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ORIGINAL ARTICLE

Host–guest complexes of docetaxel, an anti-cancer drug

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Abstract Host–guest complexes of Docetaxel **1**, an anti-cancer drug have been isolated and crystal structures are described. Docetaxel crystallized in the 1:1 molar ratio with *n*-butanol, dimethylformamide (DMF) and acetonitrile (ACN) during crystallization from the respective solvents. In all the three complexes (**1** · *n*-butanol, **1** · DMF and **1** · ACN), docetaxel formed a host framework through hydrogen bonds and the guest solvent molecules occupied the channels. The host is hydrogen bonded to the guest molecules through hydroxyl moieties. Interestingly, **1** · *n*-butanol, **1** · DMF and a literature **1** · CH_3OH · H_2O (1:1:1) host–guest complexes are isomorphs. Further, **1** · ACN complex unit cell parameters are similar (same space group) to the marketed docetaxel trihydrate polymorph (form A).

Keywords Anti-cancer drug · Docetaxel · Host–guest complex · Hydrogen bond · Inclusion compound · Supramolecular chemistry

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Introduction

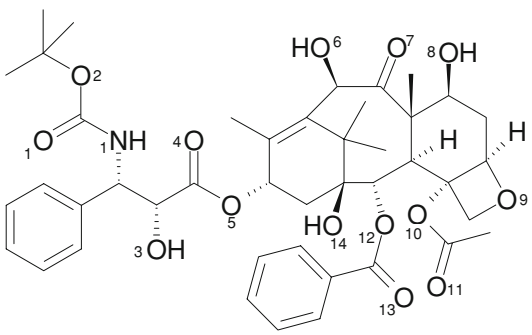
Kitaigorodskii's principle of close packing explains that molecules in the crystalline solids arrange in a regular order with close packing with minimal voids [1]. However, some molecules can not pack closely, tends to attain close packing by interpenetration or adopting different molecules in the voids (or same molecules, called as self-inclusion), well-known in the literature as "host–guest or inclusion compounds". Host–guest compounds are broadly categorized into "cavitands or molecular host compounds" with intramolecular cavities and "clathrand compounds" with extramolecular cavities that result from the aggregation of two or more molecules. In both the categories the host and the guest molecules are connected with non-covalent interactions.

In general, discoveries of inclusion compounds are result of serendipity, obtained during crystallization from various solvents [2]. However, development in supramolecular chemistry [3] and crystal engineering reveals that host–guest compounds can be rationally designed and synthesized. In this context we have to recapture Desiraju's definition of crystal engineering "*the understanding of intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design of new solids with desired physical and chemical properties*" [4]. By understanding the history of molecular arrangements in crystals, host–guest pioneers described how to design novel host materials [5–9]. The study of inclusion compounds is one of the hot topics in chemical research [10–18] since it has applications in magnetism, gas storage devices, nonlinear optical materials, targeted drug delivery, etc. [19, 20].

Generally, the pharmaceutical industry follows the solvent based process of solid Active pharmaceutical

ingredients (APIs) like precipitation, crystallization or recrystallization from a suitable single or mixture of solvents. The aim of such processes is in general to obtain a pure desired crystalline polymorphic form. However, in some instances the solvent of crystallization is adsorbed and/or entrapped into the crystal lattice of the drug substance. Such residual solvent is considered to be an impurity and regulated by authorities such as ICH guideline Q3C on residual solvents in pharmaceuticals [21]. The presence of solvent molecules in the crystal lattice confers unique physical properties to the solvate form. For drug substances stability, solubility and dissolution rates of a solvate are different from those of the corresponding anhydrate and can result in differences in bioavailability. Hence, the drug substance crystallization study in various solvents, different conditions and the resulted solid phase characterization is critical in the drug development process.

Docetaxel [(2R, 3S)-*N*-carboxy-3-phenylisoserine, N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate; Scheme 1] **1**, is an antineoplastic agent belonging to the taxoid family. Docetaxel is a semi-synthetic analogue of paclitaxel [22] (Taxol®, an extract from the pacific yew tree Taxus brevifolia) and exhibits pharmalogical properties superior to those of Taxol in the treatment of locally advanced or metastatic breast, ovarian and non-small cell lung cancers [23, 24]. It is available in the market as trihydrate under the name Taxotere® by Sanofi-Aventis U.S. LLC. Two polymorphs of docetaxel trihydrate (namely, form A and B) have been reported [25]. The marketed form A is the thermodynamically stable form, to date, under ambient conditions. It is highly lipophilic and practically insoluble in water. Taxotere is sterile, non-pyrogenic, and available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Molecular level understating of pharmaceutical molecules in the solid state is very important, even the envisaged marketed form of the drug is a solution, information about the solid-state properties of the drug may still be necessary [26].



Scheme 1 Molecular structure of docetaxel, **1**

The present work describes the crystal structures of clathrand complexes of docetaxel with *n*-butanol, dimethylformamide (DMF) and acetonitrile (ACN). The lattice inclusion complexes were isolated during crystallization of docetaxel from the respective solvents. Interestingly, the **1** · *n*-butanol and **1** · DMF crystal structures are isomorphous along with the literature **1** · CH_3OH · H_2O (1:1:1) crystal structure [27].

Experimental

Preparation

Single crystals of three inclusion complexes (**1** · *n*-Butanol, **1** · DMF and **1** · ACN) were obtained by the slow evaporation of docetaxel solution from *n*-butanol, DMF and acetonitrile, respectively at ambient conditions.

X-ray crystallography

X-ray data for the three single crystals have been collected on a Rigaku AFC-7S diffractometer equipped with Mercury CCD detector using graphite monochromated Mo-K_α ($\lambda = 0.7107$ Å) radiation. The crystal structures were solved using direct methods (SIR92 for **1** · *n*-butanol and **1** · DMF; SIR2004 for **1** · ACN) [28] and refined using the procedure of least squares (CRYSTALS, Crystal structure 3.8 software) [29]. The non-hydrogen atoms were refined anisotropically and the C–H hydrogen atoms were positioned geometrically and refined in the riding model approximation with C–H = 0.95 Å. All hydrogen atoms covalently bonded to N and O were located in the difference electron density map and refined isotropically. The 11 chiral centres of docetaxel were assigned as per the synthetic scheme (Scheme 1). The crystallographic information of the host–guest complexes are summarized in Table 1 and hydrogen bond geometries are listed in Table 2. The crystal packing diagrams were generated using X-Seed 2.0 [30, 31].

Results and discussion

Docetaxel is a large (molecular formula $C_{43}H_{53}NO_{14}$ and formula weight, 808), conformationally flexible molecule and consists of 11 chiral centres. The molecule contains four hydroxyl, one *sec*-amide NH conventional hydrogen bond donor and variety of oxygen acceptors, available for hydrogen bonding. In general, molecules with several functional groups and/or conformational flexibility are prone to exhibit polymorphism [32] and/or formation of solvates. Docetaxel is a flexible molecule with many

Table 1 Crystallographic parameters of docetaxel inclusion compounds

	1 · *n*-Butanol	1 · DMF	1 · CH_3OH · H_2O CSD Ref Code: VEJCUI	1 · $(H_2O)_3$ Form B CSD Ref Code: DARGOT01	1 · ACN	1 · $(H_2O)_3$ Form A CSD Ref Code: DARGOT
Empirical formula	$(C_{43}H_{53}NO_{14}) \cdot (C_4H_{10}O)$	$(C_{43}H_{53}NO_{14}) \cdot (C_7H_7NO)$	$(C_{43}H_{53}NO_{14}) \cdot (CH_4O) \cdot (H_2O)$	$(C_{43}H_{53}NO_{14}) \cdot (H_2O)_3$	$(C_{43}H_{53}NO_{14}) \cdot (C_2H_3N)$	$(C_{43}H_{53}NO_{14}) \cdot (H_2O)_3$
Formula weight	882	881	858	862	849	862
T (K)	298	298	298	283-303	298	283-303
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	12.958(4)	12.824(3)	12.726(8)*	12.782(5)*	8.844(4)	8.6644(5)*
b(Å)	8.823(3)	8.7432(12)	8.758(5)	8.746(5)	12.715(5)	12.7749(4)
c(Å)	20.666(7)	20.579(3)	20.816(10)	20.520(5)	39.415(17)	39.9345(16)
β (°)	98.764(4)	100.084(4)	101.06(5)	98.901(5)	90	90
V (Å^3)	2335.1(13)	2271.8(7)	2277	2266.3	4432(3)	4420.2
Z	2	2	2	2	4	4
ρ_{calc} (g cm^{-3})	1.254	1.288	1.25	1.254	1.272	1.295
Reflections collected	27027	16285			25873	
Independent reflections	5666	4295			4650	
Observed reflections	4123	3891	3438	4926	2562	
R_1	0.070	0.059	0.073	0.0973	0.080	R_{wp}: 0.093
wR_2	0.078	0.069	0.084	0.212	0.064	

* a and c unit cell parameters were interchanged for comparison with the present structures

Table 2 Hydrogen bond geometries of docetaxel inclusion compounds

Host–guest complex	D–H···A	H···A[a] (Å)	D···A (Å)	D–H···A (°)	Symmetry
1 · *n*-Butanol	O_3–H···O_{15}	1.84	2.765(5)	156	
	O_6–H···O_7	1.86	2.533(4)	123	
	O_8–H···O_6	2.05	2.771(4)	129	−x, ½ + y, 1 − z
	O_{14}–H···O_{11}	2.18	2.951(4)	134	x, −1 + y, z
	O_{15}–H···O_8	1.89	2.794(4)	152	1 + x, y, z
	N_1–H···O_9	2.33	3.330(5)	174	1 + x, y, z
1 · DMF	O_3–H···O_{15}	1.93	2.851(5)	154	x, y, 1 + z
	O_6–H···O_8	2.00	2.856(4)	144	1 − x, −½ + y, 2 − z
	O_8–H···O_{15}	1.83	2.790(4)	166	1 + x, y, 1 + z
	O_{14}–H···O_{11}	1.96	2.890(4)	156	x, −1 + y, z
	N_1–H···O_9	2.16	3.161(4)	173	−1 + x, y, z
1 · ACN	O_{14}–H···O_{11}	2.37	3.010(4)	122	−1 + x, y, z
	O_3–H···O_4	2.27	2.662(5)	103	
	O_6–H_{61}···O_3		2.878		
	O_8–H···N_2	1.87	2.797(10)	155	2 − x, −½ + y, 3/2 − z
	N_1–H···O_9	2.38	3.201(5)	138	x, 1 + y, z

[a] D–H distances were adjusted to neutron diffraction standards

degrees of torsional freedom and contains various functional groups, hence it is more prone to forms solvates and/or polymorphs. Despite the significance of the drug, very few solid state structural studies are known. Surprisingly, the Cambridge Structural Database (CSD, May '09 update) contains only **1** · CH_3OH · H_2O (1:1:1) and **1** · $(H_2O)_3$

polymorphs, A and B (three-dimensional co-ordinates are not available for the polymorphs). While studying the crystallization of docetaxel from various solvents, we have obtained single crystals of three solvent inclusion complexes, **1** · *n*-butanol, **1** · DMF and **1** · ACN. Single crystal X-ray diffraction was utilized to study the structural features to understand the assembly of docetaxel and solvent molecules in the crystal lattice. Such understanding is useful to develop a process method of the drug substance. The structural features of the inclusion complexes are described below.

The **1** · *n*-butanol complex has crystallized in the monoclinic system (space group $P2_1$) with one molecule of each of docetaxel and *n*-butanol in the asymmetric unit (Table 1). All the OH and NH hydrogen atoms of docetaxel and *n*-butanol were located in the difference electron density maps and refined isotropically. The *n*-butanol solvent molecule is in the extended

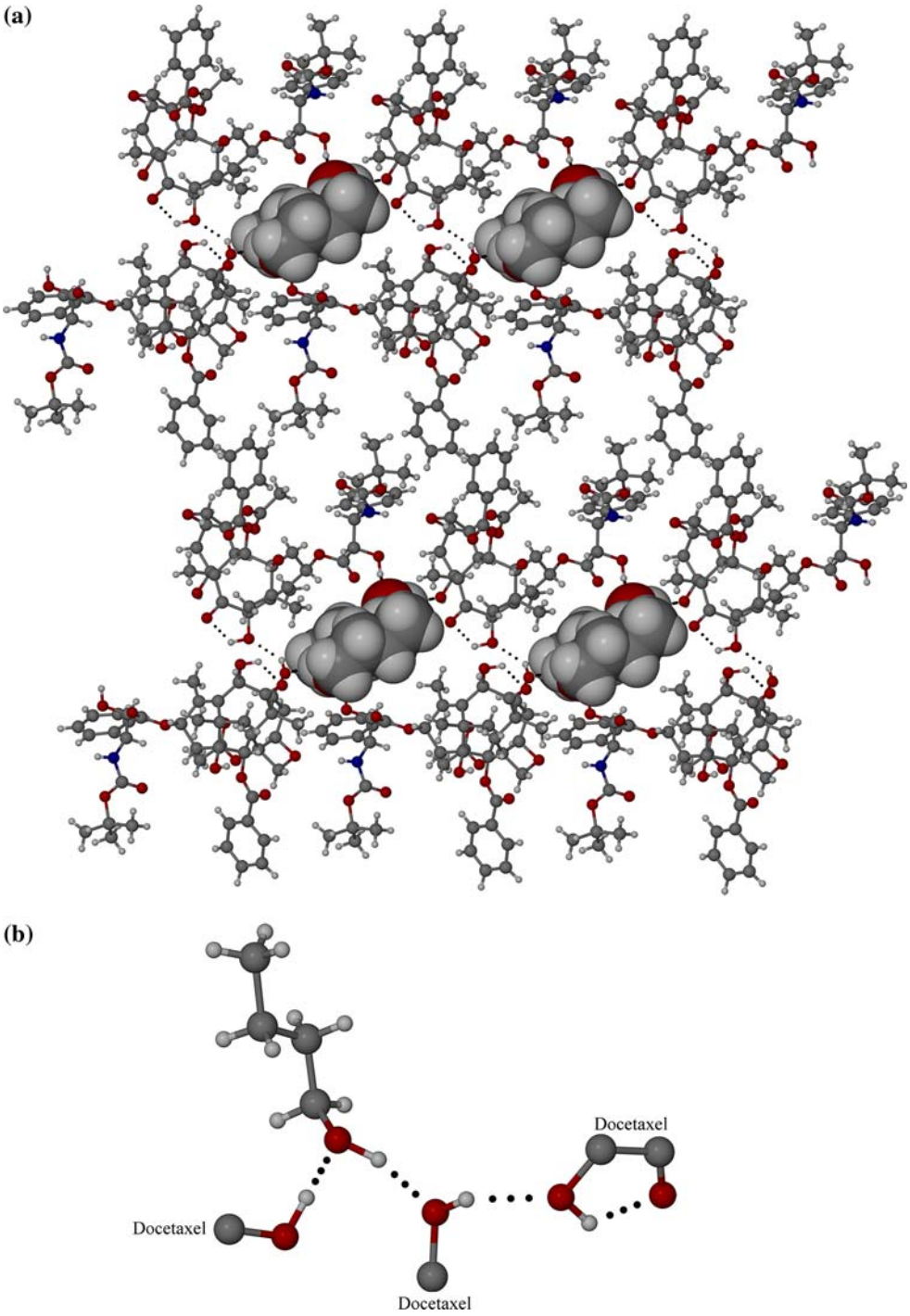


Fig. 1 Host–guest complex of **1** · *n*-Butanol. **a** The crystal packing shows the hydroxyl O–H···O hydrogen bonding between the docetaxel host molecules and with the *n*-butanol guests (shown with *space filling model*). **b** σ-Cooperative finite O–H···O hydrogen bonded chain between host and guest

conformation. All the OH and NH conventional donors are involved in the hydrogen bonding. The crystal packing shows that docetaxel forms a host framework with channels along the [010] containing the *n*-butanol molecules (Fig. 1a). Docetaxel hydroxyl moieties are forming a finite σ-cooperative four O–H···O hydrogen bonded chain along with the *n*-butanol hydroxyl group (Fig. 1b). Three out of four docetaxel and one *n*-butanol hydroxyl groups are involved in this cooperative hydrogen bonded chain. *n*-Butanol hydroxyl oxygen accepting O–H···O hydrogen bond from docetaxel O_3–H hydroxyl and donating O–H···O hydrogen bond to O_8–H hydroxyl oxygen of another docetaxel. The O_8–H forming O–H···O hydrogen bond with third docetaxel O_6–H hydroxyl oxygen and the O_6–H terminating the cooperative hydrogen bonded chain by an intramolecular O_6–H···O_7=C hydrogen bond. Such σ-cooperativity increases the strength of the hydrogen bonds in the chain, explained by mutual polarisation of donors and acceptors along the chain [33]. The N_1–H donor involved in weak N_1–H···O_9 hydrogen bonding with cyclic ether oxygen of translated docetaxel along [100]. Translated docetaxel molecules along the channel [010] are connected through hydroxyl O_{14}–H···O_{11}=C hydrogen bonds (Table 2).

The **1** · DMF complex also crystallized in the monoclinic system with $P2_1$ space group, similar to the **1** · *n*-butanol complex. The asymmetric unit consists of one molecule of each of docetaxel and DMF (Table 1). The crystal packing shows that docetaxel forming a host frame and DMF molecules are resided in the channels along [010] (Fig. 2). The guest DMF molecules are sustained by hydrogen bonding with the host docetaxel hydroxyl moieties. Unlike in **1** · *n*-butanol, The O_6–H is not involved in intramolecular hydrogen bonding with the adjacent C=O_7; however, forming a O_6–H···O_8 H-bond with O_8–H hydroxyl, which in turn forming O_8–H···O_{15} H-bond with DMF carbonyl oxygen. The O_3–H hydroxyl also forming O_3–H···O_{15} H-bond with DMF carbonyl oxygen. Similar to **1** · *n*-butanol structure, here also N_1–H involved in weak N_1–H···O_9 hydrogen bonding with cyclic ether oxygen of another translated docetaxel along [100] and translated docetaxel molecules along the channel [010] are connected through O_{14}–H···O_{11}=C hydrogen bonds (Table 2). In this complex, all the conventional donors are involved in hydrogen bonding.

The **1** · ACN inclusion complex consists one molecule of each of docetaxel and acetonitrile in the asymmetric unit. The complex crystallized in the orthorhombic system

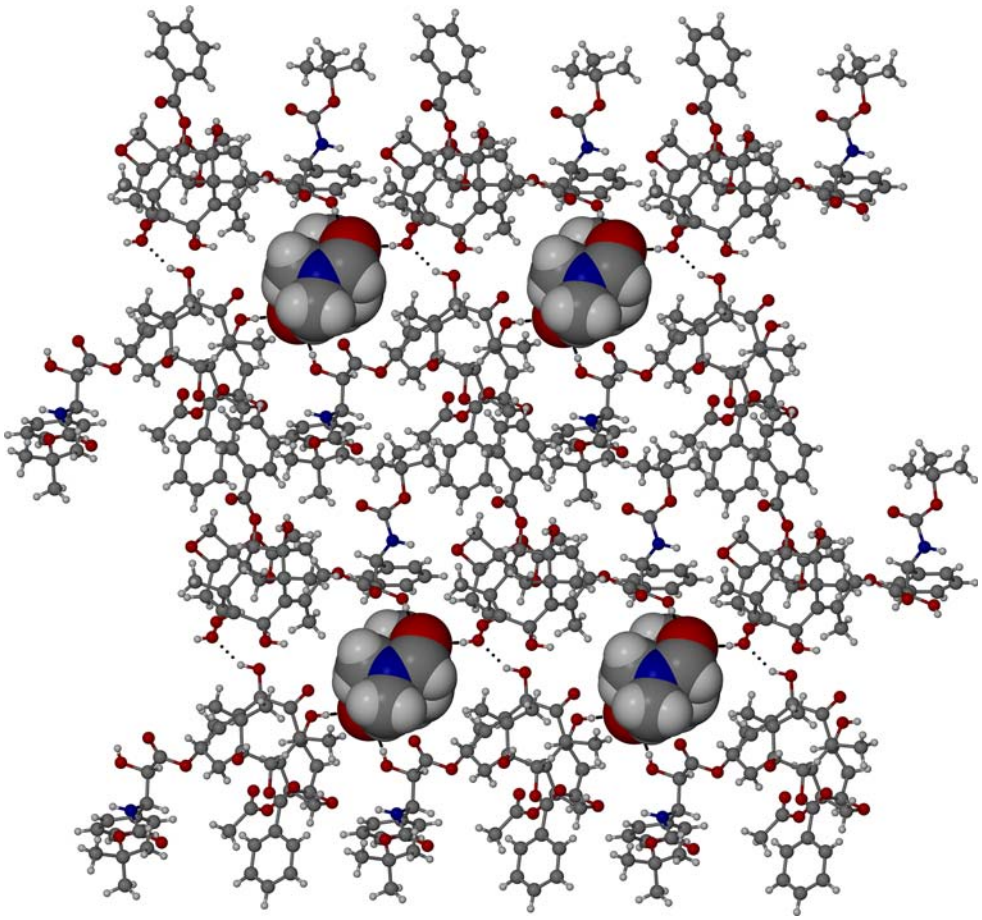


Fig. 2 Host–guest complex of **1** · DMF. The crystal packing shows the hydroxyl O–H···O hydrogen bonding between the docetaxel host molecules and with the DMF guests (shown with *space filling model*)

with $P2_12_12_1$ space group (Table 1). The O_3–H hydroxyl is involved in an intramolecular O_3–H···O_4 hydrogen bond with the carbonyl oxygen (Table 2). The crystal packing shows that docetaxel molecules are forming host framework with O_{14}–H···O_{11}=C and O_6–H_{61}···O_3 hydrogen bonds. The ACN molecules are resided in the channels along [010] and connected to the host frame through hydroxyl O_8–H···N_2 ≡ C hydrogen bonds (Fig. 3).

The only docetaxel structure in the CSD with 3D coordinates, **1** · CH_3OH · H_2O (1:1:1 stoichiometry, space group $P2_1$, CSD Ref Code: VEJCUI) was reported by Voegelein et al. [27]. In this complex also the docetaxel forms host frame and methanol and water molecules occupied the channels along [010]. Since methanol and water molecules are small in size, both the solvent molecules are resided in the channels to attain the close packing.

Zaske et al. [25] reported two polymorphs for the docetaxel trihydrate (form A and B). The authors describes that form A single crystal X-ray structure could not be solved due to strong anisotropy of crystals (thin plates), hence solved the structure using High Resolution X-ray Powder Diffraction data (synchrotron), applying an ab initio direct space method [25, 34]. Form B crystal structure was solved by the single crystal XRD. Further they say that the "form A and form B crystal structures forming bi-layers separated by water molecules. Form A bi-layers are totally superimposable to the **1** · CH_3OH · H_2O structure. Only their relative packing change, depending on the different types of solvent

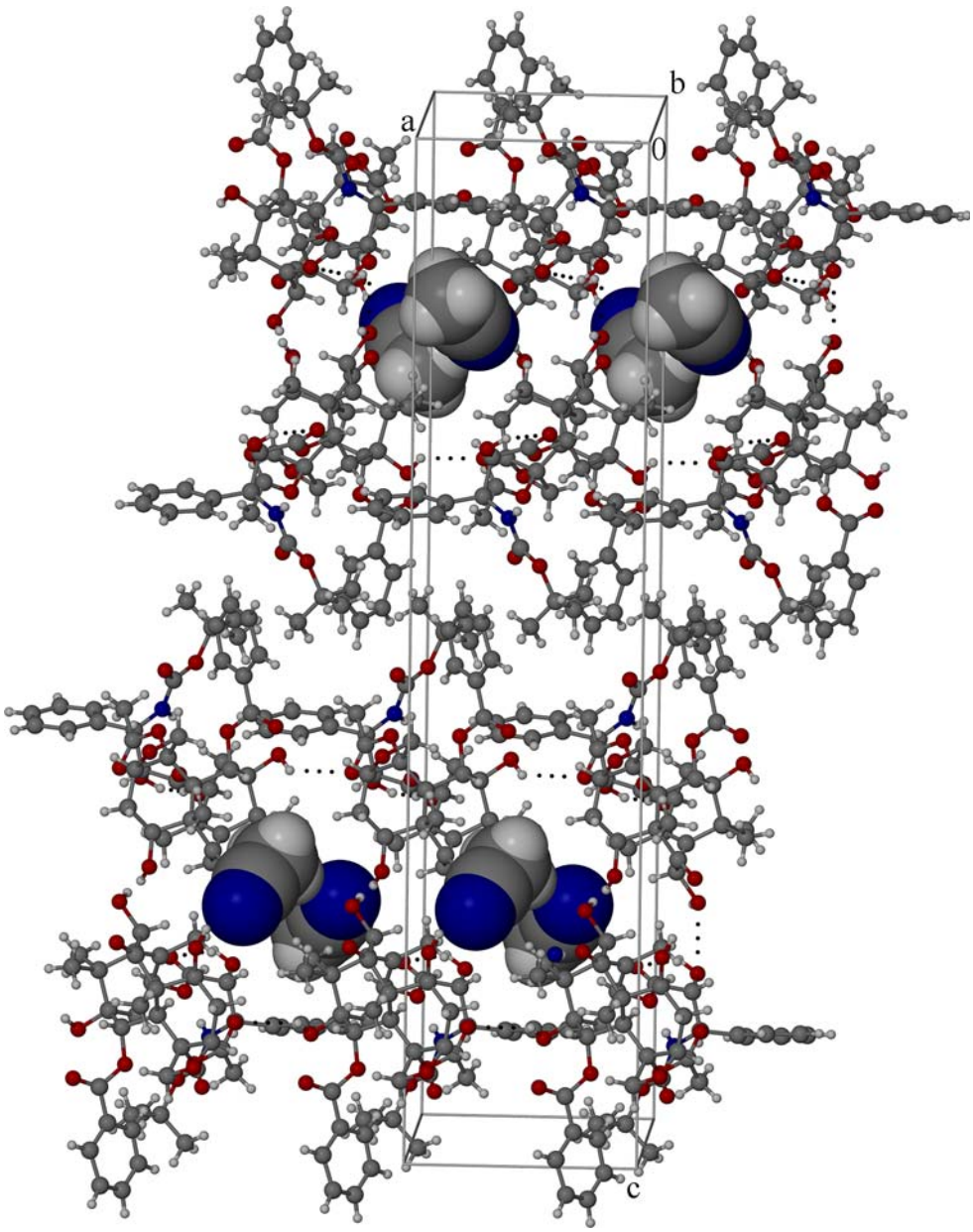


Fig. 3 Host–guest complex of **1** · ACN. The crystal packing shows hydroxyl O–H···O hydrogen bonding between the docetaxel host molecules and O–H···N with the ACN guests (shown with *space filling model*)

molecules present (water and/or methanol). Form B is, precisely, at the level of respective orientation of the bi-layers that a difference has been observed between two forms: form A the packing is rotated at 180° alternatively whereas for form B, the bi-layers pack with the same orientation" [25]. The reported **1** · CH_3OH · H_2O and **1** · $(H_2O)_3$ structural papers [25, 27, 34] does not conclude that docetaxel forms host–guest complexes.

Interestingly, the unit cell parameters, space group ($P2_1$) and crystal packing of **1** · *n*-butanol, **1** · DMF and **1** · CH_3OH · H_2O crystal structure are similar (Table 1), hence they are "isostructural" [35, 36]". The docetaxel host framework is similar in all the three crystal structures; however, the O–H moieties are oriented differently depending on hydrogen bonding with the different guest molecules in the channels. Since the CSD does not contain three-dimensional coordinates for both the **1** · $(H_2O)_3$ polymorphs (Ref codes: DARGOT and DARGOT01), we could not compare the structural features with our complexes. However, we have drawn few comments based on the unit cell parameters and space group. Interestingly, **1** · ACN unit cell parameters are similar to the marketed form A, and both refined in the same space group ($P2_12_12_1$) (Table 1). Further, form B unit cell parameters are similar to the **1** · *n*-butanol, **1** · DMF and **1** · CH_3OH · H_2O, with same space group ($P2_1$, Table 1). Hence, both the docetaxel trihydrate polymorphs are likely to exist as host–guest complexes. The present and literature results signify that docetaxel is prone to form host–guest complexes during crystallization from various solvents (Fig. 4).

The Cambridge Structural Database (CSD) study of solvent forming propensities of organic compounds reveals that water is at the top of the solvate forming solvents followed by methanol, benzene, dichloromethane, ethanol, acetone etc. [37–39]. Since few common solvents are frequently used for the crystallization of compounds, a usage correction was applied, which reveal that the likelihood forming a solvate is highest for DMF, dimethyl sulfoxide (DMSO) and dioxane [37]. In general, such entrapped solvent in the crystal lattice forms intermolecular interactions with the host molecule. In all the crystal structures, docetaxel hydroxyl moieties are hydrogen bonded to the solvent acceptors. In **1** · *n*-Butanol and **1** · (CH_3OH) · (H_2O) crystal structures, docetaxel OH's are hydrogen bonded to the guest hydroxyl/water oxygen. In **1** · DMF and **1** · ACN complexes, docetaxel OH's are hydrogen bonded to the carbonyl oxygen and CN of the guest molecules, respectively. The analysis of intermolecular interactions between the host and guest molecules suggests that docetaxel forms inclusion complexes with solvents that are capable of forming hydrogen bonds with the hydroxyl moiety. We take a note of such information for the design and synthesis of host–guest complexes of docetaxel with various acceptor containing solvents and their comprehensive structural information and thermal behavior will be studied in the future.

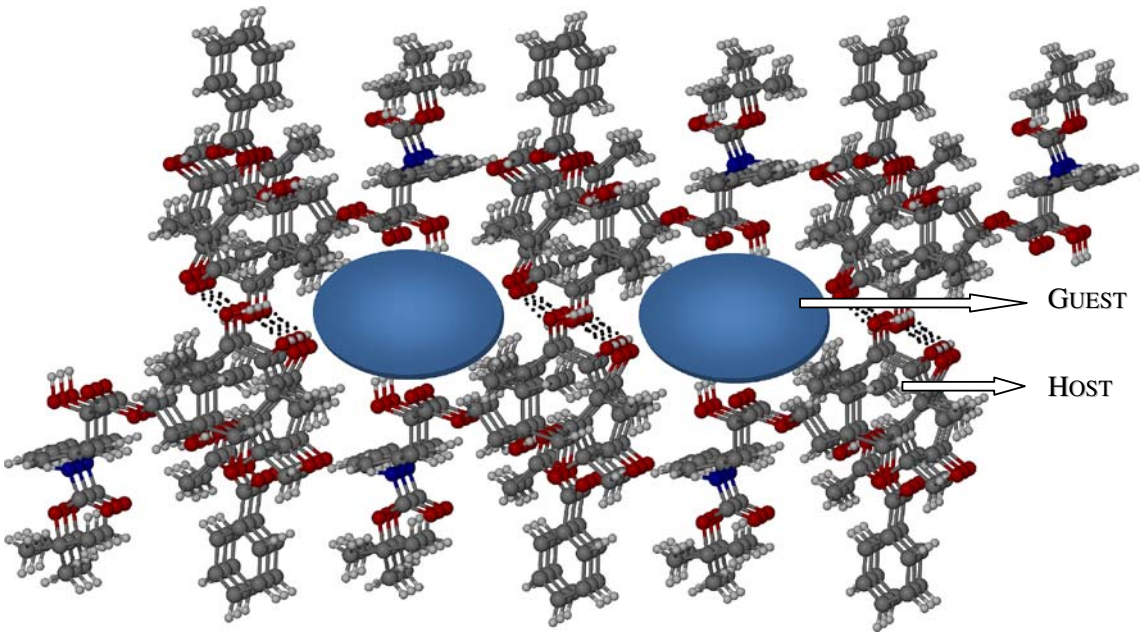


Fig. 4 A perspective view of docetaxel host framework, down [010]. The guest solvent molecules occupy the cavities, (shown with the *ellipsoids*) and forms hydrogen bonds with the host. The figure was generated using **1** · *n*-butanol crystal structure

Conclusions

Crystallization of docetaxel from *n*-butanol, DMF and ACN resulted in the formation of **1** · *n*-butanol, **1** · DMF and **1** · ACN inclusion complexes, respectively with 1:1 stoichiometry. In all the three crystal structures, docetaxel molecules formed a host framework and the solvent molecules are resided in the channels along [010]. The host docetaxel hydrogen bonded to the guest solvent molecules through hydroxyl moieties. Interestingly, **1** · *n*-butanol, **1** · DMF and a literature **1** · CH_3OH · H_2O host–guest complexes are isostructural with similar unit cell parameters, same $P2_1$ space group, and crystal packing. Further, the unit cell parameters and space group are similar to the form B of docetaxel trihydrate. **1** · ACN complex unit cell parameters and space group are similar to the marketed form A of docetaxel trihydrate. The bottom line is "docetaxel, an anti-cancer drug forms host–guest (inclusion) complexes."

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