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Multiple-sample probe for solid-state NMR studies of pharmaceuticals

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Abstract

Solid-state NMR spectroscopy (SSNMR) is an extremely powerful technique for the analysis of pharmaceutical dosage forms. A major limitation of SSNMR is the number of samples that can be analyzed in a given period of time. A solid-state magic-angle spinning (MAS) probe that can simultaneously acquire up to seven SSNMR spectra is being developed to increase throughput/signal-to-noise ratios. A prototype probe incorporating two MAS modules has been developed and spectra of ibuprofen and aspirin have been acquired simultaneously. This version is limited to being a two-module probe due to large amounts of space required for the tuning elements located next to the MAS modules. A new probe design incorporating coaxial transmission lines and smaller MAS modules has been constructed. This probe allows for close proximity of the MAS modules (within 3 cm), adequate proton decoupling power (>50 kHz), and the capability of remote tuning and sample changing. Spectra of hexamethylbenzene (HMB) have been acquired and show signal-to-noise ratios comparable to existing SSNMR probes. Adamantane line widths are also comparable to conventional probe technology. Decoupling powers of 70 kHz have been achieved using a MAS module suitable for 3 cm spacing between modules. Remote tuning has also been achieved with this new coaxial transmission line design. This probe design can be easily scaled to incorporate multiple MAS modules, which is a limitation of the previous design. The number of modules that can be incorporated is only limited by the number of transmission lines that will fit in a cross-sectional diameter of the bore and the axial field length of the magnet.

Keywords: Probe; MAS; High throughput; NMR; Solid state; Pharmaceutics; Analysis

1. Introduction

Solid-state NMR spectroscopy (SSNMR) is a very powerful technique for the analysis of pharmaceuticals and pharmaceutical formulations, because of the vast quantity of information obtained about the structure and dynamics of compounds in a formulation [1–3]. SSNMR has the capability to determine the state of a drug either in the bulk state or within a formulated product *without* having to extract the drug from the formulation. It is selective, in that the drug usually has a different chemical shift than that of the excipients, making it easy to identify the drug in the formulation. SSNMR is quantitative, and can be used to determine the relative amounts of different crystalline forms and amorphous content. Drug–excipient interactions can also be studied. Determination of mobilities can help identify why a drug may have failed (or will fail) stability tests. Controlled-release devices are complex systems which could be much better formulated if the state of the drug could be determined directly, which is possible using SSNMR.

New drug compounds are often poorly crystalline or even amorphous, have long relaxation times, and are present at low levels in a formulation. This creates a significant problem for analyzing these compounds with SSNMR. Analysis times can range from a few minutes to a few days, depending upon the state of the sample (i.e. bulk drug or formulated product; crystalline or amorphous), relative sensitivity (i.e. choice and number of different nuclei in molecule), and relaxation parameters. For example, quantitation of a mixture of two forms of a

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compound can take a few hours (for a sample with short relaxation times) to a few days. Analyzing a series of formulated products may take a month or more of spectrometer time. This leads to low throughput, high cost per sample analysis, and has relegated SSNMR in many cases to be a prohibitively expensive problem-solving technique compared to other analytical techniques such as powder X-ray diffraction (PXRD), infrared and Raman spectroscopy, and differential scanning calorimetry (DSC).

Increasing the signal-to-noise ratio (SNR) by signal averaging (in samples containing nuclei with low magnetogyric ratios, low natural abundance, and low sample concentration) is a problem if the sample has long spin-lattice relaxation times (T_1) of minutes, hours, or even days, because the number of transients acquired is limited to one to several dozen. Table 1 shows the relaxation times for many pharmaceutical solids reported in the literature [4–10]. For example, aspirin is a representative pharmaceutical solid that has a ^{1}H T_1 relaxation time of approximately 30 s at 300 MHz. In a ^{13}C cross polarization magic-angle spinning (CPMAS) experiment the delay between acquisitions must be >90 s to avoid saturation. Note that some of the compounds listed in Table 1 may have been chosen because they have relatively short relaxation times.

The SNR in an NMR experiment is proportional to the signal divided by the noise [11]. The two most common approaches to improve SNR are to increase signal or decrease noise (or both). This equation assumes that the sample and coil are at the same temperature, and does not take into consideration fixed parameters such as line width, magnetogyric ratios, spin quantum numbers, etc. A further discussion of optimizing sensitivity can be found in Freeman [11]. One potential solution to increasing signal is higher magnetic field strengths, but that also has several disadvantages for solid pharmaceuticals. First, resolution often will not increase dramatically at higher fields if the sample line width is limited by bulk magnetic susceptibility or a range of conformations (as in amorphous materials). Second, higher fields require faster spinning speeds to obtain the same separation in parts per million (ppm) between isotropic peaks and spinning sidebands. This implies smaller sample volumes and less signal. Third, for crystalline solids, especially those without methyl groups, the relaxation rate is often inversely proportional to the square of the magnetic field strength [12,13]. Going from 7.05 to 18.8 T could potentially increase relaxation delays by about a factor of seven, significantly mitigating any sensitivity gains obtained by going to higher field strengths. Another method to increase signal intensity is to increase the sample volume. However, there are several significant limitations to the development of a large MAS probe capable of CP and high-power ^{1}H decoupling. These include producing a high-power ^{1}H RF field capable of minimal decoupling for a moderately rigid proton environment, the ability to spin a large sample at the magic angle with minimal sidebands, and producing a homogeneous magnetic field over the entire sample. In fact, the direction of research in MAS has been to decrease sample size. Finally, lowering the temperature of the coil and other electronics can reduce noise, and is the approach taken in the cryoprobe [14,15]. The sensitivity gains arise from lower noise figures for both the coil and the preamplifier, and a higher Q (quality factor) [14]. Some sacrifice is made in filling factor, which limits the gains in sensitivity. In the solid state, especially for MAS systems, cooling the coil without cooling the sample would be extraordinarily difficult, although there are current research efforts in this area [16]. Even cooling the entire MAS system is technically challenging.

Oldfield recognized almost a decade ago that throughput was a significant issue on high-field NMR spectrometers [17]. He designed a probe that contained three different samples simultaneously located in the homogeneous region of the magnetic field. Although in his design all of the samples were static, he proposed that at least one could incorporate sample spinning. The resolution of this system was quoted as ~1 ppm. This concept has been extended to solution NMR spectroscopy [18–25]. Raftery and coworkers have shown that up to four different samples could

Table 1
Recycle delays for various pharmaceutical compounds

Compound	^{1}H frequency	Delay (s)	Delay at 9.4 T (s)	Ref.
ROY[a]	300	40–70	70–125	[4]
Cimetidine	360	15	18	[5]
LY297802	400	5–10	5–10	[6]
Ephedrine	200	1.5	6	[7]
Aspirin	300	90	160	[b]
Salicylic acid	300	1000	1780	[b]
Prednisolone t-butylacetate	200	3	12	[8]
Acetaminophen	200	2	8	[9]
Carbamazepine	200	3	12	[10]
Enalapril maleate	200	2	8	[9]
Ibuprofen	200	2	8	[9]

[a] 5-methyl-2-[(2-nitropheny)amino]-3thiophenecarbonitrile.
[b] From our laboratory.