tetrahydro-2-furoyl) piperzinyl monohydrochloride was initially isolated as an anhydrous crystalline solid. Terazosin is a potent anti-hypertensive agent marketed as Hytrin.[1–6] During the development of a tablet formulation a dihydrate form of the drug was discovered. Terazosin hydrochloride was later shown to be effective in the treatment of benign prostate hyperplasia (BPH).[7,8] Although the bioavailability of the original Hytrin formulation was not dissolution dependent the formulation did show an initial peak in the pharmacokinetic profile. Reformulation was undertaken for this new indication, during which a second anhydrous polymorphic form of terazosin hydrochloride was identified.

Individual crystal forms or polymorphs can exhibit different physical properties reflective of the crystal lattice.[9–15] In order to assure ourselves that no crystal forms of terazosin existed that would adversely affect the bioavailability of Hytrin formulations an extensive polymorph investigation was undertaken

The number of stable forms that can exist at room temperature is often small. In this study, we will summarize the results of our studies performed on the solid-state forms of terazosin hydrochloride.[16–21] There are a large number of reasonably stable crystal forms that can exist at room temperature. The relative stability of these forms has been determined or estimated using the physical and spectroscopic rules derived by Burger and Ramberger.[22] The compound can also exist in the form of a solvate. In many cases where a compound forms a solvate and the solvent is removed, the crystal arrangement changes. However, in other instances, the crystal structure is not altered and an isomorphic solvent-free form results. This isomorphic desolvated solvate may or may not be an activated species, which, due to the

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voids created in the lattice, actively reabsorbs solvents or water.[23] Extensive investigation of terazosin hydrochloride indicates that the compound can exist in four solvent-free forms that can be prepared directly to two solvates; a dihydrate, a methanolate, and also an isomorphic solvent-free form can be prepared by desolvation of the methanolate. Other less characterized hydrates, referred to as monohydrate and polyhydrates can exist at relative humidity extremes. This study presents the spectral characterization of each of these stable forms, methods of preparation, and determination of relative stabilities. Structural information on several forms was obtained by using a combination of single crystal X-ray data and molecular modeling software.[24–35]

MATERIALS AND METHODS

Reagents

Terazosin monohydrochloride was synthesized at Abbott Laboratories, North Chicago, IL.

Infrared Spectroscopy

Near infrared (NIR) spectra of solid terazosin were generated using either a Nicolet model 750 Magna-IR™ spectrometer with a CaF_2 beam splitter, and with a Nicolet SabIR near-infrared (NIR) diffuse reflectance fiber optic probe accessory equipped with a PbS detector or a Nicolet Model Avatar 360 N spectrometer with CaF_2 beam splitter, an InGaAs detector and UpDrift diffuse reflectance sample accessory. Either 16 or 64 scans were run using a resolution of 8/cm over a range of 1.0–2.4 μm with the Model 750 Magna-IR spectrometer. All spectra obtained with the Avatar 360 N spectrometer were acquired at a resolution of 4/cm with 256 scans. Mid-infrared spectra of solid terazosin were also acquired using a Nicolet model 750 Magna-IR spectrometer with a DTGS detector and 16 scans at a resolution of 4/cm. The spectrum was collected from 4000 to 400/cm. Solution mid-infrared spectra were obtained as a thin film on a KBr disc using a Nicolet Magna 750.

X-Ray Diffraction

X-ray powder diffraction patterns were obtained using a Nicolet I-1 X-ray powder diffractometer using Cu Kα ($\lambda = 1.54178$ angstroms) radiation and a scan rate of 2° per min. Samples were ground to a fine powder with a mortar and pestle.

Solid State Nuclear Magnetic Resonance (NMR)

Solid-state ^{13}C NMR spectra were obtained on a Bruker AMX-400 instrument operating at a carbon frequency of 100.6 MHz. The ^{13}C spectra were collected using a Variable Amplitude Cross-Polarization Magic-Angle Spinning pulse sequence (VA-P2LEV) in 7-mm sample rotors, which were spun at a 7 kHz spin rate. The Hartmann-Hahn matching condition for the VA-Cp2LEV pulse sequence was calibrated using an external sample of hexamethylbenzene (HMB). The ^{13}C spectra were collected using 3000 scans, with a contact time of 2.5 ms and a recycle delay time of 5 s. The carbon chemical shifts were measured relative to an external HMB sample, using the methyl resonance at 17.3 ppm as the reference signal Solution proton NMR was performed in d6-DMSO using an AMX Bruker 400 MHz instrument.

Thermal Analysis

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) were performed using a Thermal Analysis (TA) Instruments controller Model 5100 in conjunction with a model 2910 DSC module and a model 2950 Hi-Res TGA module. DSC data were obtained in a closed uncrimped aluminum pan using a sample weight of about 10 mg and a heating rate of 5°C per min and a nitrogen flow of 40 mL/min. TGA data were collected using a sample weight of about 15 mg, heating rate of 5°C per min and a nitrogen flow of about 40 mL/min.

Solubility Studies (Saturation Point)

Solubility studies were performed by slowly adding portions of the appropriate crystal form to approximately 100 mL of solvent and stirring at controlled temperature (5°C or 25°C) in a temperature controlled room, until complete dissolution by visual inspection. Portions of the solid were added until residual undissolved solid remained. Stirring was continued and periodically aliquots were taken and filtered. The supernatants were analyzed by HPLC versus an

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external standard using a C18 column and detection at 254 nm until a saturation concentration plateau was reached.

Dynamic Moisture Sorption Gravimetry

Hygroscopicity studies were performed using a VTI Corporation Model MB 300 G Dynamic-Moisture Sorption Gravimetric Analyzer-Integrated Microbalance System without drying cycle. Sample weights between 20 and 30 mg were used with a critical equilibrium weight of 3 mcg and a controlled temperature of 25°C.

Microscopy

Melting points were determined by hot stage microscopy performed at 5°C/min using a Nikon Micropbot FXA polarized microscope in conjunction with a Mettler Model FP82HT Hot Stage cell and Mettler FP80 central controller.

Molecular Modeling

Molecular modeling studies were performed with the Cerius2 software package running on Hewlett Packard Apollo 700 model 735-99 workstations. The Polymorph Predictor methodology was used for the generation of crystal packing alternatives.[23,24] Energy calculations were performed using the Dreiding 2.21 force field[25] with Ewald summation of the electrostatic interactions. Atomic charges were fitted to the electrostatic potential calculated by the MOPAC program with the MNDO approximation. The DBWS program was used for Rietveld refinement of the simulated structures against experimental powder diffraction data.[26,27]

Preparation of Various Forms of Terazosin Monohydrochloride

Preparation of Terazosin Monohydrochloride Form I

To 700 g of 2-chloro-4-amino-6,7-dimethoxyquinazoline[3] in 50 mL methoxyethanol was added 10.8 g tetrahydrofuroyl piperazine, and the mixture was refluxed 3 h. The clear solution was concentrated and an aqueous solution of potassium bicarbonate was added. The resultant solid that formed was filtered and washed with water. It was then added to methanol and the resulting suspension was acidified with a solution of hydrogen chloride in isopropyl alcohol. The resulting solution was concentrated and the residue crystallized from isopropyl alcohol giving 8.12 g of terazosin monohydrochloride form I.

Preparation of Terazosin Monohydrochloride Form II

Terazosin monohydrochloride dihydrate (620 mg, 1.35 mmol) was dissolved in 100 mL of hot absolute ethanol in a 250-mL Erlenmeyer flask. The solution was slowly cooled to room temperature and allowed to stand overnight. The resulting white crystalline precipitate was collected by vacuum filtration to yield 100 mg of terazosin monohydrochloride form II.

Preparation of Terazosin Monohydrochloride Form III

A 1 g sample of terazosin monohydrochloride dihydrate was dissolved in 15 mL of distilled water and lyophilized. The dry solid was determined to be amorphous by X-ray powder diffraction. Six hundred forty three milligrams of the this amorphous solid was added to 25 mL of hot (just below reflux) ethanol. After initial dissolution a solid quickly precipitated. The solid was collected by vacuum filtration and air-dried. Approximately 265 mg of terazosin monohydrochloride form III was isolated.

Preparation of Terazosin Monohydrochloride Form IV

Sixty grams (0.25 mole) of 4-amino-2-chloro-6,7-dimethoxyquinazoline and 56.8 g (0.308 mole) of N-(2-tetrahydrofuroyl)piperazine were added to a stirred solution of 500 g Methyl Cellosolve® (ethylene glycol monomethyl ether) and 37.9 g triethylamine. The reaction mixture was heated and maintained at a temperature of between 115°C and 120°C for 8 h, and then allowed to cool to room temperature overnight. The Methyl Cellosolve® was removed by vacuum distillation, the residue was taken up in 1920 mL of 45°C distilled water, and the temperature of the solution was readjusted to 45°C. The pH was then adjusted to pH 2.5 with concentrated hydrochloric acid and the solution mixed for 1 h. The solution was then filtered and the pH adjusted to pH 8.3 with filtered ammonia water (28%). After heating for 1 h at 65°C, the solution was cooled to 15°C and held

at a temperature of between 15°C and 20°C for 16 h. The resulting crystalline product was filtered, washed with cold water (15°C), and dried in vacuo at 65°C to yield 84 g of terazosin monohydrochloride form IV.

Preparation of Terazosin Monohydrochloride Dihydrate

The hydrochloride salt of the dihydrate of the compound was prepared by slurrying 10 g of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(tetrahydro-2-furoyl)-piperazine in 150 mL of 190 proof Formula 3A alcohol, heating the slurry to about 35°C, adding 2.5 mL of concentrated (aqueous) hydrochloric acid thereto, and heating the mixture to about 70°C. The reaction mixture was carbon treated, the carbon was filtered off and the filtrate was cooled overnight at approximately 5°C. The product was then filtered off and dried at 60°C to obtain 10 g of terazosin monohydrochloride dihydrate. The product was shown to contain two moles of water by TGA and Karl Fischer analysis.

Preparation of Terazosin Monohydrochloride Methanolate

A saturated solution of hydrogen chloride in isopropyl alcohol was added dropwise to a suspension of 1.18 g (3.1 mmol) of 1-(4-amino-6, 7-dimethoxy-2-quinazolinyl)-4-(tetrahydro-2-furoyl)-piperazine in 100 mL of dry methanol until the suspended solids had completely dissolved. The solvent was then removed under vacuum to yield 1.32 g (2.9 mmol, 93.4%) of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(tetrahydro-2-furoyl)piperazine monohydrochloride methanolate. The presence of methanol was demonstrated by TGA and GC analysis. DSC data indicates that the methanol is lost at approximately 107°C indicating that the methanol is present as a solvate

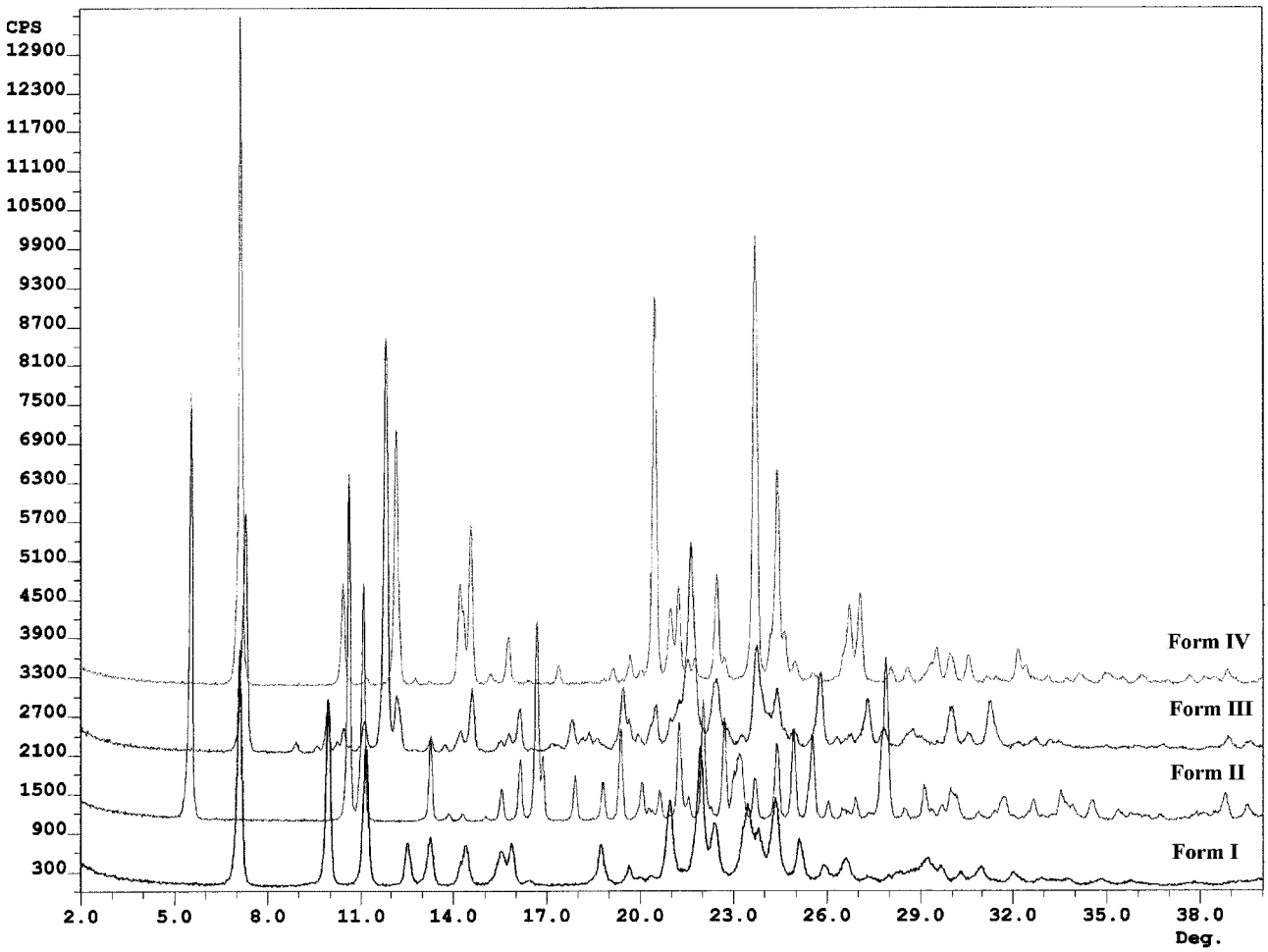

Figure 1. Powder X-ray diffraction patterns for four terazosin solvent-free polymorphs.

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Preparation of Various Crystal Forms of Terazosin Monohydrochloride via the Methanolate

Preparation of Isomorphic Methanolate Desolvate

The solvent was slowly removed from 1 g of terazosin monohydrochloride methanolate by warming at 37°C under vacuum (approx 127 Torr) for 24 h. The remaining solid was solvent free but exhibited the identical X-ray diffraction pattern of terazosin monohydrochloride methanolate.

Preparation of Form I from Methanolate

Terazosin monohydrochloride methanolate (1.06 g, 2.3 mmol) was dissolved in approximately 10 mL of hot absolute ethanol in a 250-mL Erlenmeyer flask. The solution was slowly cooled to ambient temperature and allowed to stand undisturbed overnight. The precipitated solids were collected by vacuum filtration on a Buchner funnel and washed with dry acetone to yield 0.76 g (1.8 mmol, 77.9%) of terazosin monohydrochloride, which was shown by its powder X-ray diffraction pattern to conform to the nonsolvated form I crystalline polymorph.

Preparation of Form II from Methanolate

To a 100-mL round-bottom flask containing 0.760 g (1.7 mmol) of terazosin monohydrochloride methanolate was added 25 mL of absolute ethanol. The flask was fitted with a reflux condenser and the slurry was heated under reflux for approximately 24 h. The mixture was cooled and the precipitated solids collected to yield 0.390 g (0.92 mmol, 54.1%) of terazosin monohydrochloride, which was shown by its powder X-ray diffraction pattern to conform to the nonsolvated form II crystalline polymorph.

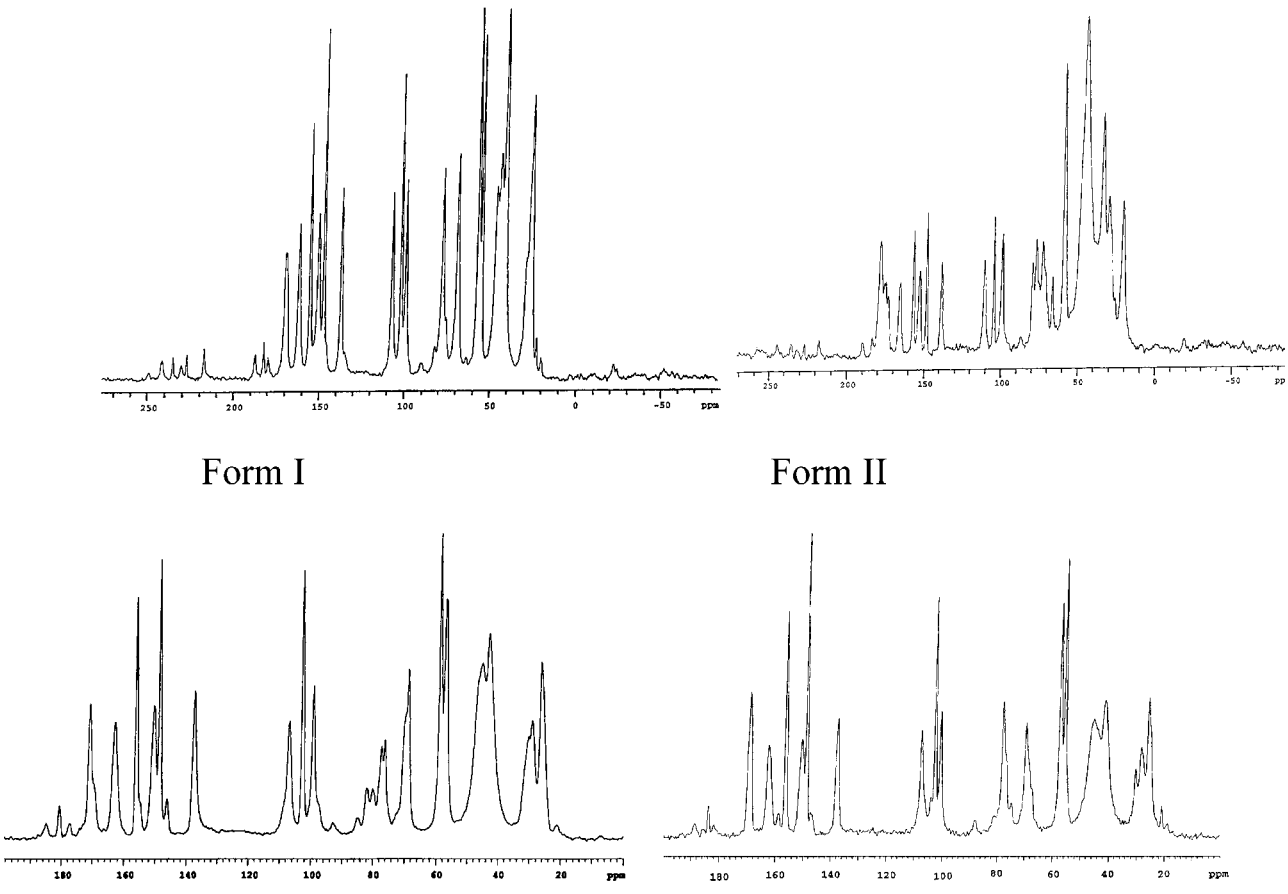

Figure 2. Solid state C13 NMR spectra for four terazosin solvent-free polymorphs.

Preparation of Form III from Methanolate

To a 250-mL round-bottom flask containing 1-(4-amino-6,7-dimethoxy-2-quinazoliny)-4-(tetrahydro-2-furoyl)-piperazine monohydrocyhloride methanolate (2.1 g, 4.6 mmol) was added 50 mL of dry acetone. The resulting slurry was stirred and heated at 50°C for 10 min. Following this treatment, the solution was cooled in an ice bath for 30 min after which the precipitated solid was collected by filtration to yield 1.9 g (4.5 mmol, 97.4%) of terazosin monohydrochloride, which was shown by its powder X-ray diffraction pattern to conform to the nonsolvated form III crystalline polymorph.

Preparation of Dihydrate from Methanolate

Terazosin monohydrochloride methanolate (3.7 g, 8.1 mmol) was added to a 125-mL Erlenmeyer flask and 30 mL of distilled water was added. The resulting mixture was warmed for 10 min during which time the solids did not completely dissolve. The slurry was stirred overnight and the solids collected by filtration and allowed to air-dry for 30 min. The product (1.7 g, 3.7 mmol, 46% yield) was found by its powder X-ray diffraction pattern to conform to terazosin monohydrochloride dihydrate.

RESULTS AND DISCUSSION

Four solvent-free polymorphs of terazosin monohydrochloride have been prepared by unique routes involving variations in solvent and crystallization temperature. Each of the polymorphs has been characterized by powder X-ray diffraction (Fig. 1 and Tab. 3) and ^{13}C solid- state NMR (Fig. 2 and Tab. 4), which also confirmed the identity of each form as terazosin monohydro-

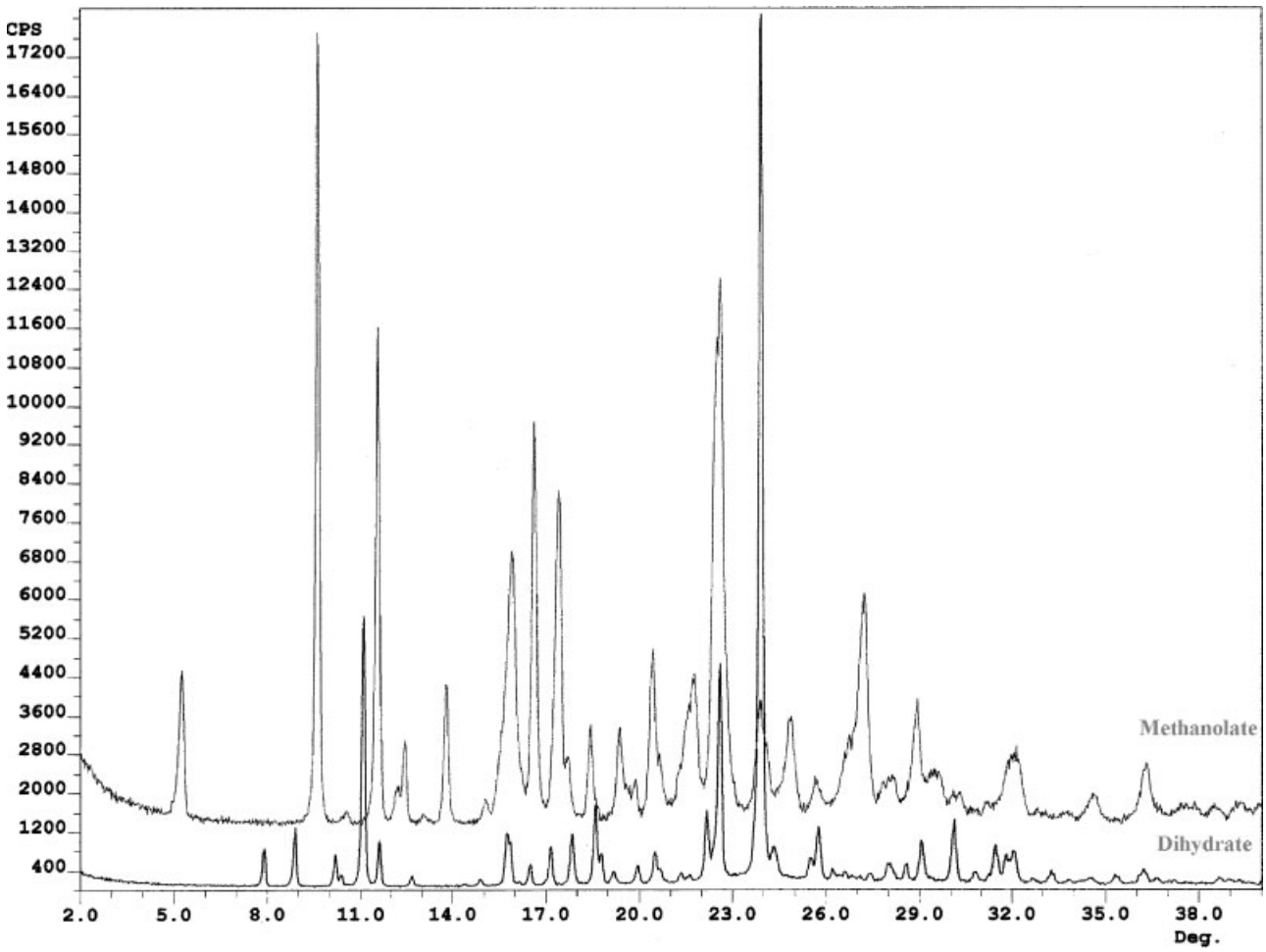

Figure 3. Powder X-ray diffraction patterns for terazosin dihydrate and terazosin methanolate.

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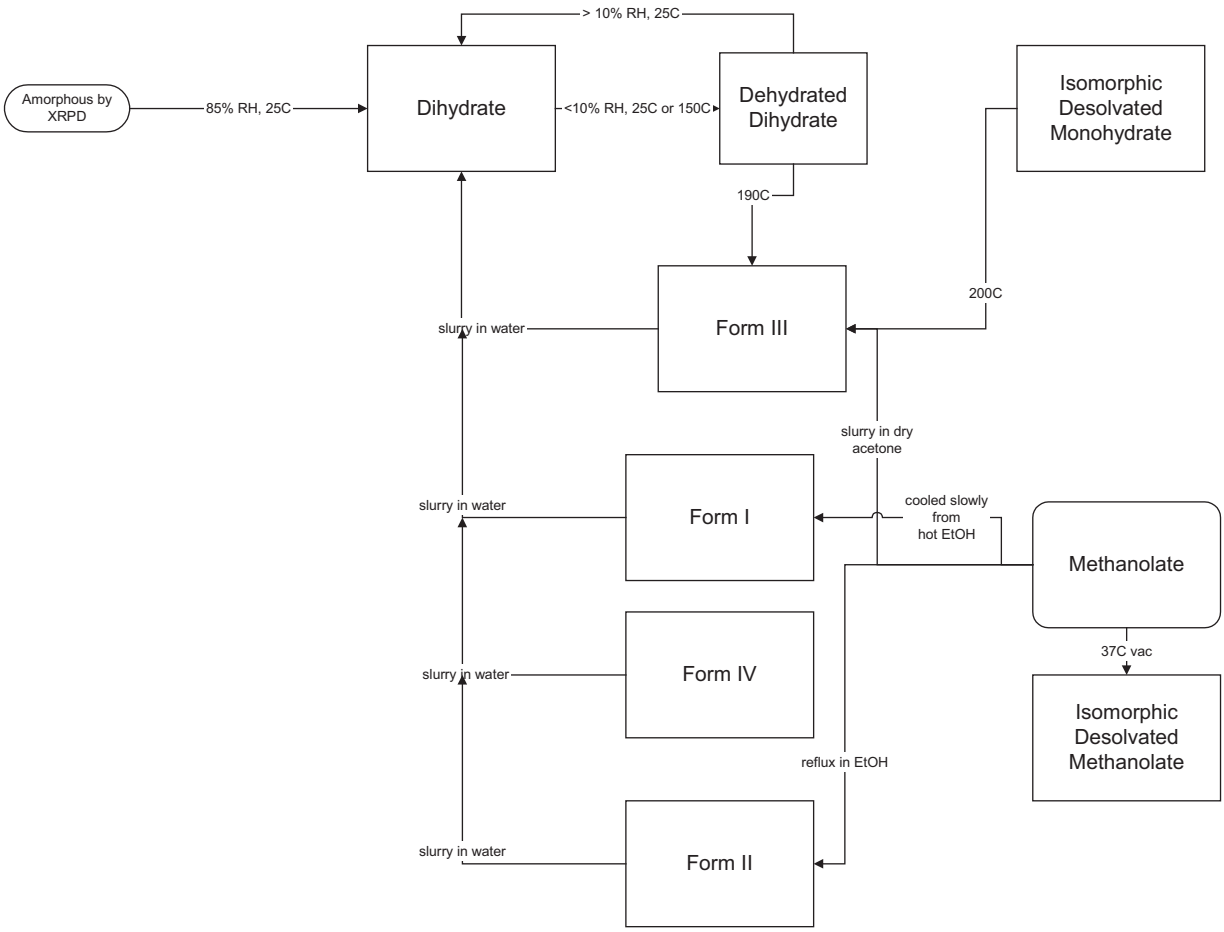
chloride. Further characterization was performed using near-infrared and mid-infrared spectroscopy, differential scanning calorimetry and hot stage microscopy. When terazosin monohydrochloride is crystallized from aqueous media, a stable stoichiometric dihydrate is produced. Upon desolvation of solid terazosin monohydrochloride dihydrate by heating (60°C, 3 h) the crystal structure is destroyed and amorphous terazosin monohydrochloride is formed. Crystallization of terazosin monohydrochloride from methanol produces a methanolate, which can be isolated and used to prepare several of the crystal forms of terazosin. Desolvation of the methanolate by storage at 37°C for several hours in vacuum produces a stable desolvated solvate, which is isomorphic with the methanolate. X-ray diffraction patterns of the solvates are shown in Figure 3 and characteristic two theta positions are listed in Table 3. The pattern of the methanolate desolvate matches that of the methanolate. As shown in Scheme I the methanolate can be converted to forms I, II, III, dihydrate, and methanolate desolvate by variations in solvent and temperature of crystallization. The anhydrous forms of terazosin monohydrochloride are very soluble in water in the range of 500 mg/mL, however, as would be expected they equilibrate to the solubility of the dihydrate (29 mg/mL). Aqueous solubility data could not be directly compared to estimate relative stabilities of these forms, Although the solubility of the various forms eventually equilibrated at that of the dihydrate the rate of equilibration to dihydrate solubility was slower for form II than forms I, III, and IV.

In so far as the rate of conversion to dihydrate in a saturated solution of each polymorph is indicative of the difference in free energy between that form and the solvated state and, therefore, the solubility, the slower rate of conversion for form II would imply that it is the most stable anhydrous form. In order to more directly determine the most stable anhydrous form, equal amounts of forms I, II, III, IV, and desolvated methanolate were



Scheme I. Terazosin HCl solid state phase transitions observed.

Table 1. Differential Scanning Calorimetry Data for Terazosin Crystal Forms

Crystal Form	Form I	Form II	Form III	Form IV	Methanolate	Dihydrate
Endotherms[a]	267.3°C	271.0°C	268.5°C	270.4°C	71.9, 107.0°C	80.6, 153.7°C
Exotherms[a]	216.8 J/g	244.4 J/g	231.3 J/g	232.5 J/g	192.4°C	198.2°C
Melting endotherm[a]					264.1°C	259.4°C
Enthalpy of fusion [b]					199.1 J/g	191.2 J/g

[a]Onset values.s
[b]DSC calibrated with indium.

suspended in methylene chloride. After stirring at room temperature for 7 days, the solid residue was completely converted to form II confirming that it is the most stable nonsolvated form. As would be expected when this experiment was repeated in either methanol or water, the methanolate and dihydrate were the predominant forms, respectively. The relative thermodynamic stability of the forms is reflected in the DSC data shown in Table 1. These DSC data indicate that the polymorphs I, II, III, and IV are monotropic and the melting temperatures and enthalpy of fusion values would support a relative order of stability of II > IV > III > I. Both the methanolate and the dehydrate show desolvation endotherms and an exothermic transition to Form III between 190°C and 200°C. Second derivative measurements indicated transitions during melting for all forms except form II.

Investigation of the hygroscopicity of forms I, II, III, and IV was performed by dynamic moisture sorption gravimetry (DMSG). The results are shown in Figure 4 and demonstrate a similar order of stability with form II, which is nonhygroscopic from 0% to 95% relative humidity followed by form IV, which is converted to a polyhydrate at 85% RH and forms III and I, which convert at approximately 80% RH.

Crystal Structure Determination of Methanolate, Dihydrate, and Anhydrous Forms I and IV by Single Crystal X-Ray Diffraction

Single crystals were successfully grown for several forms of terazosin. Single crystal X-ray data were obtained for terazosin dihydrate, terazosin methanolate, and anhydrous forms I and IV. Cell parameters obtained from these data are presented in Table 2.

Crystal Structure Determination of Anhydrous Forms II and III from Powder X-Ray Diffraction Data Using Molecular Modeling

The crystal structures of the nonsolvated forms II and III could not be determined directly from their X-ray powder diffraction data because that data was of insufficient quality. However, the X-ray powder diffraction pattern of form II could be indexed, indicating space group P-1 and a density

Table 2. Cell Parameters of Terazosin Crystal Forms

Form	a	b	c	
I[a]	12.01(1)	14.100(4)	25.923(8)	
II[b]	9.4482	18.1259	7.1675	
III[b]	13.6422	9.2578	9.2579	
IV[a]	9.25(1)	24.729(3)	14.460(2)	
Methanolate[a]	34.69(3)	9.528(1)	13.522(3)	
Dihydrate[a]	10.871(1)	11.786(2)	10.030(2)	
Form	Alpha	Beta	Gamma	Space group
I[a]	90	102.71(4)	90	C2/c
II[b]	112.101	64.123	84.52	P-1
III[b]	85.827	63.209	85.957	P-1
IV[a]	90	38.59	90	P21/c
Methanolate[a]	90	90	90	Pbcn
Dihydrate[a]	108.33(1)	113.33(1)	89.95(1)	P-1

[a]Obtained from single crystal data.
[b]From structure modeling software.

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Table 3. Characteristic X-Ray Peaks (2 Theta) for the Various Crystal Forms of Terazosin

Form I	Form II	Form III	Form IV	Dihydrate	Methanolate
7.27	5.5	7.29	7.15	8.91	5.09
10.08	10.6	11.81	10.44	11.1	9.63
11.3	11.1	14.59	14.56	11.62	11.64
21.06	16.7	19.43	20.48	15.72	15.32
22.08	19.4	20.4	21.23	17.14	16.63
23.55	21.3	21.61	22.47	17.83	21.25
23.56	22	22.36	23.7	18.56	22.24
24.43	22.7	23.69	24.43	22.16	22.28
29.27	23.1	24.34	27.11	22.58	26.62
	24.4	24.8		23.88	28.93
	24.9	25.75		25.74	
	25.5	27.29		29.06	
	27.8	29.96		30.11	
		31.2		31.42	

of 1.45 g/cm^3. The X-ray powder diffraction pattern of form III could not be indexed. Since terazosin hydrochloride is produced as a racemate, only centro-symmetric space groups such as P21/c, P-1, Pbcn and C2/c needed to be considered in the search for crystal packing alternatives.

Table 4. Characteristic C13 ssNMR Peaks (ppm) for the Various Crystal Forms of Terazosin

Form I	Form II	Form III	Form IV
170.64	186.28	185.22	183.88
162.66	180.35	180.76	169.34
156.29	173.18	177.42	162.59
151.54	171.71	170.85	158.81
148.42	163.93	162.92	156.22
138.23	154.99	156.15	150.53
108.12	151.05	150.55	148.81
103.00	146.31	148.65	137.63
100.19	136.83	146.35	107.54
78.74	109.04	137.60	102.58
70.08	102.86	106.99	100.64
58.11	97.54	102.71	78.12
56.11	86.47	99.37	69.82
47.38	77.74	92.99	57.55
45.07	75.44	84.60	55.88
42.37	70.98	81.86	45.59
26.68	69.33	80.05	41.84
	57.39	77.28	30.65
	43.64	76.29	28.67
	32.26	68.93	26.12
	28.37	58.89	21.27
	20.94	57.22	
		45.51	
		43.22	
		29.38	
		26.56	
		21.38	

Analysis of the known crystal structures of the methanolate, dihydrate, and anhydrous forms I and IV showed that the terazosin molecule adopts a similar conformation in three of the four structures (the exception being the dihydrate). The protonation site, and thus the spatial orientation of the chlorine anion with respect to the organic cation, is the same in all four structures.

MNDO electrostatic potential fitted charges were calculated for the salt complex. Lattice energy minimizations were performed on the four known crystal structures to validate the Dreiding force field for this compound. It appeared necessary to modify the force field to adequately reproduce the geometries of the four known crystal structures. The charge on the chlorine anion was scaled down to -0.8 to give a fair representation of polarization effects. The overall charge on the organic cation was scaled down to $+0.8$. The van der Waals radius of the chlorine ion was increased from the default 3.95–4.10 Å. It has to be noted here that the resulting force field was by no means accurate enough to reliably predict crystal structures of terazosin hydrochloride from first principles. Nevertheless, the modified force field was good enough for the generation of crystal packing alternatives, which could be used in conjunction with experimental powder X-ray diffraction data to identify and solve the observed crystal structures.

Using the known conformation of the salt complex from anhydrous form IV as a starting point, the polymorph predictor methodology was used to

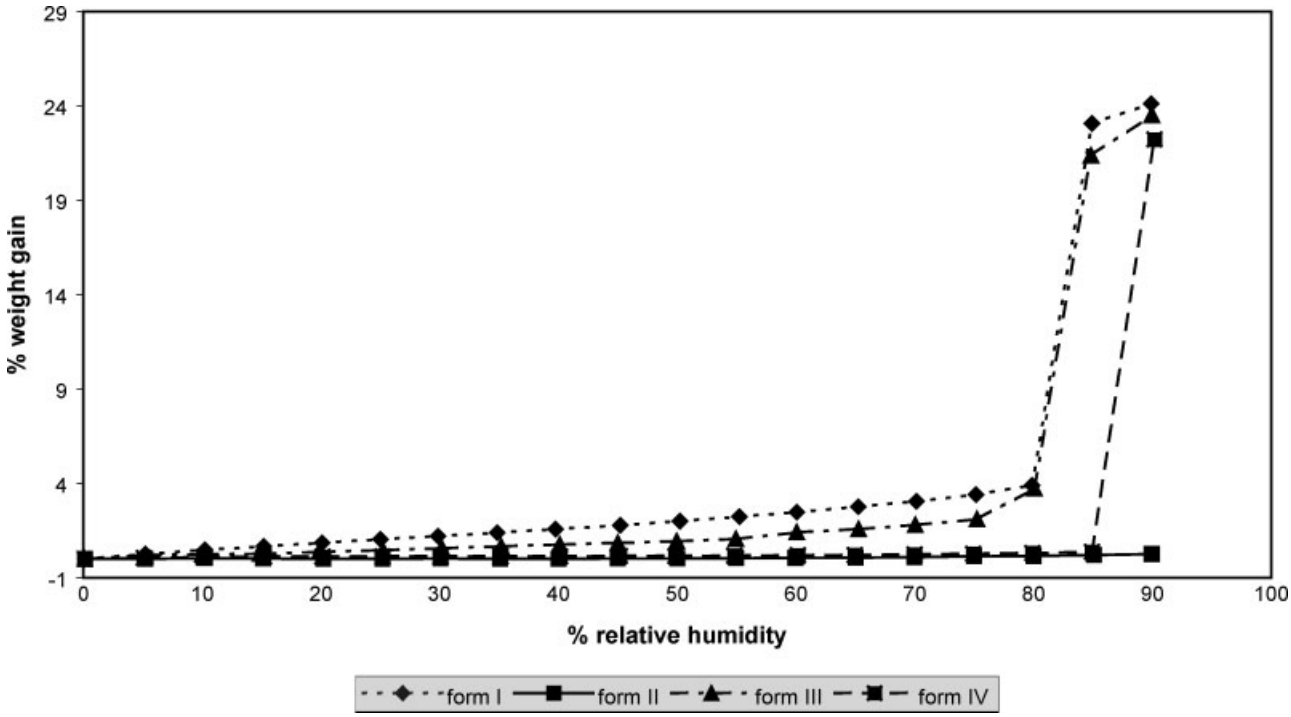

Figure 4. Dynamic moisture sorption gravimetry scans of four terazosin solvent-free polymorphs.

generate a comprehensive set of crystal packing alternatives in the P-1 space group. Searches in the P21/c, Pbcn and C2/c space groups were also started but were interrupted when it emerged that the X-ray powder diffraction patterns simulated for two of the crystal structures generated in the P-1 search matched the experimental X-ray powder diffraction patterns of forms II and III.

The simulated powder X-ray diffraction pattern of one of the predicted low-energy crystal structures showed a good agreement with the experimental powder pattern of form II in the low 2Theta range, indicating that the unit cell dimensions and general crystal packing motif were predicted correctly. There was, however, considerable disagreement in the higher 2Theta range, suggesting that the molecule adopts a different conformation in this polymorph. The disagreement was too large to allow for Rietveld refinement. Therefore, the molecular conformation was changed, while maintaining the predicted lattice parameters, in order to trial other low-energy conformations. The simulated X-ray powder diffraction pattern of one of these crystal structures showed a good overall fit with the experimental powder pattern. Rietveld refinement was performed to a R-factor of 30.8%, and a density of 1.45 g/cm^3. Considering the low quality of the experimental data, this R-factor is acceptable. The unit cell dimensions and density are in excellent agreement with the powder indexing results.

Form II of terazosin hydrochloride has a high density in comparison to the other crystal structures of this compound. A higher density usually means that a polymorph is more stable, which is indeed the case here. Molecular mechanics energy calculations, using exactly the same force field as used in the search for crystal packing alternatives, showed that the conformational energy of the compound in form II is considerably higher than the conformational energy of the compound in the other crystal structures. The less favorable intramolecular (conformational) energy in form II is more than compensated for by the more favorable inter-molecular energy due to the denser crystal packing.

Crystal Structure of Form III

The simulated powder X-ray diffraction pattern of one of the predicted low-energy crystal structures showed a good overall fit with the experimental powder pattern of form III. Rietveld refinement was performed in the P-1 space group, leading to a R-factor of 28.3%. Considering the low quality of the experimental data, this R-factor is acceptable.

The hydrogen bonding network observed in this crystal structure is consistent with the patterns found in the terazosin hydrochloride crystal structures, which were determined by single crystal X-ray diffraction techniques. There is a small amount of empty space in the crystal in the vicinity of the furane moieties, which is also consistent with the observation that these moieties are disordered in all the known crystal structures of terazosin hydrochloride. In order to simulate this disorder, the P-1 crystal structure of form III was transformed into a P1 crystal structure and the lattice energy reminimized to allow the furanes to move independently. A final Rietveld refinement was performed to a R-factor of 26.9% and a density of 1.35 g/cm^3, which is consistent with the terazosin hydrochloride crystal structures determined by single crystal X-ray diffraction techniques.

The cell parameters for the individual crystal forms of terazosin are shown in Table 2

CONCLUSION

Terazosin monohydrochloride was shown to exist in seven different crystal forms. A dihydrate, methanolate, desolvated methanolate and four solvent-free polymorphs have been characterized. (Scheme I). In aqueous conditions the dihydrate predominates, while form II has been demonstrated to be the most stable solvent-free form.

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