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Crystallization of an amorphous solid studied by nuclear quadrupole double resonance

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ABSTRACT

Nuclear quadrupole double resonance (NQDR) is proposed as a method for quantitative observation of crystallization of amorphous solids. NQDR signals from amorphous and crystalline parts of a sample may be separated. The intensity I of the NQDR signal from the crystalline part of the sample is proportional to its mass. With increasing time the amorphous phase in the sample transforms to the crystal phase and the intensity I approaches its limiting value I_0 corresponding to the complete transformation to the crystal phase. The ratio I/I_0 is equal to the mass fraction of the crystalline part of the sample. The same experimental method can be used to determine the mass fraction of a given crystal polymorph in a mixture of crystal polymorphs. As an example we studied crystallization of amorphous nifedipine at 100 °C. The results of the NQDR study are compared to the published results of other studies.

1. Introduction

Metastable amorphous phases are frequently encountered, especially in organic systems. They are of great importance in diverse fields including basic physics, polymer science, ceramics, metallurgy, food science, and pharmaceutical sciences.

In pharmaceuticals amorphous phases are often intentionally produced to improve the dissolution and bioavailability of poorly soluble compounds [1–3], to stabilize the tertiary structure of proteins [4], or to improve the mechanical properties of excipients (e.g., lactose). However, amorphous solids are physically unstable because of their high energy state, and crystallization during storage may present a problem.

Amorphous materials, exhibiting the glass transition, are known to crystallize above and below the glass transition temperature T_g [5–7]. The process of crystallization is known to comprise two major steps: nucleation and crystal growth, and the rates are generally governed by molecular mobility affecting the diffusion rate of molecules and thermodynamic factors such as the Gibbs free energy and nucleus/amorphous interfacial energy [8–12]. Several experimental studies demonstrated that the molecular mobility of amorphous pharmaceuticals is one of the important factors affecting the crystallization rate [13,14].

However, the crystallization rate of amorphous pharmaceuticals cannot be determined only by molecular mobility [15,16] and the influence of various thermodynamic factors to the crystallization process is not yet completely understood. Several experiments performed under various experimental conditions are still necessary to reach definitive conclusions about the crystallization process.

Recently solid-state NMR has been used increasingly in the field of amorphous pharmaceuticals [17,18]. One reason is the relatively high ^{13}C signal-to-noise ratio nowadays routinely observed with the CPMAS technique combined with efficient proton decoupling. Unlike for example X-ray powder diffraction NMR is not dependent on long-range order for determinations of structure.

Here we propose ^{1}H–^{14}N nuclear quadrupole double resonance (NQDR) as a suitable method for quantitative observation of crystallization of amorphous solids. The technique has a high sensitivity and a relatively high resolution. We show how the NQDR signal from the amorphous part of the sample can be separated from the NQDR signal from the crystalline part of the sample. The intensity I of the NQDR signal from the crystalline part of the sample is proportional to its mass. Measurement of the intensity I at different stages of crystallization together with the intensity I_0 of completely crystalline sample can be used to follow the fractions of the crystalline and amorphous parts of the sample during the

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crystallization. Crystallization of amorphous nifedipine, an antihypertensive drug, whose crystalline form was previously the subject of a detailed ^{14}N NQR study of photo degradation [19] is used to illustrate the technique.

2. ^{1}H–^{14}N NQDR in inhomogeneous samples

2.1. ^{14}N NQR and ^{1}H–^{14}N NQDR

The nitrogen nucleus ^{14}N has a spin $I = 1$ and exhibits in zero magnetic field three generally non-degenerated nuclear quadrupole energy levels. The transition frequencies between these levels (NQR frequencies) are named as ν_+, ν_- and $\nu_0 = \nu_+ - \nu_-$ ($\nu_+ \geqslant \nu_- \geqslant \nu_0$). They depend on two parameters, the quadrupole coupling constant e^2qQ/h and the asymmetry parameter η of the electric-field-gradient (EFG) tensor at the position of the nitrogen nucleus, as [20]

$$\begin{aligned} \nu_+ &= \tfrac{e^2qQ}{4h}(3+\eta) \\ \nu_- &= \tfrac{e^2qQ}{4h}(3-\eta) \\ \nu_0 &= \nu_+ - \nu_- = \tfrac{e^2qQ}{2h}\eta \end{aligned} \quad (1)$$

The ^{14}N nuclear quadrupole coupling constant and asymmetry parameter η can be measured by NMR in a single crystal. In a polycrystalline sample this represents a difficult task because the widths of the quadrupole broadened NMR lines are typically several MHz. Pulse ^{14}N NQR and several ^{1}H–^{14}N nuclear quadrupole double resonance (NQDR) techniques are used instead. In an amorphous sample the NQR lines are expected to be broad and the sensitivity of pulse NQR may be too low to detect them. On the other hand the sensitivity of NQDR is high so it can be used to observe broad NQR lines. In the present study we have used the NQDR techniques using cross relaxation [21–23], multiple frequency sweeps and two-frequency irradiation [24,25].

The NQDR spectrometer and the experimental procedures are described in details in two previous papers [26,27]. Here we give only a brief summary. In a NQDR experiment the sample shuttles between two magnets. First in a high magnetic field B_0 the proton magnetization M reaches its equilibrium value M_0. Then the sample is adiabatically transferred to the second magnet where the magnetic field B is much lower than B_0. The sample is left in the low magnetic field for a fixed time τ. During this time the proton magnetization relaxes from its initial value M_0 towards its equilibrium value in the low magnetic field which is equal to M_0B/B_0. This period is called the relaxation period. At the end of the relaxation period the proton magnetization reaches a value $M(\tau)$, $M_0 > M(\tau) > M_0B/B_0$. Then the sample is adiabatically transferred back into the first magnet and the proton NMR signal is measured. Its intensity is proportional to the proton magnetization $M(\tau)$.

When the ^{14}N spin–lattice relaxation rates are high as compared to the proton spin–lattice relaxation rate, we perform a ν_H scan at a fixed duration τ of the relaxation period and observe quadrupole dips. This technique is called the cross relaxation spectroscopy. A quadrupole dip is observed when the proton NMR frequency ν_H in the low magnetic field B, $\nu_H = \gamma_H B/2\pi$, matches a ^{14}N NQR frequency. In such a case an additional proton spin–lattice relaxation process via the ^{14}N spin system takes place. This additional relaxation process decreases $M(\tau)$ and makes the proton NMR signal at the end of the magnetic field cycle smaller.

When the quadrupole dips are not observed in the cross-relaxation spectrum, what is due to low ^{14}N spin–lattice relaxation rates, we apply multiple frequency sweeps of an *rf* magnetic field and the ν_H scan. The ^{14}N NQR frequencies ν_+ and ν_- are not known, but we often know the frequency range in which the two ^{14}N NQR frequencies are expected to be found. The frequency limits $\nu_{\min}$ and $\nu_{\max}$ of the sweeps are chosen so that a linear frequency sweep covers this frequency range. The rf magnetic field excites the ^{14}N quadrupole spin system always when its frequency passes a ^{14}N NQR frequency. When we perform the ν_H scan under the influence of multiple frequency sweeps, we observe the quadrupole dip at $\nu_H = \nu_0$. This dip is strong only when the sweeps cover both higher ^{14}N NQR frequencies ν_+ and ν_-. The intensity of this dip strongly decreases when the sweeps cover only one higher ^{14}N NQR frequency. We can thus locate the frequencies ν_+ and ν_- by varying the frequency limits $\nu_{\min}$ and $\nu_{\max}$. We fix the proton Larmor frequency at $\nu_H = \nu_0$ and the frequency limit $\nu_{\max}$ above ν_+. Then we perform the $\nu_{\min}$ scan. We observe a strong increase of the proton NMR signal when the frequency limit $\nu_{\min}$ passes the ^{14}N NQR frequency ν_- from below. In a similar way we locate the ^{14}N NQR frequency ν_+ by performing the $\nu_{\max}$ scan.

The basic idea of the two-frequency irradiation technique is that simultaneous irradiation of the ^{14}N quadrupole spin system with two *rf* magnetic fields with the frequencies $\nu_1 = \nu_+$ and $\nu_2 = \nu_-$ saturates the ^{14}N NQR transitions and makes the populations of the three ^{14}N quadrupole energy levels equal. When the two-frequency irradiation is applied during the relaxation period and the low static magnetic field B is chosen so that the proton NMR frequency ν_H matches the lowest ^{14}N NQR frequency ν_0, energy transfer from the "hot" ^{14}N quadrupole spin system to the "cold" proton spin system in a short time destroys the proton magnetization. No proton NMR signal is observed at the end of the magnetic field cycle. The two-frequency irradiation technique is also used to refine the NQDR spectrum.

2.2. Inhomogeneous samples

In an inhomogeneous sample consisting of two components of a given chemical substance (two crystal polymorphs or a mixture of amorphous and crystalline phase) the fractions of the two components can be determined by NMR. When for example the two components of a sample differ in an NMR parameter, say T_1, T_2, or chemical shift of a nucleus, the analysis of the biexponential longitudinal or transverse relaxation or the comparison of the chemical shift spectrum of the inhomogeneous sample and the chemical shift spectra of the two pure components can be used to determine the fraction of each component. As an alternative we propose here ^{1}H–^{14}N NQDR for the same purpose. Two possible advantages of NQDR are that it can be used also when the longitudinal and transversal relaxation rates of the two components are not very much different. Also the resolution of NQDR ($\Delta\nu\nu \sim 10^{-3}$) usually exceeds the resolution of the chemical shift spectra in solids. The technique is applicable only to the samples containing hydrogen and nitrogen atoms.

Suppose we are dealing with a two-component sample of a given chemical substance (two crystal polymorphs or a sample consisting of amorphous and crystalline fraction) and we know the ^{14}N NQR frequencies $\nu_0(A)$, $\nu_-(A)$ and $\nu_+(A)$ of one crystalline component. We want to determine the mass fraction of component A in the sample. To do it we first perform in the inhomogeneous sample a ν_H scan around $\nu_H = \nu_0(A)$ at a fixed duration τ of the relaxation period. Then we perform the same scan under the influence of two rf magnetic fields with the frequencies $\nu_1 = \nu_+(A)$ and $\nu_2 = \nu_-(A)$. In the second scan we obtain a smaller proton NMR signal at $\nu_H = \nu_0(A)$. The difference of the two proton NMR signals measured at $\nu_H = \nu_0(A)$ with no and with the two-frequency rf irradiation we call the NQDR signal intensity I. Next we perform the same experiment with a sample of the same mass consisting only of component A and obtain the NQDR signal intensity I_0. The ratio I/I_0 is equal to the mass fraction of the component A in the inhomogeneous sample. The difference $1 - I/I_0$ is equal to the mass fraction of the second component in the two-component sample.