Encapsulation of Indomethacin in PVP: Solid-State NMR Studies

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Summary: ^{13}C solid-state NMR and ^{1}H relaxation time measurements have been used to determine the structure of the crystalline and amorphous forms of the pharmaceutical drug indomethacin. Cross-polarization dynamics parameters were calculated for individual NMR resonances providing an insight into the mobility of functional groups in two forms of indomethacin. The changes of mobility in indomethacin/polyvinylpyrrolidone (PVP) formulation have been investigated *via* ^{1}H-^{13}C solid-state NMR methods.

Differences between the amorphous material and its crystalline counterpart have been observed. The γ-amorphous indomethacin rapidly crystallizes with time. It has been shown that encapsulation in the PVP stabilizes the amorphous form of the drug by preventing crystallization due to reduced mobility of the guest in the formulation.

Keywords: drug delivery; dynamics; NMR; noncrystalline polymer; pharmaceuticals

Introduction

Polymorphism is the ability of a substance to crystallize into two or more crystalline states that possess the same chemical formula but exhibit different physical properties. The formation of polymorphs may affect the physical properties of a substance, which in turn can affect the stability, dissolution and bio-availability. Solids may also exist in the amorphous form and can be compared to super-cooled liquids as they do not have the three-dimensional (3D) long-range order that is observed in crystalline solids.[1] Various phase transitions may occur during pharmaceutical processes including the inter-conversion of polymorphs, hydrate formation and conversion from the crystalline state to the amorphous form. These changes can alter the transport properties of a particular drug.

Many drugs are taken orally in tablet form and it is therefore often necessary to use the amorphous form or a suitably soluble polymorph of the substance as differences in solubility may enhance or reduce absorption of the active drug from its dosage form. The use of amorphous forms is limited as they tend to readily crystallise at ambient temperature with further risk of crystallisation during processes such as granulation and tableting.[2] In order to prevent their recrystallisation, increase their stability, solubility and bioavailability, it is often necessary to complex pharmaceutical drugs with other compounds.

Performance of many acidic drugs has been enhanced by complexation with cyclodextrins (CDs). Indomethacin has been found to form complexes with β-CD and γ-CD in a PEG-6000 carrier.[3] This complexation with CDs greatly increases the solubility of indomethacin at pH = 6 resulting in an increase in bio-availability.

The encapsulation in the polymer carriers can be used as an alternative pathway for enhancing drug delivery. The polyvinylpyrrolidone (PVP, Scheme 1) is used to form solid dispersions with many pharma-

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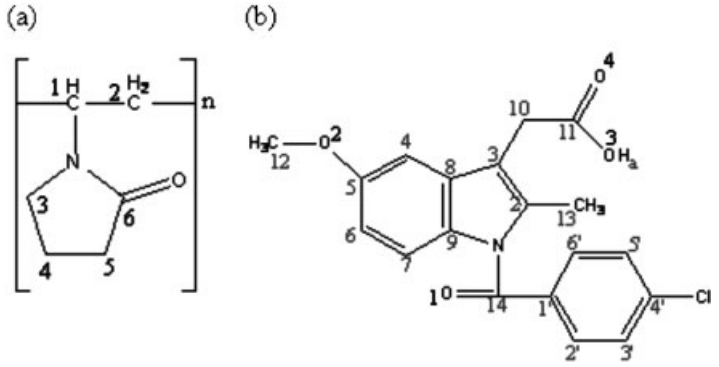

Scheme 1.
(a) repeating unit of the polyvinylpyrrolidone (PVP) and (b) chemical structure of indomethacin.

ceuticals to prevent crystallisation from the more soluble amorphous state.[4–6] The IR and FT Raman spectroscopic studies by Taylor *et al*. suggest that PVP disrupts the hydrogen bonding between indomethacin molecules and therefore allows the proton donating carboxylic acid group to form hydrogen bonds with the oxygen present in PVP.[7] These findings confirm that the addition of PVP to indomethacin prevents crystallization from the amorphous state to either α- or γ-crystalline forms[7,8] and therefore increases stability and enables the amorphous form to be utilized in the pharmaceutical industry.

Solid-state NMR is an essential technique for characterising solids as it provides chemical information and valuable crystallographic information from the short-range interactions between nuclei. NMR studies on indomethacin encapsulated in a hydrophilic PVP polymer were carried out to determine if the amorphous state can be stabilized and understand the interactions involved. Therefore, it is important to analyze the structural and dynamic differences between different forms of indomethacin in order to understand the effects of PVP on the drug. Cross-polarization dynamics have been used alongside with relaxation time studies in order to provide an insight into the molecular level structure, bonding and mobility of individual functional groups.

Experimental Parts

Materials

Samples of γ-crystalline and amorphous indomethacin were provided by the research group in The University of Manchester (Prof. R. Davey). The γ-amorphous solids were prepared by melting the corresponding crystalline polymorph at its melting temperatures (T_m γ-crystalline indomethacin = 161 °C). Samples of PVP and the PVP/indomethacin (4:1) formulations were provided by a research group in the Queen Mary University of London (Dr. J. A. Daar). The PVP-indomethacin composite was prepared in super-critical carbon dioxide.[9] The samples were lightly ground before being packed into a 4 mm zirconia rotor.

Solid-state NMR

^1H–^{13}C cross-polarization solid-state NMR (CP/MAS) spectra were acquired at 400.16 MHz for ^1H and 100.56 MHz for ^{13}C using a RAMP CP pulse sequence. The spinning rate was 7.0 kHz, ^1H $\pi/2$ pulse length was 3.40–4.40 μs and the pulse delay 10.0 s. TPPM decoupling[10,11] was used during the acquisition. The Hartmann-Hahn was set with hexamethylbenzene (HMB). The ^{13}C chemical shifts are quoted in ppm with respect to TMS. Variable spin-lock ^1H relaxation time in the rotating frame ($T1_\rho^H$-VSL) was measured at a

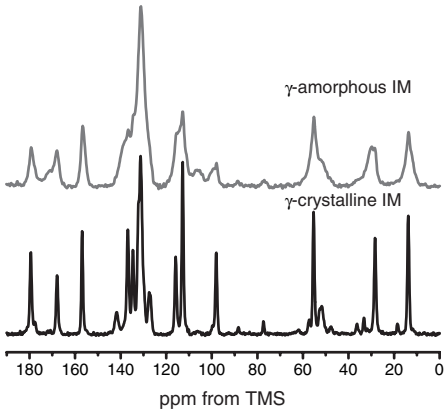

Figure 1.
^{1}H-^{13}C CP/MAS NMR spectra of indomethacin.

spinning rate of 7 kHz using a modified CP pulse sequence.[12] Prior to CP, the ^{1}H magnetisation is locked along the *y* axis for a variable time τ ranging from 0.01 to 12 ms. The ^{1}H magnetisation evolves under the effect of the homonuclear dipolar interaction during the time t. As a result, the intensity of the cross polarised peaks depend on the efficiency of the ^{1}H relaxation in the rotating frame. The contact time during CP was 1.0 ms.

Results and Discussion

Solid-state NMR Spectra of Indomethacin

Indomethacin is poorly soluble in water and therefore its oral bio-availability is limited by the slow dissolution rate. Therefore, the amorphous form is often preferred in the pharmaceutical industry. The spectra of the γ-crystalline and amorphous indomethacin are presented in the Figure 1. Only a single line is observed for every chemical environment for γ-crystalline indomethacin, in agreement with the crystalline structure indicating the presence of two equivalent molecules in the unit cell. The dimers are formed by hydrogen bonding of the carboxylic acid groups. A broadening of the resonances due to the lack of long-range ordering is observed in the amorphous form. The main difference between the spectra for the crystalline and amorphous forms is observed for the peaks corresponding to –N–C=O sites exhibiting an

Table 1.
^{1}H-^{13}C CP Kinetics Parameters of the Main Resonances of Indomethacin.

Assignment	δ(ppm)		T_{IS}^{*}, ms	$T_{1\rho}^{H}$, ms	λ^{**}	T_{df}, ms
C11	179.45	Cryst	0.72	13.7	–	–
		Amorp	0.59	25.1	–	–
C14	167.92	Cryst	2.01	19.4	–	–
		Amorp	1.76	36.5	–	–
C5	156.97	Cryst	0.94	16.8	–	–
		Amorp	0.88	30.0	–	–
		Formul	0.83	14.7	–	–
	131.40	Cryst	–	21.2	0.91	1.33
		Amorp	–	30.9	0.75	1.65
		Formul	–	17.2	0.77	1.36
C7	112.81	Cryst	–	16.2	0.83	1.06
		Amorp	–	26.7	0.73	1.22
		Formul	–	13.6	0.67	1.05
C4	98.08	Cryst	–	18.5	0.59	1.20
		Amorp	–	38.0	0.41	0.92
		Formul	–	31.2	0.80	0.65
C12	55.37	Cryst	–	19.2	0.67	0.62
		Amorp	–	34.6	0.54	0.65
		Formul	–	20.1	0.77	0.35
C10	28.44	Cryst	–	15.6	0.52	0.86
		Amorp	–	28.2	0.33	0.40
C13	13.81	Cryst	–	21.1	0.67	0.57
		Amorp	–	36.0	0.46	0.55

* the data analysed using the I-S model;
** the data analysed using the I*-I-S model.

additional sites at 171.50 ppm. This line can be ascribed to a different H-bonding motif involving –COOH and –N–C=O groups from different molecules. Such motif has been confirmed for the α-form of indomethacin by analysis of its crystalline structure.[13]

The dynamic behaviour of both crystalline and amorphous indomethacin was evaluated by variable contact time cross-polarisation. The CP kinetics, the dependence of the intensity of a resonance *vs.* contact time, were analysed using either I-S model or I-I*-S models[14] (Table 1). The derived time constants in the I-S model include the T_{IS} time, related to the internuclear distances and molecular mobility and the $T_{1\rho}^{H}$ relaxation time describing the decay of intensity for longer contact times. In addition to the $T_{1\rho}^{H}$ time the I-I*-S model gives the ^{1}H spin-diffusion time constant T_{df}, describing the strength of the homonuclear dipolar interactions and the homogeneity of the *I* spin pool, and parameter λ defined by the number n of ^{1}H spins attached to the ^{13}C spin under study ($\lambda = 1/(n+1)$).

Faster CP build-ups are observed for the amorphous form of indomethacin as suggested by the shorter value of T_{IS} and T_{df} times. Longer $T1_{\rho}^{H}$ times are observed for all the resonances in the amorphous form indicating an increase of the local mobility (similar observation with regard to the relaxation times have been reported recently by Apperley *et al.*[15]). This can be related to the lack of organisation and the changes in the H-bonding network. Amorphous indomethacin is unstable and recrystallises over time even when stored at low temperature as suggested by the sharpening of the resonances (Figure 2). The crystallisation of amorphous indomethacin is accompanied by the shortening of the $T1_{\rho}^{H}$ relaxation times.

PVP

^{1}H–^{13}C CP/MAS NMR spectra of the pure PVP and the PVP/indomethacin formulation (Figure 3) do not show any effect of encapsulation of the drug on the chemical shift of the resonances corresponding to the PVP. At such low loading level in indomethacin, no changes in the linewidths and relative intensities are observed in the formulation (Table 2).

Variable spin-lock $T1_{\rho}^{H}$ measurements were carried out to evaluate the effect of

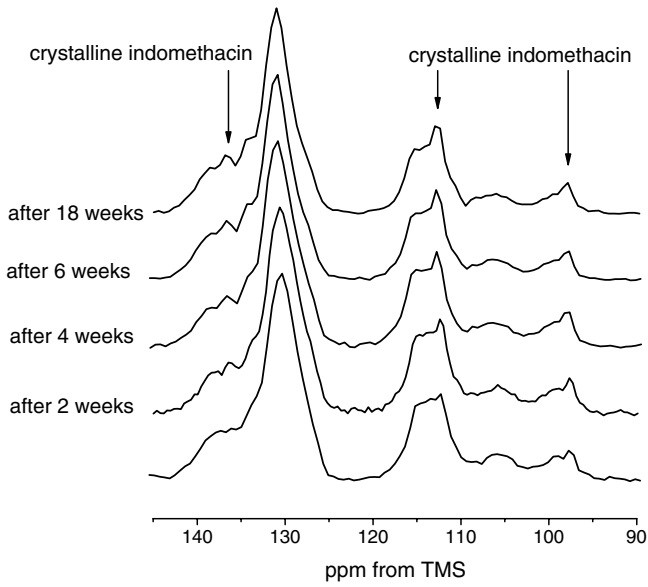

Figure 2.
Aromatic region of γ-amorphous indomethacin at different storage time.

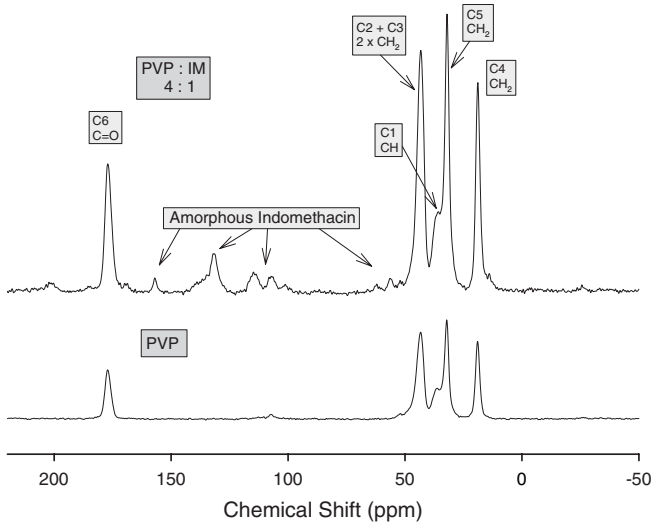

Figure 3.
^{1}H-^{13}C CP/MAS NMR spectra of pure PVP and PVP/indomethacin 4:1 formulation.

indomethacin on the dynamic properties of the polymer (Table 2). Similar relaxation behaviour is observed in the presence of indomethacin which suggests the guest has a limited effect of the local mobility of PVP. The CP kinetics analysis (data not shown) leads to similar results. This indicates at such low loading level (*ca* 13:1 molar), the effect of indomethacin on the PVP could not be detected by solid-state NMR.

Indomethacin in Formulation

Encapsulation of the drug in amorphous PVP polymer has been found to increase the rate of dissolution and to prevent recrystallisation of indomethacin. The IR studies indicated that PVP disrupts hydrogen bonding between carboxylic dimers in indomethacin and new bonds form between the drug (COOH) and the polymer (CO).[7] However, very little is known about the mobility of indomethacin in the formulation as such information is not accessible from the IR-spectroscopy. The knowledge of dynamics in pharmaceutical formulations is crucial for understanding the molecular level mechanism of the release of a drug from polymeric matrix.

The encapsulated guest in the PVP is in the amorphous state confirmed by the XRD and solid-state NMR. Even at relatively low loading level, the resonances of the drug (Figure 3) can be used to asses its dynamics in the formulation. Since the indomethacin is in the amorphous state in the formulation, the CP kinetics should be compared to the ones of the pure amorphous phase rather than the crystalline polymorph. It should be noted that the resonances corresponding to the amide carbonyl (C14) and

Table 2.
The parameters for the $T1_{\rho}^{H}$ relaxation of the PVP resonances.

Assignment	ppm	Pure PVP			PVP/indomethacin 4:1		
		$\Delta\nu$ (Hz)	A	$T1_{\rho}^{H}$ (ms)	$\Delta\nu$ (Hz)	A	$T1_{\rho}^{H}$ (ms)
C6	177.59	257	158	15.0 ± 0.2	296	178	14.2 ± 0.4
C2, C3	43.47	313	336	16.1 ± 0.2	329	356	16.5 ± 0.4
C1	36.2	362	141	16.0 ± 0.3	386	161	15.5 ± 0.3
C4	32.42	203	233	15.9 ± 0.1	206	235	16.7 ± 0.2
C5	19.25	189	180	16.1 ± 0.2	209	188	16.1 ± 0.4

carboxylic acid (C11) groups responsible for the hydrogen bonding cannot be analysed as they are masked by the signal corresponding to the carbonyl group in PVP.

In the PVP/indomethacin formulation, significantly shorter $T1_{\rho}^{H}$ times are observed for all the sites suggesting the local mobility of indomethacin is reduced in formulation in comparison with the pure amorphous indomethacin. The spin-diffusion process is more efficient for amorphous encapsulated indomethacin as indicated by the shorter T_{df} times. An increase of λ - which is inversely proportional to the number of ^{1}H involved in CP[14] is observed for C12 and C4.

These changes confirm PVP disrupts the organisation of the drug in the formulation and decrease its mobility in comparison with the pure amorphous phase. It can be assumed therefore that encapsulation of indomethacin in PVP stabilises the amorphous form of the drug by reducing its mobility as a result of dispersing the drug in the polymer.

Conclusions

Solid-state NMR study of PVP- indomethacin composite is presented. The amorphous and crystalline forms of indomethacin exhibit different motional states with a higher local mobility for the amorphous form. Solid-state NMR confirms that recrystallisation of amorphous indomethacin upon storage occurs even at low temperatures and is accompanied by the reduction in its mobility. The recrystallisation is prevented in PVP-indomethacin formulation due to the formation of intermolecular H-bonds between the PVP and indomethacin. While indomethacin has a limited effect on the dynamics of PVP host due to its low loading level, the local mobility of the amorphous encapsulated guest is reduced in comparison with the pure amorphous indomethacin. The hindered mobility combined with the dispersion of the drug molecules in the polymer matrix hampers the reorganisation of indomethacin in the formulation.

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