Research Article

Vapor-Induced Phase Transformations in Docetaxel

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Abstract. Vapor-induced transformations of docetaxel anhydrous (form D_A) under ambient conditions have been studied using methanol, ethanol, and water as the solvent media. The online vapor-induced transformations were monitored by powder X-ray diffractometry. New solid forms (solvates/hydrates/anhydrous) of docetaxel anhydrous were obtained in stoichiometric ratios which were characterized completely using powder X-ray diffraction, differential scanning calorimeter, thermogravimetric analysis, and spectroscopic (^{13}C solid-state nuclear magnetic spectroscopy, solution ^1H NMR, and Fourier transform infrared) techniques. The new forms namely methanol solvate (D_M), ethanol solvate (D_E), monohydrate (D_{MH}), trihydrate (D_{TH}), and anhydrous (D_{AN-I} and D_{AN-II}) were identified through structural analysis.

KEY WORDS: docetaxel anhydrous; FT-IR spectroscopy; nuclear magnetic spectroscopy; p-XRD; thermal analysis; vapor-induced transformations.

INTRODUCTION

Polymorphic screening of active ingredients has attracted much recent attention in the pharmaceutical and agrochemical industry. Due to its increasing importance, both innovator and generic pharmaceutical companies are actively pursuing the polymorphic screening of drug substances. Polymorphic changes can significantly alter the physicochemical properties such as solubility, dissolution rate, flowability, compressibility, stability, and also the bioavailability (1) of the compounds. Solid-phase transitions may occur during various processing steps involved in the preparation of active pharmaceutical ingredient (APIs; for example purification, crystallization, extraction, *etc.*), during formulation (*i.e.*, milling, granulation, drying and compaction) and also upon storage. These transitions occur depending upon the thermodynamic and kinetic stability of the forms. In recent years, there has been an increased regulatory interest to characterize and to control the physical form of active pharmaceutical ingredients in dosage forms (2). Polymorphs of a compound may be prepared by various methods (3). The classical methods include sublimation (4), crystallization from a single solvent (5), evaporation of a binary mixture of solvents (6), vapor diffusion (7), thermal treatment (8), crystallization from the melt (9), desolvation of crystalline solvents (10), anti-solvent addition, grinding (11), and vapor-induced transformations (12). In addition to polymorphs, hydrates, solvates, salts,

and co-crystals are other various solid forms of an API, which are frequently explored for drug development.

In the pharmaceutical sciences, the effect of vapor-induced transformations on drug substances and drug products has been investigated extensively in relation to solvation and desolvation phenomena because such transformations can often affect the physical properties and bioavailability of drugs (13,14). Vapor-induced transformation has been exploited to accelerated reaction in the solid state (15). Another important aspect of exposure of a solid material to solvent vapors is to understand whether any changes of crystal structure occur, as structure clearly has an important bearing on the physical, chemical, and biological properties of the material. Studies concerning polymorphic phase transformations of active ingredients under different experimental and storage conditions are of particular interest, since they provide fundamental information to establish the suitable conditions at which the desired polymorphs are most stable.

Docetaxel [1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl-4-acetate-2-benzoate-13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-3-phenyl propanoate}; Scheme 1] is an antineoplastic agent belonging to the taxoid family. Docetaxel is a semisynthetic analogue of paclitaxel [taxol, an extract from the Pacific yew tree (*Taxus brevifolia*)] and exhibits pharmacological properties superior to those of taxol in the treatment of locally advanced or metastatic breast and ovarian and non-small cell lung cancers. It is available in the market as trihydrate under the name Taxotere by Sanofi-Aventis U.S. LLC. Previously, the preparation and solid-state characterization of docetaxel solvates have been investigated and reported (16). In this study, docetaxel anhydrous (D_A) was crystallized in equimolar ratios with *n*-butanol, dimethyl-formamide, and acetonitrile to obtain corresponding solvates.

The objective of this research was to obtain a phenomenological study of vapor-induced transformations of docetaxel

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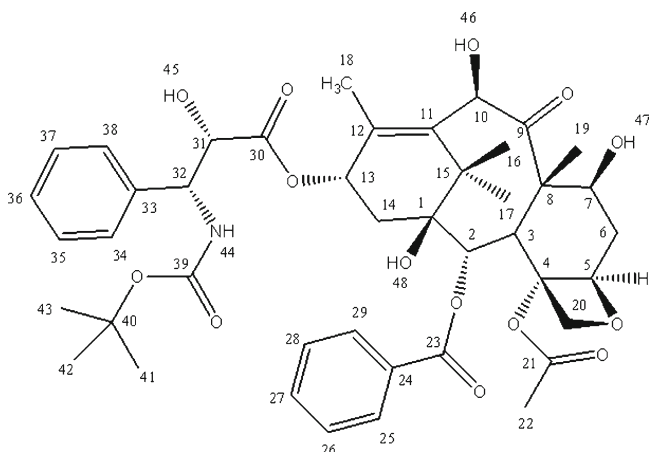
Scheme 1. Structure of docetaxel anhydrous with carbon numbering

Scheme 2. Summary of results of experiments involving exposure of docetaxel anhydrous to solvent vapor

anhydrous. The specific objectives include the importance of phase transformations in the presence of solvent vapor and solid-state characterization of the solid forms obtained after solvation, desolvation, and hydration under a variety of conditions by using powder X-ray diffraction (p-XRD), differential scanning calorimeter (DSC), thermogravimetric analysis (TGA), and spectroscopic techniques [^{13}C solid-state nuclear magnetic spectroscopy (^{13}C SSNMR), ^{1}H NMR, and Fourier transform infrared (FT-IR)] as the main characterization tools.
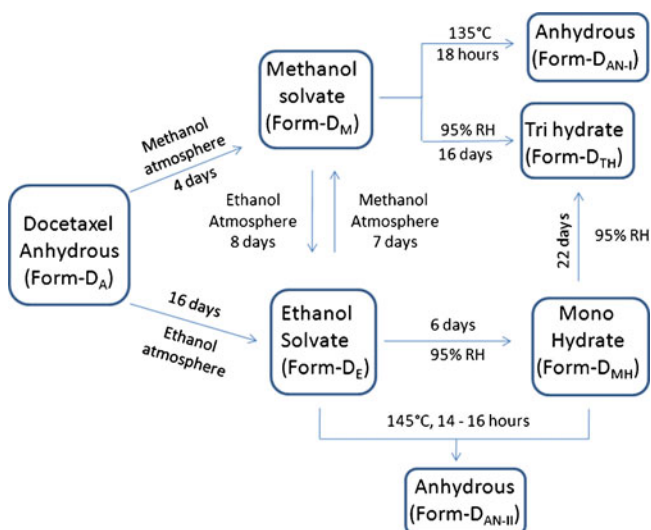
MATERIALS AND METHODS

Materials

Docetaxel anhydrous (m/z 807, $C_{43}H_{53}NO_{14}$) and docetaxel trihydrate (m/z 861, $C_{43}H_{59}NO_{17}$) were synthesized at Aptuit Laurus Private Limited (Hyderabad, India). Methanol and ethanol (HPLC grade) were procured from Merck chemicals (Bangalore, India). Lead nitrate (AR grade) was procured from Loba Chemie Pvt. Ltd. (Mumbai, India).

Preparation of Docetaxel Solid Forms

D_A was transformed to methanol solvate (D_M) and ethanol solvate (D_E) on exposure to vapors of methanol (4 days) and ethanol (16 days), respectively. The form D_{AN-I} was obtained with D_M kept at 135°C in a vacuum oven for about 18 h. On exposure to water vapor (95 % RH), a transformation of D_E to monohydrate (D_{MH}) is observed in approximately 6 days. On prolonged exposure to water vapor (95 % RH), D_M and D_{MH} transform to trihydrate (D_{TH}). The form D_{AN-II} was obtained with D_E, and D_{MH} was kept at 145°C in a vacuum oven for about 14–16 h. Besides, form D_M and form D_E are interconvertible and the transformations are summarized in Scheme 2.

Powder X-ray Diffractometry

The p-XRD patterns were obtained using a Rigaku Mini-Flex powder diffraction system, equipped with a horizontal goniometer in the θ/2θ mode (Tokyo, Japan). The X-ray source was nickel-filtered Kα emission of copper (1.54056 Å). Samples were packed into a glass holder and were scanned over the range of 3° to 45° 2θ, at a scan rate of 2.0° 2θ/min.

Thermal Analysis

DSC analysis was performed on TA Q 200 series (TA Instruments, New Castle, Delaware, USA) using the Q-advance software. Indium metal (TA Instruments) was used as the calibration standard. Approximately 2–4 mg of sample was placed into Tzero aluminum pans; the pan was covered with a perforated lid and then crimped. The sample cell was heated under a nitrogen purge (50 mL/min) at a rate of 10°C/min, from 50°C up to a final temperature of 250°C. Reported temperatures are the onset temperatures.

TGA was carried out on TA Q 500 series (TA Instruments, New Castle, Delaware, USA) using the Q-advance software. Approximately 4–8 mg of sample was weighed into a platinum pan. Two-point calibration of the temperature was performed with ferromagnetic Ni, Curie point standards (TA instruments). Heating rates of 10°C/min were applied, and dry nitrogen was used as a purge gas (sample purge 60 mL/min and balance purge 40 mL/min).

Spectroscopy

FT-IR spectra were recorded using FT-IR spectrometer Spectrum-100 (PerkinElmer, USA) using an analyzing software (Spectrum 6.1 version). Potassium bromide (spectroscopy grade; Merck, Darmstadt, Germany) was used for sample preparation. Pellets were prepared by mixing 1:100 ratio of the sample with potassium bromide in a mortar and compressed at a pressure of about 15,000 psi. Each spectrum was derived from a 16 single averaged scans collected in the mid IR region of 400–4,000 cm^{-1} at a spectral resolution of 2.0 cm^{-1}.

The spectrometer was equipped with a solid-state probe and cross-polarization magic angle spinning (CP/MAS-II), and ^{13}C SSNMR spectra were recorded with Bruker Avance-II 75 MHz spectrometer (Bruker, Switzerland) with TOPSPIN
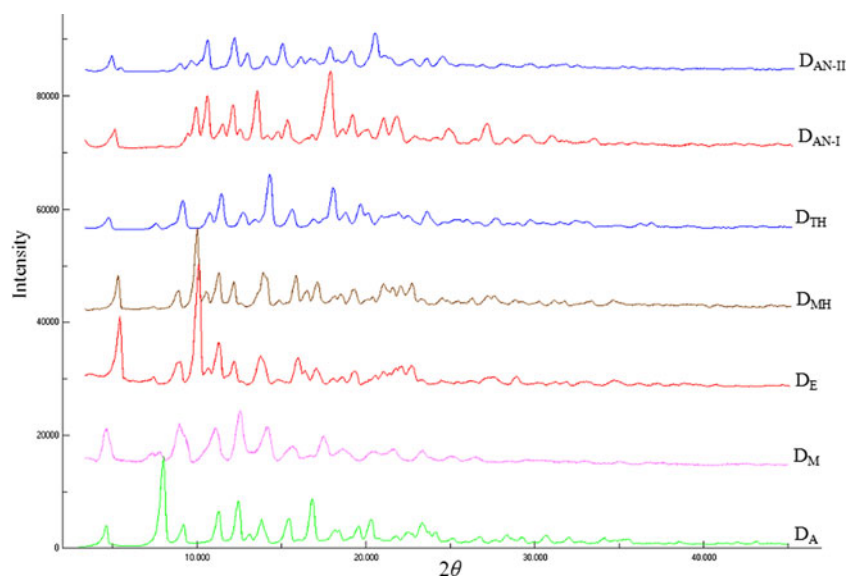
Fig. 1. Overlaid p-XRD diffractograms of D_A, D_M, D_E, D_{MH}, D_{TH}, D_{AN-I}, and D_{AN-II}

version 2.0 software. The static field of the superconducting magnet was 7.05 T, and cross-polarization total suppression of spinning side bands pulse sequence was used to perform the experiments. The instrument was operated at a spinning rate of 5 KHz. The cross-polarization magic angle and ^{13}C signal were optimized using KBr and glycine as standards, respectively.

The solution ^{1}H NMR spectrum was acquired at ambient temperature on a Bruker Avance-II 300 MHz at a ^{1}H Larmor frequency of 300.131 MHz. The sample was dissolved in $CDCl_3$. The spectrum was acquired with ^{1}H pulse width of 10.50 μs, a 3.64-s acquisition time, a 5-s delay between scans, a spectral width of 15 ppm, and 32 co-added scans. The free induction decay was processed using TOPSPIN version 2.0 software and an exponential line broadening factor of 0.2 Hz to improve the signal-to-noise ratio. The residual peak from

incompletely deuterated $CDCl_3$ (99.8 % isotopic purity) is at approximately 7.26 ppm. The relatively broad peak at approximately 1.56 ppm is due to water. The spectrum was referenced to TMS peak at 0.00 ppm.

RESULTS AND DISCUSSION

The required solvents (methanol, ethanol, and water) were placed in the bottom compartments of the desiccators, and the drug substance was placed on a glass plate in the upper compartments, exposed to the solvent vapors under closed conditions. All the vapor-induced phase transformation experiments were carried out at ambient temperature. Aliquots of the samples exposed to solvent vapors were removed on every alternate day from the desiccators and packed into a p-XRD sample holder. The p-XRD patterns were recorded on

Table I. Comparison of the p-XRD Data (2θ) of Docetaxel Anhydrous and Its Solid Forms

Form D_A	Form D_M	Form D_E	Form D_{MH}	Form D_{TH}	Form D_{AN-I}	Form D_{AN-II}
4.62	4.58	5.40	5.14	4.58	4.78	4.56
8.02	7.24	7.32	7.20	7.36	9.06	5.10
9.20	7.72	8.98	8.74	8.30	9.62	8.62
11.30	9.26	10.10	9.82	8.96	10.28	9.26
12.46	11.00	11.30	10.36	10.54	11.18	9.84
13.82	12.56	12.20	11.10	11.24	11.78	10.26
15.46	14.10	13.68	12.00	12.52	12.24	11.84
16.84	15.56	15.98	13.70	13.22	13.24	12.60
19.60	17.42	17.02	15.68	14.10	14.46	13.76
20.32	21.58	19.28	16.34	15.44	15.02	14.70
23.34	–	–	16.94	17.88	16.52	15.78
–	–	–	19.08	18.62	17.28	16.20
–	–	–	20.84	19.52	17.58	16.62
–	–	–	21.46	23.48	18.30	17.48
–	–	–	21.84	–	18.90	18.78
–	–	–	22.54	–	19.80	20.20
–	–	–	–	–	20.74	20.76
–	–	–	–	–	21.50	22.38
–	–	–	–	–	–	23.24
–	–	–	–	–	–	24.10

a Rigaku Miniflex-II diffractometer to monitor the structural changes that had occurred. For samples that responded with a change in the p-XRD pattern, the exposure to the solvent vapors was maintained until necessary, such that the p-XRD pattern indicated that the transformation had reached completion and significant changes were observed in the forms D_M, D_E, D_{MH}, and D_{TH}, characterized by appearance of new peaks and disappearance of existing peaks. If no further changes were observed in the p-XRD patterns of the different forms when stored for more than 1 week, it was assumed that the transformation has been completed. However the time taken for the transformation of D_{MH} to D_{TH} was exceptionally higher (22 days) than the other forms.

Powder X-ray Diffraction

It is a well-known fact that p-XRD is one of the most sensitive and foolproof methods for solid-state characterization as the results are obtained directly from the molecular arrangements of the crystalline material (17). The p-XRD pattern of each solid form was featured by a scattering peak unique to each form at a scattering angle (2θ) where no diffraction was observed for the other form, hence permitting an unambiguous identification and distinction between them. The distinct differences in the diffraction patterns of forms D_A, D_M, D_E, D_{MH}, D_{TH}, D_{AN-I}, and D_{AN-II} are attributed to modifications in the arrangement of molecules in the crystal lattice and different crystal structures. Among the seven forms, D_E, D_{MH}, D_{TH}, and D_{AN-I} are highly crystalline, as shown by the sharp diffraction peaks in their individual p-XRD patterns. However, the p-XRD patterns of form D_M show the presence of some amorphous content, as indicated by the broad peaks. The forms D_E and D_{MH} show many similarities in their p-XRD patterns except for a few reflections after 2θ 15.0° (Fig. 1). It can be assumed from these data that there exists a similarity in the packing of these forms and the solvents ethanol and water may both be included as channeled solvates. The desolvation and dehydration of D_E and D_{MH} respectively resulted in generation of an identical form D_{AN-II} which was quite different from the other anhydrous forms (D_A and D_{AN-I}). This in principle again reinforces our assumption that both D_E and D_{MH} have a strikingly similar crystal packing.

The p-XRD patterns of the seven solid forms (Fig. 1) are quite distinct which alludes to prominent structural differences. The following characteristic 2θ peak positions were summarized in Table I. The p-XRD pattern of form D_A and D_{TH} is identical to those reported in literature (18).

Thermal Analysis

Thermal analysis by DSC and TGA was carried out on docetaxel anhydrous (form D_A), D_M, D_E, D_{MH}, D_{TH}, D_{AN-I}, and D_{AN-II}. TGA (Fig. 2) of docetaxel anhydrous (form D_A) showed no weight loss from 30.0 to 150.0°C; this information correlates with the DSC thermogram (Fig. 3) where no thermal transitions were observed up to 150.0°C. The DSC thermogram showed an endotherm at 158.2°C corresponding to its melting point. The solid forms D_M, D_E, D_{MH}, and D_{TH} showed thermal transitions at about 40.0°C corresponding to gradual desolvation and dehydration process. The DSC
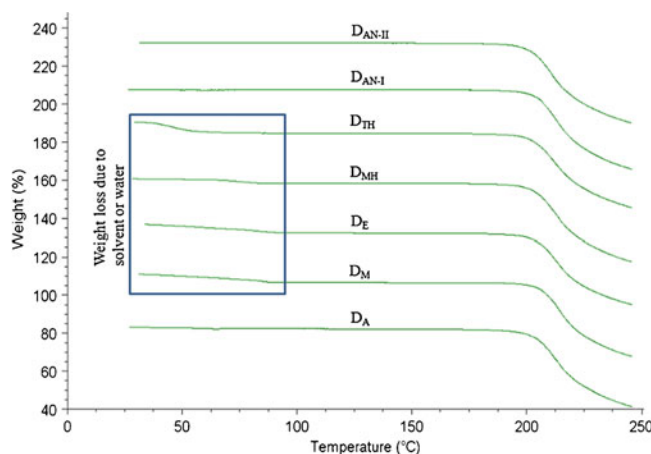

Fig. 2. Overlaid TGA thermograms of D_A, D_M, D_E, D_{MH}, D_{TH}, D_{AN-I}, and D_{AN-II}

thermograms of these forms exhibited broad endotherms with high enthalpies as tabulated in Table II.

Interestingly, the form D_M after desolvation exhibited a melting endotherm at about 188.6°C which was much higher compared to the other forms. This observation was consistent when the experiments were performed several times. Similarly, the forms D_E and D_{MH} exhibited melting endotherms at about 163.4 and 166.9°C, respectively, which are higher than anticipated. To investigate if D_M, D_E, and D_{MH} converted to new forms upon desolvation and dehydration, heat/cool/heat experiments were performed. As expected, during the first cycle of heating with a ramp rate of 10°C/min, the form D_M (heated up to 135.0°C), form D_E (heated up to 145.0°C), and form D_{MH} (heated up to 145.0°C) lost methanol, ethanol, and water completely. In the second cycle, the desolvated and dehydrated forms were cooled to the room temperature with a ramp rate of 10°C/min. When the DSC of these samples were run again, only the endotherm corresponding to the melting was observed at 187.8, 164.9, and 164.9°C, respectively, indicating that there was a possible change of form D_M, D_E, and D_{MH} to higher melting, thermodynamically stable forms. A desolvated form of D_M was generated (D_{AN-I}) by keeping the D_M at 135°C under vacuum for 18 h. Similarly desolvated form of D_E (D_{AN-II}) and dehydrated form of D_{MH} (D_{AN-II})
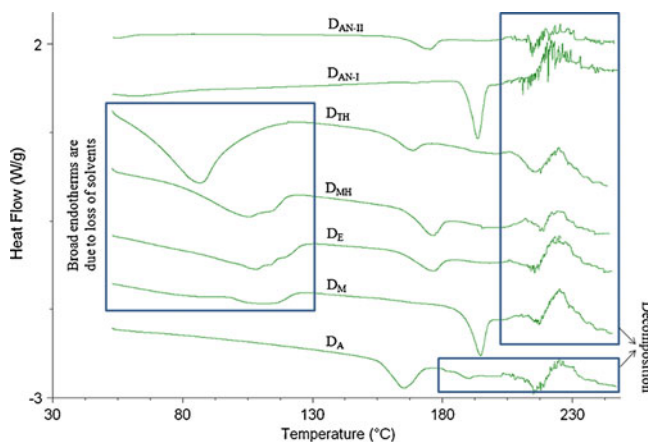

Fig. 3. Overlaid DSC thermograms of D_A, D_M, D_E, D_{MH}, D_{TH}, D_{AN-I}, and D_{AN-II}

Table II. Comparisons of the DSC and TGA Data of Docetaxel Anhydrous and Its Solid Forms

Solid form	Endotherm (°C)[a]	Enthalpy ΔH (J/g)	Endotherm (°C)[b]	Enthalpy ΔH (J/g)	Weight loss (%)	Expected weight loss (%)
Form D_A	–	–	158.2	21.8	–	–
Form D_M	39.6	78.1	188.6	22.5	3.9	3.8
Form D_E	65.2	121.6	163.4	13.8	5.3	5.4
Form D_{MH}	81.1	53.8	166.9	14.1	2.2	2.2
Form D_{TH}	60.3	154.2	158.9	9.0	6.3	6.3
Form D_{AN-I}	–	–	187.8	21.3	–	–
Form D_{AN-II}	–	–	164.9	13.3	–	–

[a] Endotherms correspond to loss of solvent
[b] Endotherms correspond to onset temperature of solid forms

were generated by keeping D_E and D_{MH} at 145°C under vacuum for 14–16 h. The DSC of these desolvated and dehydrated forms confirmed a profile obtained in the final cycle of heat/cool/heat experiments of D_M, D_E, and D_{MH}.

In an attempt to estimate the solvent/water of hydration in docetaxel solid forms of D_M, D_E, D_{MH}, and D_{TH}, a comparison was made between the weight loss observed in the TGA thermograms and the expected weight loss for a stoichiometric inclusion (Table II), and a good agreement between the experimental and theoretical weight loss was observed. The experimental results indicate that the solvent/water molecules existed in stoichiometric ratios within the lattice. No weight loss was observed in case of form D_{AN-I} and D_{AN-II}.

FT-IR Spectroscopy

FT-IR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing, and hydrogen bonding arrangements for different solid-state forms of an organic compound (19). The shift and splitting of absorption bands in the FT-IR spectrum usually indicate a change in force constant, corresponding to a change in the environment of the corresponding bond, such as the bond length and bond angle. The FT-IR spectra of solid forms D_A,

D_M, D_E, D_{MH}, D_{TH}, D_{AN-I}, and D_{AN-II} are shown in Fig. 4. When compared with the other forms such as D_M, D_E, D_{MH}, D_{TH}, D_{AN-I}, and D_{AN-II}, the IR spectrum of D_A has clear differences in the range 3,600 to 3,300 (–NH and –OH stretching) cm^{-1} and 1,690 to 1,768 (C=O stretching) cm^{-1}. The wave numbers are tabulated in Table III. The differences in the peak positions indicate the different environment of the carbonyl groups in these six solid forms of docetaxel and probably arise due to the hydrogen bonding between the –OH group of solvents with the C=O group present in docetaxel. Hydrogen bonding alters the force constant of C=O and the differences in conformation and crystal packing.

13C Solid-State NMR Spectroscopy

^{13}C SSNMR spectroscopy with cross-polarization and magic angle spinning is emerging as a powerful technique for addressing molecular structural problems in solid-state pharmaceutics, especially in the study of polymorphism. It is a nondestructive technique that has the ability to probe the chemical environment of each carbon nucleus, resulting a unique spectrum for each form. Once resonances have been assigned to specific atoms of the molecule, information on the nature of the polymorphic variations can be obtained, therefore identifying the number of crystallography in
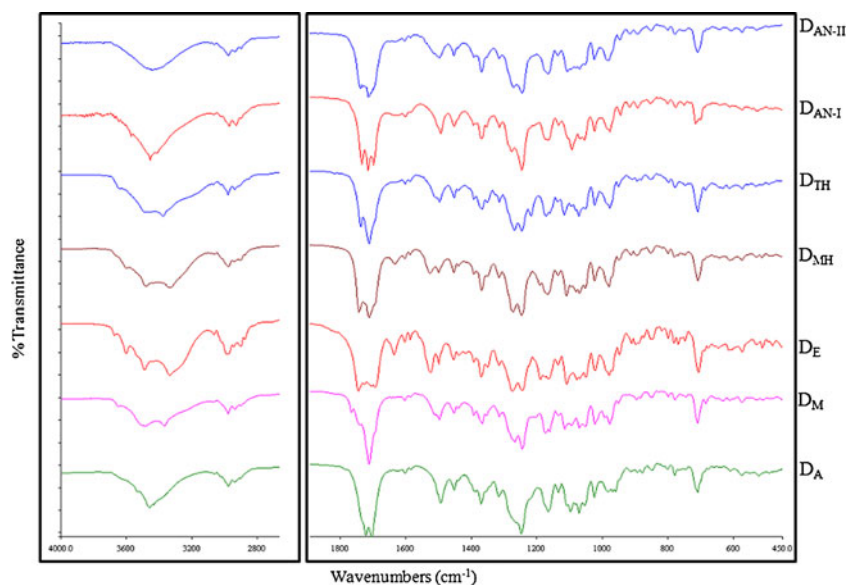

Fig. 4. Overlaid FT-IR spectra of D_A, D_M, D_E, D_{MH}, D_{TH}, D_{AN-I}, and D_{AN-II}

Table III. FT-IR Frequencies of Docetaxel Anhydrous and Its Solid Forms

Solid form	–NH and –OH stretching frequency (cm^{-1})	C=O stretching frequencies (cm^{-1})
Form D$_A$	3,459	1,723[a], 1,704[a]
Form D$_M$	3,654, 3,487, 3,369	1,766[b], 1,740[b], 1,712[a]
Form D$_E$	3,604, 3,491, 3,336	1,745[a], 1,727[a], 1,705[a], 1,694[a]
Form D$_{MH}$	3,484, 3,337	1,743[a], 1,712[a]
Form D$_{TH}$	3,462, 3,376	1,738[a], 1,712[a]
Form D$_{AN-I}$	3,457	1,734[a], 1,716[a], 1,698[a]
Form D$_{AN-II}$	3,444	1,738[a], 1,714[a], 1,699[a]

[a] Strong stretching vibration
[b] Weak stretching vibration

equivalent sites in a unit cell and also understanding the hydrogen bond networks, molecular conformation, molecular mobility, and molecular structure on the basis of the chemical shifts of the individual resonances (20,21). SSNMR spectroscopy can be used either qualitatively or quantitatively and can provide structural data such as the identity of solvents bound in a crystal lattice.

^{13}C SSNMR spectra of docetaxel anhydrous and its solid forms are shown in Fig. 5. The solution state ^{13}C NMR was used to assign the chemical shifts of D$_A$. A comparison of the chemical shifts obtained in the SSNMR and the solution-state NMR is made in Table IV. The spectra of docetaxel anhydrous (form D$_A$) and of solid forms (D$_M$, D$_E$, D$_{MH}$, D$_{TH}$, D$_{AN-I}$, and D$_{AN-II}$) exhibited
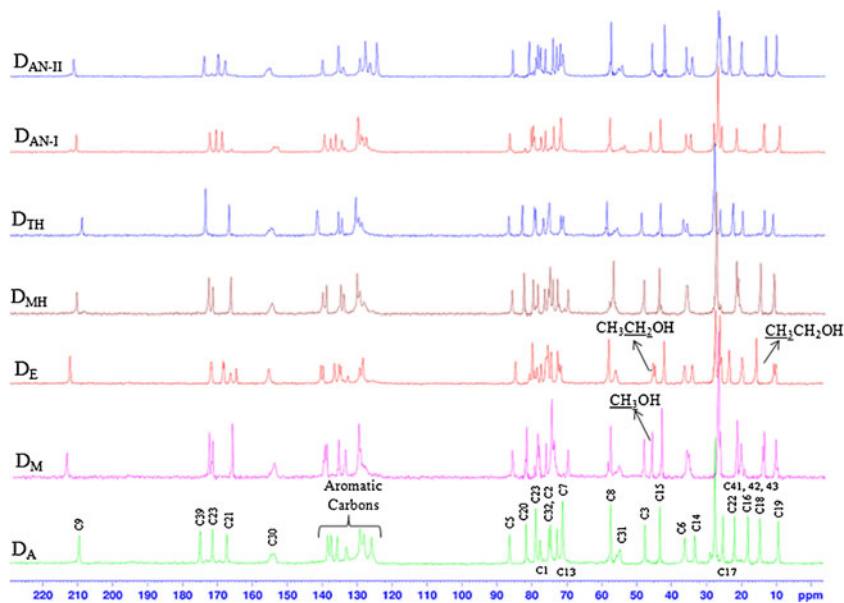
Fig. 5. Overlaid ^{13}C SSNMR spectra of D$_A$, D$_M$, D$_E$, D$_{MH}$, D$_{TH}$, D$_{AN-I}$, and D$_{AN-II}$

Table IV. ^{13}C SSNMR Chemical Shifts (δ/Part Per Million) of Docetaxel Anhydrous and Its Solid Forms

| Carbon atom	Solution state	Solid state						
	Form D$_A$	Form D$_A$	Form D$_M$	Form D$_E$	Form D$_{MH}$	Form D$_{TH}$	Form D$_{AN-I}$	Form D$_{AN-II}$
C6	37.00	36.23	35.95	36.52	35.73	36.11	35.88	35.87
C9	211.33	209.57	214.12	212.65	210.90	208.88	211.08	211.22
C14	35.71	33.35	35.37	34.33	35.73	35.00	34.48	34.23
C21	170.29	171.40	172.17	172.19	171.82	173.40	170.92	169.83
C23	167.01	167.30	166.51	168.45	166.65	166.61	169.24	167.84
C30	155.32	153.97	154.45	155.67	154.79	154.50	154.39	155.09
C39	172.67	174.94	173.19	168.78	173.01	173.40	172.70	174.94
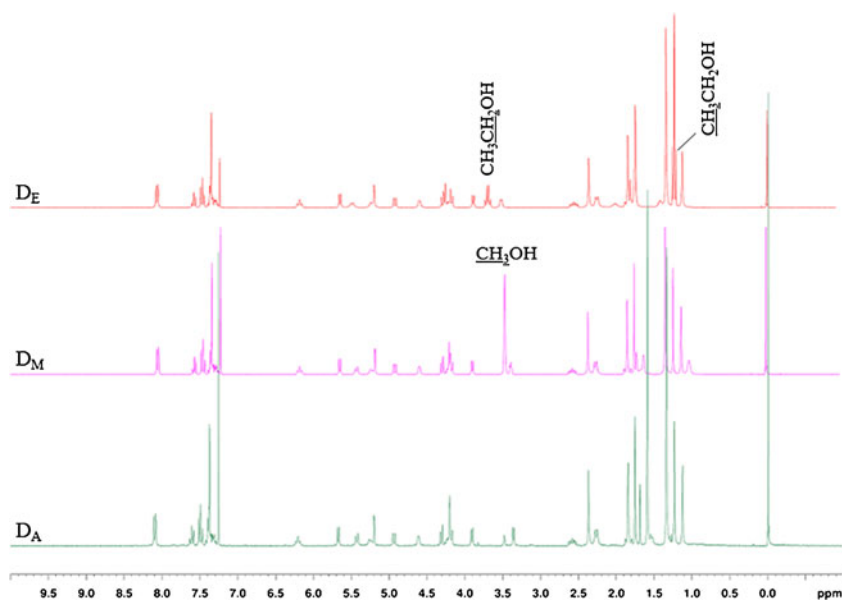
Fig. 6. Overlaid ^{1}H NMR spectra of D_A, D_M, and D_E

distinct chemical shifts—for example, in the case of form D_M the carbonyl carbon C9 assigned to the resonance farthest downfield at δ 214.12 ppm; the three carboxylate carbon, C21, C23, and C30, and amide carbon C39 are assigned to the peaks at δ 172.17, 166.51, 154.45, and 173.19 ppm, respectively. A noticeable difference in the chemical shift of the methyl carbon C22 was observed (δ 22.02 *vs* 27.86 ppm) in the anhydrous forms D_A and D_{AN-I} respectively, indicating that there could be a different molecular arrangement in the crystal lattice. The phenyl ring carbons (C24–C29 and C33–C38) are assigned to the peaks between 125 and 140 ppm. Whereas for CH_3 carbons are assigned below 28.0 ppm, CH_2 aliphatic CH and aliphatic quaternary carbons are assigned below 86.0 ppm.

Because the resonances of C6, C9, C14, C21, C23, C30, and C39 are relatively well separated from those of the other carbons, the chemical shifts of these carbons are chosen to distinguish the different morphs. Only one resonance was observed at δ 173.40 ppm for the two caboxylate carbons of C21 and C39 for form D_{TH}. Moreover, peaks assigned to the solvents are clearly seen at 49.58 ppm in form D_M and 15.97 and 45.47 ppm in form D_E, respectively. In this aspect, NMR is more informative than p-XRD for the identification of solvates.

Solution ^{1}H NMR Spectroscopy

The ^{1}H NMR spectra (Fig. 6) were recorded for the solid-state forms of D_M and D_E in order to quantify the molecular proportions of solvate present in the solid forms. The stoichiometric ratios of solvents assessed by ^{1}H NMR experiments are consistent with observations based on TGA measurements. These results are also in concordance with the theoretically calculated values considering a 1:1 stoichiometry for the host and guest (Table V).

CONCLUSIONS

Solid forms D_M (methanol solvate), D_E (ethanol solvate), D_{MH} (mono hydrate), D_{TH} (trihydrate), D_{AN-I} (anhydrous), and D_{AN-II} (anhydrous) were obtained. The inclusion of solvent vapors in the crystal lattice was observed in forms D_M and D_E, whereas the transformations in forms D_{MH} and D_{TH} were characterized by a solvent exchange process induced by water vapor under ambient atmosphere. Forms D_M and D_E are interconvertible upon exposure to vapors of ethanol and methanol, respectively. Form D_M when maintained at 135°C under vacuum for about 18 h converts to form D_{AN-I}. Similarly forms D_E and D_{MH} yield form D_{AN-II} when maintained at 145°C under vacuum for about 14–16 h. The desolvation and dehydration of D_E and D_{MH} resulted in generation of form D_{AN-II}. The conversion of form D_A to D_{AN-I} and D_{AN-II} proceeds via the formation of solvates followed by desolvation. The forms D_{AN-I} and D_{AN-II} do not convert to form D_A; hence, all the three anhydrous forms (D_A, D_{AN-I}, and D_{AN-II}) are monotropically related. Based on the solid-state characterization data, the similarity between the crystal structures of forms D_E and D_{MH} can also be interpreted. As shown in this study, exposure of solid materials to solvent vapor can produce interesting and specific effects to modify solid-state structures and physicochemical properties.

Table V. Quantitative Analysis Results from Solution-State ^{1}H NMR Experiments of Form D_M and D_E

Solid form	Chemical shift (δ_H/ppm)	Assignment	Molar ratio (solvent to docetaxel)
Form D_M	3.48	CH_3	1.00
Form D_E	1.22	CH_3	–
	3.70	CH_2	1.03

ACKNOWLEDGMENT

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