Detection of polymorphism in pharmaceutical products using ^{14}N NQR spectroscopy

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Aim: The value of Nuclear Quadrupole Spectroscopy (NQR) in nondestructive and reliable detecting of polymorphism in active pharmaceutical ingredients (API).

Abstract

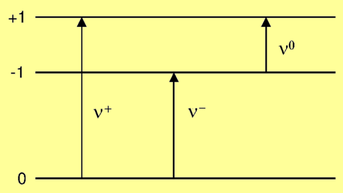
The golden standard in determination of polymorphism in an active pharmaceutical ingredient (API) is the X-ray diffraction (XRD) method. However, it usually requires a special sample preparation and is less suitable for checking the possible appearance of polymorphism in drugs during the production process and after suspicious shelf life.
In this study, we examined the value of nitrogen nuclear quadrupolar resonance (^{14}N NQR) spectroscopy in nondestructive and reliable detection of polymorphism in the antibacterial drug sulfanilamide. The advantage of this method is that there is no special sample preparation. Solid samples in their initial forms (powders, granulates, tablets etc.) can be used even in their original package if it is not completely metallic. This quick and reliable proof of polymorphism appearance could become a method of choice in determination and/or confirmation of polymorphism in solid drugs containing nitrogen.

Method

Nuclear quadrupole resonance (NQR) is a nondestructive, contactless radiofrequency (RF) spectroscopic method related to nuclear magnetic resonance (NMR). Unlike NMR, NQR transitions of nuclei can be detected in absence of magnetic field (so called "Zero Field NMR"). NQR is based on the electric interaction between nuclei with non zero electric quadrupole moment (spin ≥ 1) and the internal electric field gradient (EFG). Since the EFG at the location of a nucleus in a given substance is determined primarily by the valence electrons involved in the particular bond with other nearby nuclei, the NQR frequency at which transition occurs is unique for this substance.

^{14}N nucleus has spin I=1 and three NQR transition frequencies

$$\nu^{\pm} = \frac{1}{4}Q_{cc}(3 \pm \eta),\ \ \nu^{0} = \nu^{+} - \nu^{-} = \frac{1}{2}Q_{cc}\eta,$$



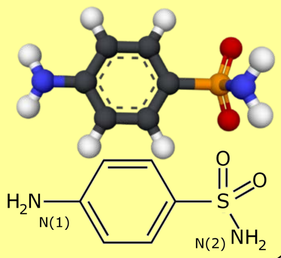
which depend on a quadrupole coupling constant Q_{cc} and an asymmetric parameter η.

$Q_{cc} = \frac{e^2qQ}{h}$ is proportional to nuclear electric quadrupole moment eQ and maximal component $eq = q_{zz}$ of electric field gradient (EFG) tensor (e is the electron charge and h is the Planck constant). The asymmetry parameter is defined as $\eta = |q_{xx} - q_{yy}|/q_{zz}$.

In this study, we examined the presence of polymorphism in the antibacterial drug sulfanilamide, which has three known polymorphic forms α, β and γ and two chemically nonequivalent ^{14}N atoms:
N(1) - para amino nitrogen, and N(2) - sulfonamide nitrogen,
which give two sets of three transition frequencies (ν^+, ν^-, ν^0), which are determined by transitions between NQR levels and are different for each polymorph forms α and β were obtained by crystallization of commercially available sulfanilamide (Sigma-Aldrich) in:
i) isoamyl or n-butyl alcohol for α, and ii) ethyl alcohol for β polymorph.

At T > 390 K α and β polymorphic forms exhibit a transition to γ polymorph.

All three polymorphs are stable at room T.

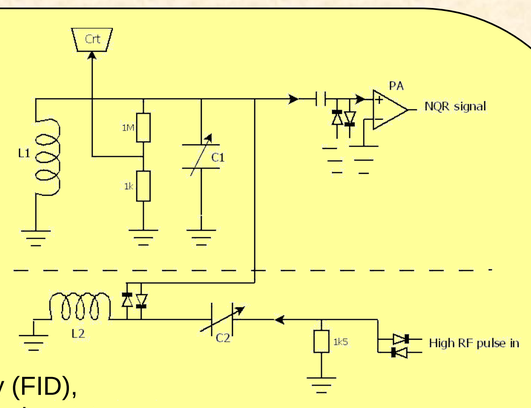


Measurements

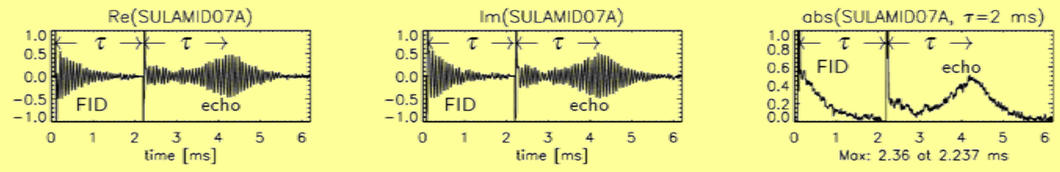
We used a standard pulsed NQR spectrometer consisting of two tunable coupled LC circuits:

1) with a sample in the solenoid coil L1, preamplifier and receiver
2) with "step-up" coil L2 attached to the RF pulse programmable unit (Spin Core) and the power RF amplifier (Tomco)

The whole spectrometer was operated from a PC.

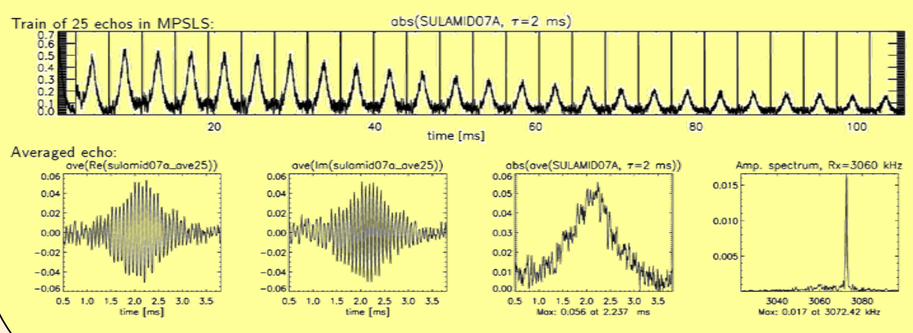


Typical measurement: initial RF pulse generates free induction decay (FID), followed by so called refocusing RF pulse at time τ, which creates an echo at $\Delta t = \tau$



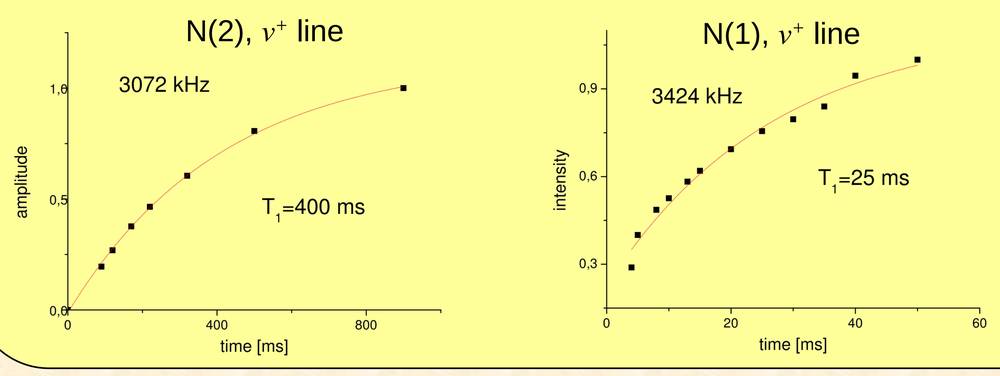
To improve S/N and to speed up these measurements, we applied the Multi-pulse spin-locking sequence MPSLS[1] :

$t_\phi - (\tau - t_{\phi+90} - \tau)_n$, where

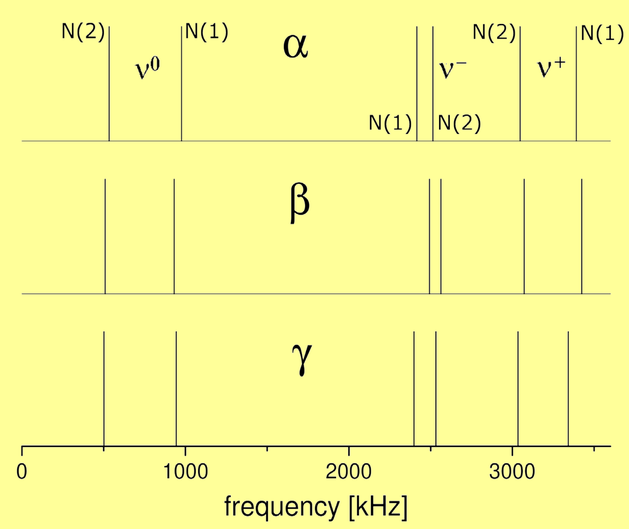


- t_ϕ is a duration of initial RF pulse ($\pi/2$-pulse in NMR), which generates FID
- $t_{\phi+90}$ is a duration of echo forming refocusing pulse (π-pulse in NMR), where (90) denotes 90º phase shift relative to the previous t_ϕ pulse
- τ is time delay between t_ϕ and first $t_{\phi+90}$ pulse. It is also a time between a given $t_{\phi+90}$ pulse and the next echo peak.
- n is total number of $t_{\phi+90}$ pulses in MPSLS sequence.

Results: Spin-lattice relaxation time T_1 for β polymorph

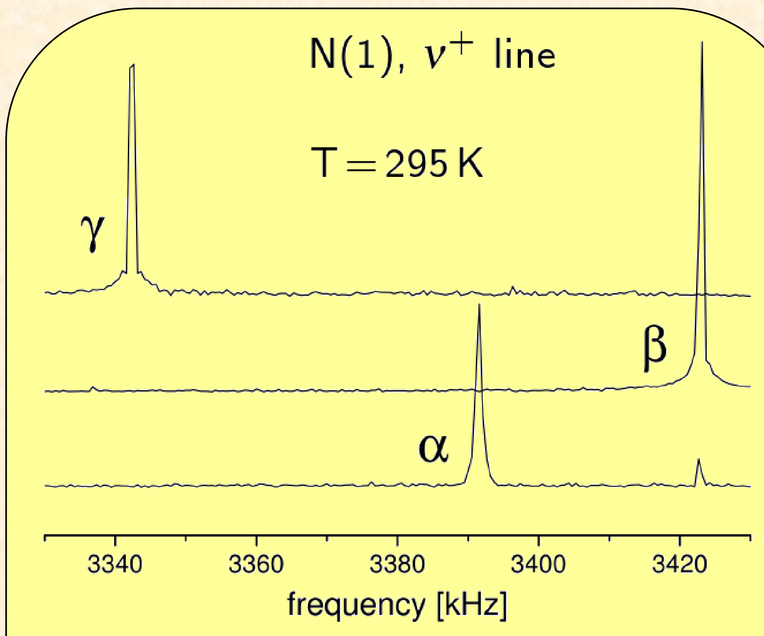


Results

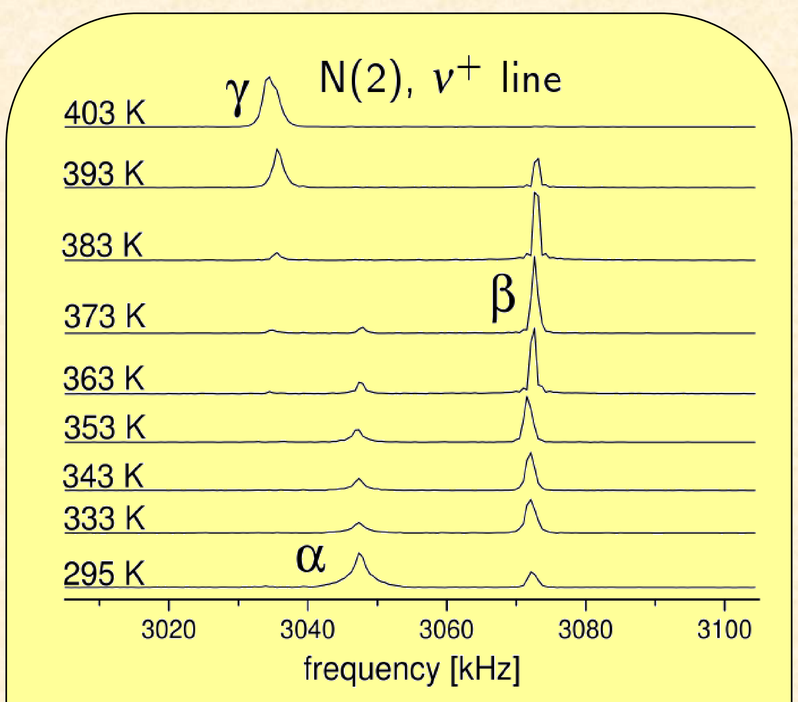


^{14}N NQR parameters of α, β and γ polymorphs of sulfanilamide at room temperature: transition frequencies (ν^+, ν^-, ν^0), nuclear quadrupole coupling constants Q_{cc}, asymmetry parameters η and spin-lattice relaxation time T_1.

polymorph	atom	ν^+ [kHz]	ν^- [kHz]	ν^0 [kHz]	Q_{cc} [kHz]	η	T_1 [ms]
α	N(1)	3391	2415	976	3871	0.50	25
	N(2)	3047	2514	533	3707	0.29	400
β	N(1)	3424	2493	931	3945	0.47	25
	N(2)	3072	2563	509	3757	0.27	400
γ	N(1)	3342	2398	944	3827	0.49	25
	N(2)	3034	2532	502	3711	0.27	25



Part of ^{14}N NQR spectra of nitrogen (N1) with the frequency ν^+: 3391 kHz for α, 3424 kHz for β and 3342 kHz for γ polymorph. Note the traces of presence of β polymorph in the ^{14}N NQR scan of α polymorph.



^{14}N NQR spectra of nitrogen N(2) (ν^+ line) displaying a transition of the initial α polymorph at 295 K (with traces of β form) to the final γ polymorph. The sulfanilamide sample was thermally treated at different temperatures, denoted at the left side of each ^{14}N NQR scan, prior to the ^{14}N NQR measurements.

Reference:
[1] R.A. Marino, S.M. Klainer, Multiple spin echoes in pure quadrupole resonance, J. Chem. Phys. 67: 3388-3389 (1977)