

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.

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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 ^1H 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 ^1H decoupling. These include producing a high-power ^1H 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	^1H 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]

^a5-methyl-2-[(2-nitrophenyl)amino]-3thiophenecarbonitrile.

^bFrom our laboratory.

be located simultaneously in the homogeneous region of the magnetic field [18]. However, the increase in the number of samples simultaneously present in the homogeneous region of the magnetic field comes at a cost of smaller sample volumes. This design does not easily allow for incorporation of MAS for multiple samples at typical (0.5 cm^3) solid sample sizes.

Our approach to increasing sensitivity and throughput uses the fact that in SSNMR, the spin–spin relaxation time, T_2 , is usually several orders of magnitude shorter than T_1 [12]. This means that the preparation and acquisition time in a Fourier Transform SSNMR experiment is typically tens of milliseconds. Before the sample can be pulsed again, it must relax for several seconds to several hours as the bulk magnetization returns to its equilibrium value. During this time the sample must remain in a large static magnetic field, but is not required to be in a homogeneous magnetic field. We exploit this fact by shuttling multiple MAS systems through the magnet bore.

2. Experimental

2.1. Probe concept

The basic probe design consists of multiple MAS systems that are located in the bore of the superconducting magnet dewar. One possible design of this probe is shown in Fig. 1. The MAS modules can be moved into the homogeneous region of the magnet for signal acquisition. When the

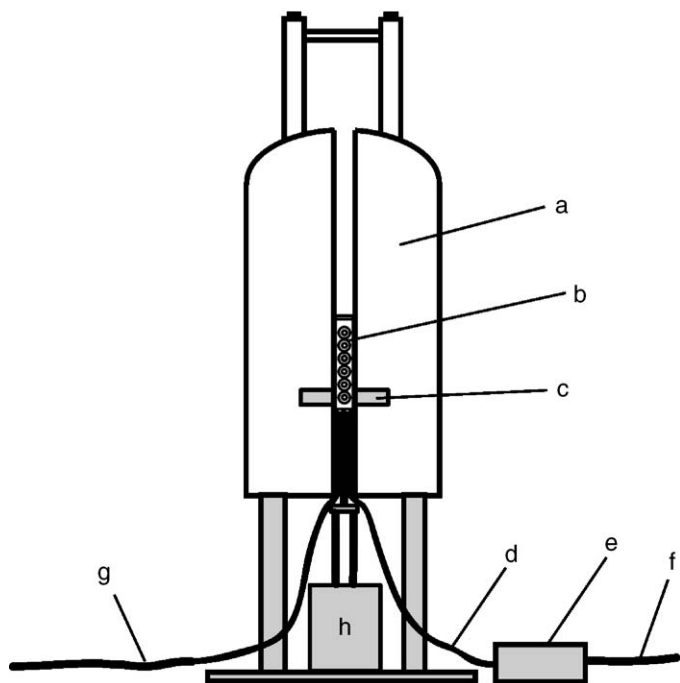


Fig. 1. Schematic of experimental design: (a) superconducting magnet dewar; (b) MAS modules in magnet bore; (c) homogeneous region of magnet; (d) coaxial cables supplying each module; (e) RF switching and external tuning device; (f) connection to X and H high-power RF amplifiers; (g) air supply lines; (h) microstepping probe positioning motor.

signal is not being acquired, the spinning systems may be moved into a non-homogeneous magnetic field. The MAS modules are moved in the bore of the magnet using an electric, hydraulic, or other mechanism that can change the location of the MAS modules in the magnet bore. In Fig. 1, the concept of using a stepping motor assembly to move the probe in the magnetic field is shown. Ideally, each spinning system would feature its own air supply lines, radio-frequency (RF) connections, and magic-angle adjustment mechanism, although some or all of these features may be combined. In the design shown in Fig. 1, there is a remote RF tuning and switching box that serves two purposes. First, each MAS module/circuit can be selected independently for signal acquisition. Second, it allows each circuit to be tuned independently outside the bore of the magnet dewar. Each module may have variable-temperature capability, independent spinning speed control, and independent shimming parameters.

There are several advantages of this probe design. First, it has the capability of increasing throughput by a factor of 2–10, depending upon the number of spinning modules/samples that could be analyzed. This number could be significantly higher, if the analysis time for one sample was several days. During that time, the samples in the other spinning modules could be changed several times without disturbing the sample with the long analysis time. Moreover, this system has the capability of being automated, because the probe would be designed so that all of the MAS modules could be accessed from below the magnet. The throughput advantage could be increased to 10–50 compared to a probe with no autosampler, if the samples were changed five times during an overnight run or over a weekend. If the choice is made to run the same sample nine times, then the SNR would be tripled. It would take nine times as long to triple the SNR by signal averaging using just one spinning module. Moreover, there should be little or no loss in field homogeneity, sensitivity, MAS speed, or ^1H decoupling field strength compared to conventional NMR probes, nor is there a need to develop specialized spinning modules, pulse sequences, or RF technology. While this approach can be used at any magnetic field strength, it would work better at higher field strengths, where T_1 relaxation rates are much longer than at lower field strengths [13]. Higher fields also imply faster spinning systems and therefore smaller sample volumes and MAS modules. This would mean that more spinning systems could be placed in the static magnetic field, enabling more samples to be run.

There are also some limitations to this probe design. For example, this probe design is not as useful for studying nuclei in samples that have short relaxation times, such as many quadrupolar nuclei. Also, additional sample is needed if an increased SNR is desired. The modules would be self-contained, which could limit the experiments to fixed angle, double resonance, and room temperature. The constant moving of the probe may make it more prone to mechanical breakdown, and the multiple spinning

modules/circuits will increase maintenance problems. Finally, having multiple spinning modules will require significantly more compressed air. All of these limitations are relatively minor compared to the gains in throughput/sensitivity that would be achieved with this probe.

2.2. Effect of magnetic field strength along superconducting solenoid axis

The ideal superconducting magnet for the multiple-sample probe would have a magnetic field strength that remained approximately constant for as long as possible along the axis of the solenoid. A diagram of the field strength for an Oxford (Oxford, UK) 9.4 T, 89 mm bore magnet is shown in Fig. 2. The effective field, defined as the point at which the field remains >80%, is ~ 18 cm from the center of the solenoid. If all samples were confined to an 18 cm range, then only the two outer samples would feel a magnetic field of <95%, and then only while one of the outer samples was being analyzed.

2.3. Solid-state NMR spectra

All spectra were acquired using a Chemagnetics (Fort Collins, CO) CMX-II SSNMR spectrometer equipped with a Magnex 300 (Yarnton, UK) superconducting magnet operating at 75.6 MHz for ^{13}C . Samples were spun at the magic angle at a rate of ~ 3000 Hz. Variable-amplitude

cross polarization (VACP) [26,27] was used to acquire all spectra. Proton decoupling powers of 40–80 kHz were used to acquire all spectra. Acquisition parameters for hexamethylbenzene (HMB) were: 512 data points, 30 kHz spectral width, and 17 ms acquisition time. All spectra were zero-filled to 4096 points prior to Fourier transform. No apodization was used. SNR measurements of HMB spectra were made by using a macro feature of the Spinsight software. Noise was sampled over a 30 ppm chemical shift range. Signal intensity was determined from the methyl peak of HMB. SNR was reproducible within 5% on consecutive acquisitions.

3. Results

The results section of this manuscript is divided into two parts. In the first part the design and testing of a two-module prototype probe are described. The second describes the design and testing of a single-module probe that can be scaled up to seven modules.

3.1. Two-module prototype

A two-sample probe based upon a lumped element (Hester–Waugh) [28] tuning circuit was developed to test the feasibility of multiple-sample probe technology. A picture of the probe is shown in Fig. 3. The probe is designed with an axis of symmetry to facilitate construction. There are four main components of the probe: MAS modules, air lines, tuning circuits, and RF transmission lines. Standard Varian (Palo Alto, CA) 7.5 mm spinning modules were used. The modules are ~ 1.5 " in diameter and spin 7.5 mm rotors up to 7000 Hz. Flexible plastic tubing, 1/8" i.d., supplies compressed air to delrin plastic supports. The delrin supports hold the spinning module in place and deliver the compressed air to the drive and bearing systems. The tuning circuit is comprised of several elements based on the Hester–Waugh [28] design. The coil is made from four turns of 16-gauge solid copper wire. American Technical Ceramics (Huntington Station, NY) fixed capacitors, and Polyflon variable capacitors (Norwalk, CT) are used to match and tune the circuit. A quarter wavelength isolation element was made by using 1/2" copper pipe and 3/16" solid copper wire to complete the tuning circuit. Tuning wands made of mixed plastic and brass parts are used to adjust the variable capacitors from outside the magnet. RF power is supplied to the tuning circuit via 1/8" semi-rigid copper coaxial cable.

Fig. 4 shows a photograph of the two-module probe in the bore of the superconducting magnet dewar. A PVC probe guide is used to avoid having the probe body rub against the magnet bore while moving. An Emerson Electric Co. (St. Louis, MO) model DXM-138 stepper motor, controlled via model MO35138 controller, is attached via pulley to a worm screw. The worm screw could raise/lower an assembly (shown in Fig. 4b)

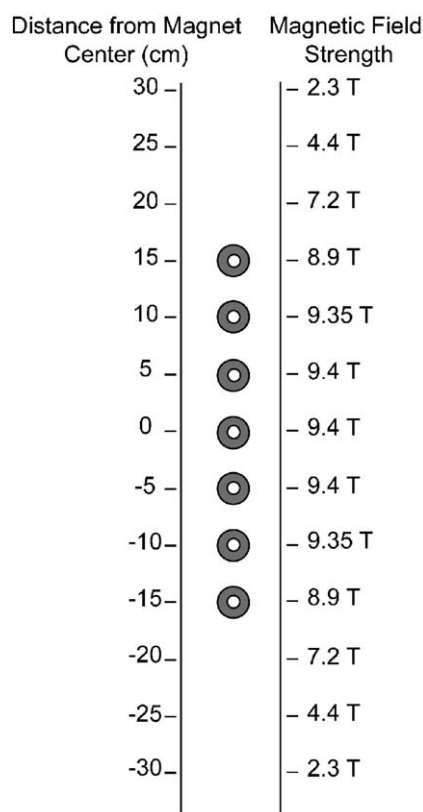


Fig. 2. Schematic of modules positioned 5 cm apart (center to center) in the field gradient of a 9.4 T Oxford superconducting magnet.

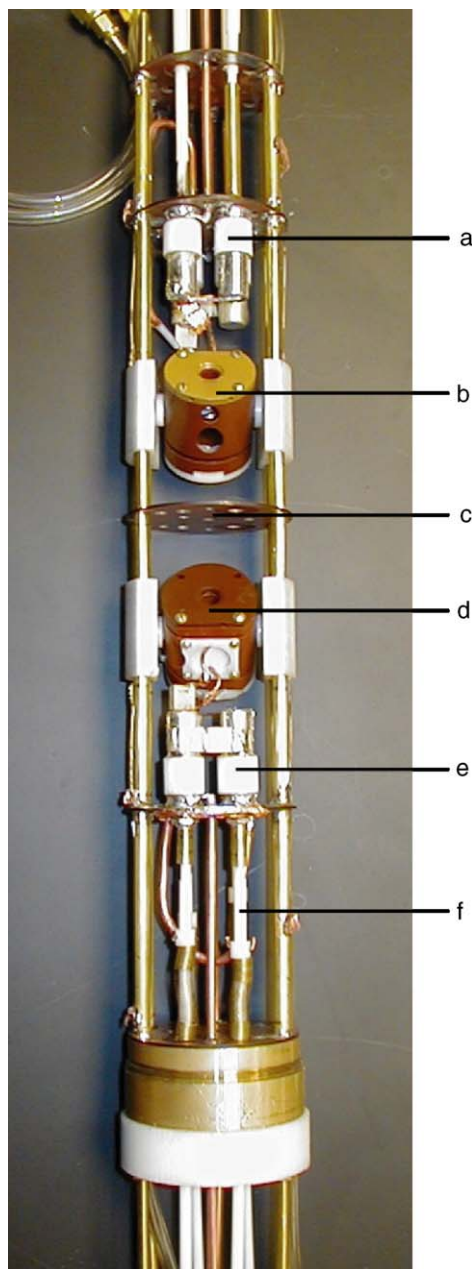


Fig. 3. Picture of multiple-sample probe with lumped element (Hester–Waugh) tuning circuits: (a) top tuning circuit, (b) top MAS module, (c) RF isolation plane, (d) bottom MAS module, (e) bottom tuning circuit, (f) tuning wands.

approximately 20 cm. Operation of the stepper motor under the magnet had no noticeable effect on the spectra.

The samples in the MAS modules were located ~ 12 cm apart in the probe. When the top module was located in the homogeneous region of the magnet, it took ~ 1 s to move the bottom module into the homogeneous region of the magnet. For some reason, possibly related to the controller software, it took ~ 2 s to move the opposite direction. A PC running a Microsoft Excel macro was used to control movement height and speed. Although it is possible to interface the movement control to the spectrometer

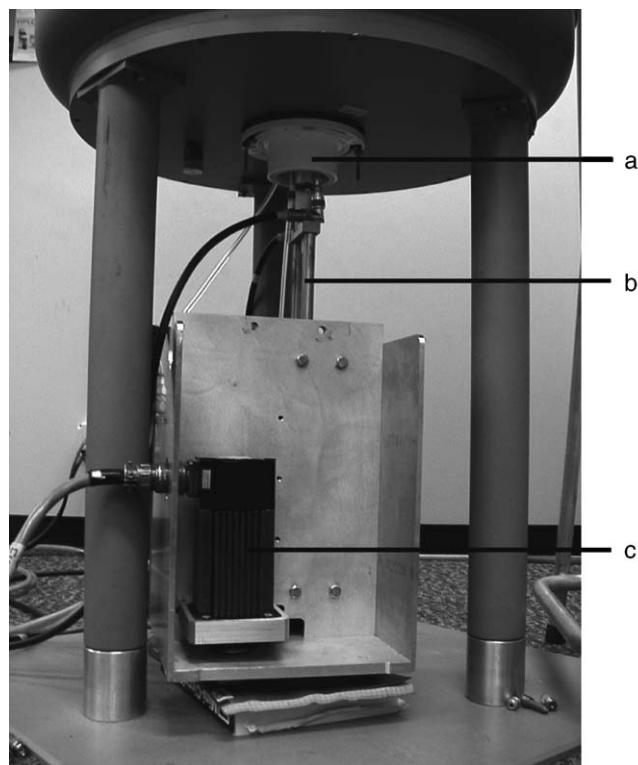


Fig. 4. Photograph of probe in magnet. The probe is moved using a stepper motor assembly: (a) probe guide in magnet, (b) probe movement assembly, (c) stepper motor.

hardware, the difficulty in synchronizing the two programs prompted us to delay interfacing until a new motor/controller and spectrometer console arrived.

The spectra of HMB acquired in both the top and bottom spinning modules are shown in Fig. 5. The SNR for the top module was ~ 320 , which is comparable to that observed using our conventional probes at the time. The SNR of the bottom module was ~ 250 . The reduced SNR probably reflects poor RF shielding. The ^1H 90° pulse widths for both modules was $\sim 4.0 \mu\text{s}$. The spectra in Fig. 5 were acquired by alternating each acquisition between the top and bottom module, showing that it is possible to return each module in the probe to the homogeneous region of the magnet.

Fig. 6 shows a spectrum of HMB acquired using the bottom module. The purpose of this experiment was to synchronize the acquisition with the movement. The schematic in Fig. 6a shows the timing sequence of the movement and the spectral acquisition. It was determined that the following cycle took 4.8 s, where the order refers to which sample is in the homogeneous region of the magnet: bottom module (1 s), move to top (1 s), top module (1 s), move to bottom module (2 s). Since the movement was very reproducible, spectral acquisition with a 4.8 s repetition time between pulses was used, starting with the bottom module in the homogeneous region of the magnet. The HMB spectrum obtained is comparable to one acquired without movement.

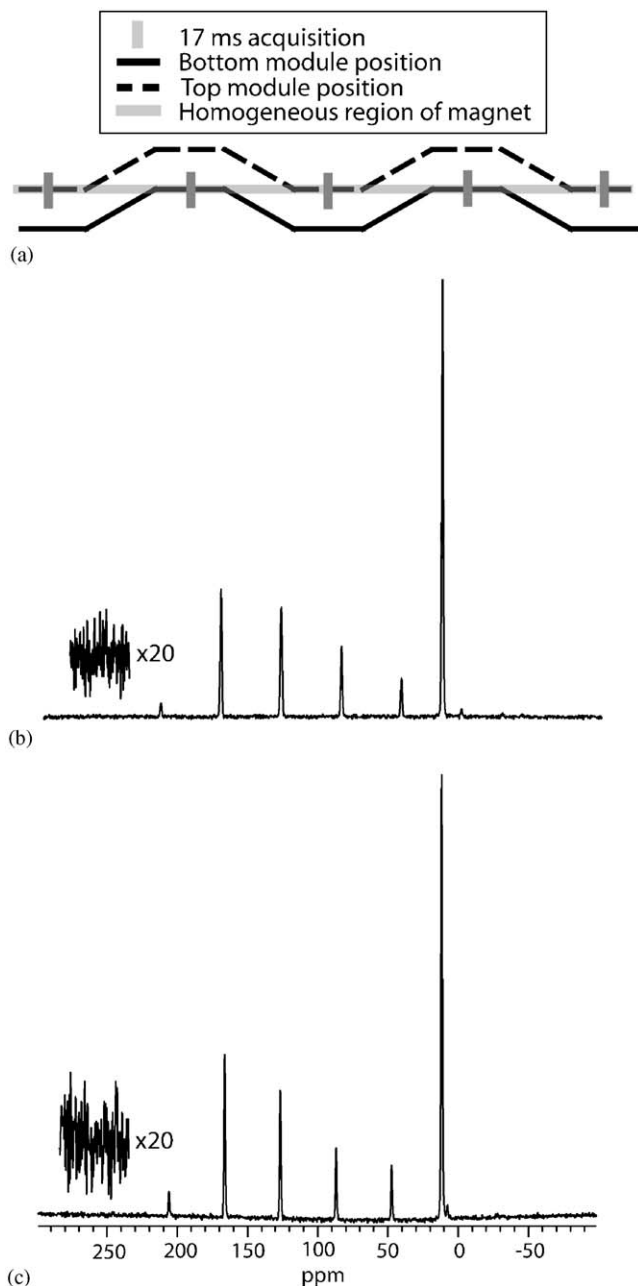


Fig. 5. HMB spectra acquired from top and bottom module. Each spectrum was 12 acquisitions and each acquisition was alternated between the modules: (a) schematic of module position in magnet and pulse timing, (b) spectrum acquired in top module, (c) spectrum acquired in bottom module.

Fig. 7 shows the ^{13}C CPMAS NMR spectra of aspirin and ibuprofen. Crystalline aspirin has a ^1H T_1 of ~ 30 s at 7.05 T. To obtain quantitative spectra, which is often important for solid pharmaceuticals, a relaxation delay of 5 times T_1 must be used. For this experiment a 90 s delay was used, and 64 transients were acquired (Fig. 7b). The spectrum of aspirin in the top module is shown in Fig. 7a. During the delay the top module was moved out of the homogeneous region of the magnetic field, and the bottom module, containing ibuprofen, was moved into the

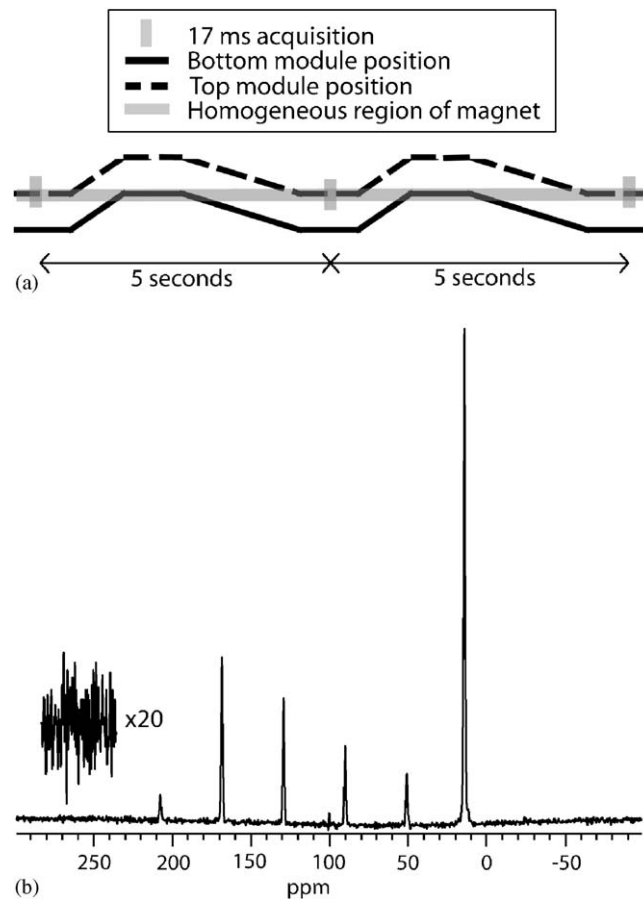


Fig. 6. Spectrum of HMB acquired using the bottom module with the pulse sequence timing chosen to coincide with probe movement: (a) schematic of timing of probe movement and spectral acquisition, (b) HMB spectrum.

homogeneous region. Thirty transients of ibuprofen using a 3 s recycle delay were acquired before moving the top module back into the homogeneous region of the magnet. A total of 1920 transients were acquired on ibuprofen while the 64 were acquired on the aspirin sample. Several interesting features can be observed from the spectra in Fig. 7. First, the spectra of aspirin acquired with and without movement are indistinguishable. Second, the field at which the aspirin was located while the spectrum of ibuprofen was acquired must have been very close to 7 T in order for the Boltzmann population difference to return to the same value as in the spectrum acquired without movement. Finally, the concept of sample shuttling as a method of simultaneous acquisition in a superconducting magnet has been demonstrated.

3.2. Scalable prototype probe

The next step in developing a practical multiple-sample probe was designing an MAS module and tuning circuit that could accommodate six or more samples. Various concepts were evaluated based upon the Hester–Waugh design, but the disadvantage of that design is the necessity

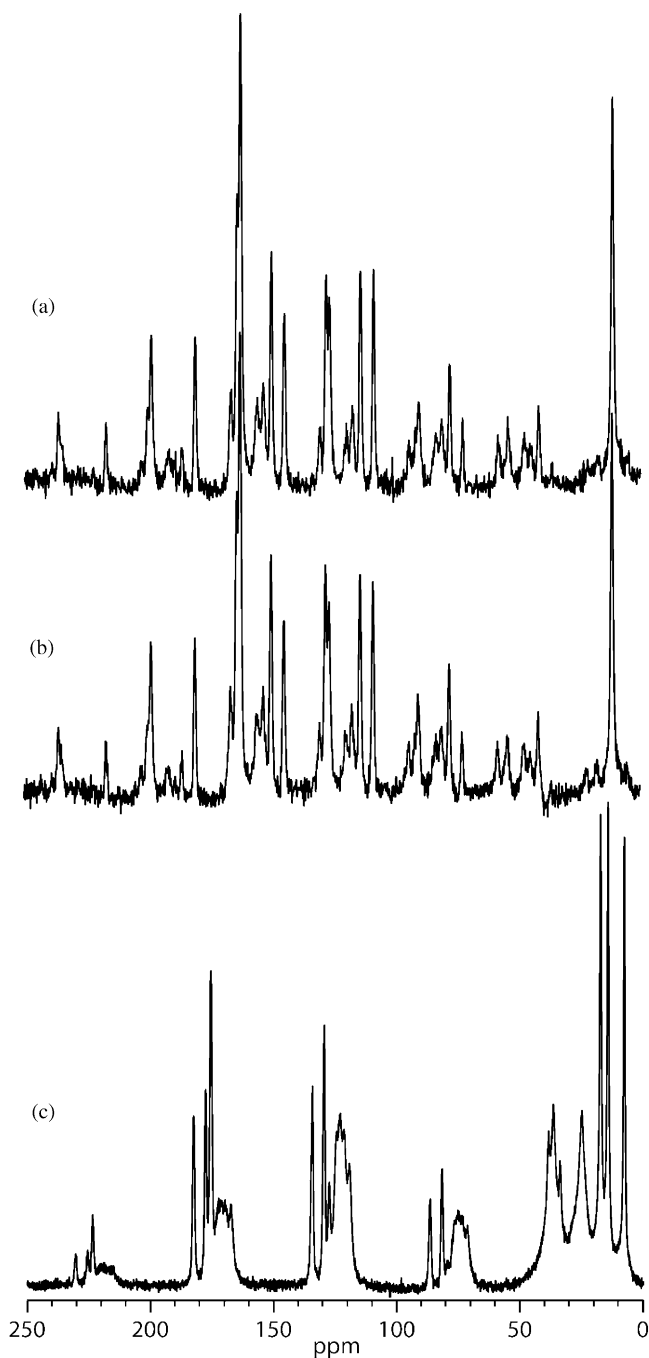


Fig. 7. Spectra of aspirin and ibuprofen: (a) aspirin acquired without motion, (b) aspirin acquired with motion and switching, (c) ibuprofen acquired with motion and switching.

of having 24 tuning wands, 12 air lines, and 12 RF coaxial cables emerging from the bottom of the probe. In addition, four variable capacitors, several fixed capacitors, and one $\lambda/4$ transmission line isolation element would have to exist between each module. During this evaluation process we began to consider the McKay $\lambda/4$ transmission design. A detailed description of this probe design can be found in Stejskal and Memory [29]. This probe design was commercialized by Chemagnetics in the late 1980s, and is still used in our laboratory. In the Chemagnetics probe, the

transmission line is ~ 4 cm in diameter, with the $\lambda/4$ tap point for the X nucleus located approximately at the midpoint of the transmission line. The advantage of this probe design is that the tuning elements are all located outside the magnet bore, and the only RF connection between the module and the tuning elements is the transmission line.

At a ^1H frequency of 300 MHz, the transmission line extends out of the magnet just enough to be tuned with a capacitor. Our concern was that all of the tuning elements for a six module probe could not be outside the magnet bore, due to the extra length of transmission line required to reach the top module, so rather than using a $\lambda/4$ design, we chose a $3\lambda/4$ design. Transmission line design theory states that a $\lambda/4$ and $3\lambda/4$ should be equivalent in terms of tuning elements. The extra length of a $3\lambda/4$ design would allow all of the tuning elements to be located outside the magnet. The disadvantage of the $3\lambda/4$ design is that the RF performance may suffer, especially since the transmission line diameter must be decreased to ~ 2.5 cm to accommodate > 5 MAS modules.

A $3\lambda/4$ probe was constructed to test the performance of the proposed tuning circuit. The transmission line from an unused Chemagnetics $\lambda/4$ probe was replaced with a Dielectric Communications (Raymond, ME) 7/8" o.d. air core transmission line with a tap point at the $3\lambda/4$. A picture of the $3\lambda/4$ probe is shown in Fig. 8. The Varian 7.5 mm MAS module was replaced with a 7 mm MAS module purchased from Revolution NMR (Fort Collins, CO). This new module has a considerably smaller outside diameter (~ 2 cm) compared to the module used in the previous probe (~ 4 cm). A smaller MAS module diameter is critical to be able to space the modules as closely as possible. The probe was configured for ^{13}C - ^1H double resonance by soldering an appropriate capacitor between one coil lead and ground. The only probe elements extending from the base of the probe to the MAS module are the transmission line, drive and bearing gas lines, and magic-angle adjustment. Because both the center and outer conductors of the transmission line are hollow, it should be possible to divert the gases for spinning through the transmission line, saving additional space in the probe.

Table 2 shows the RF performance of the $3\lambda/4$ probe for various numbers of coil turns. The performance of a conventional probe equipped with a Varian 7.5 mm MAS module and equivalent amount of sample in the rotor is shown for comparison. Different numbers of coil turns



Fig. 8. Photograph of prototype $3\lambda/4$ coax probe, with a 7 mm OD MAS module.

Table 2
90° pulse width and SNR of various coils in $1\lambda/4$ and $3\lambda/4$ probes

Turns in coil	90° pulse width (μs)	SNR
6 ($1\lambda/4$)	3.8	348
6 ($3\lambda/4$)	2.9	257
7 ($3\lambda/4$)	3.2	354
8 ($3\lambda/4$)	3.6	368
9 ($3\lambda/4$)	3.8	423

were evaluated when it was determined that the original coil design, which was a six turn coil, had a very poor SNR. The data in Table 2 clearly shows that the $3\lambda/4$ probe can deliver an improved SNR with effective ^1H decoupling fields (>60 kHz) compared to current $\lambda/4$ probe technology in our laboratory. The primary disadvantage of the probe was that additional decoupling power ($\sim 2\times$) was required to achieve the equivalent ^1H decoupling field found on the commercial probe. However, no RF breakdown (i.e. arcing) was observed with the $3\lambda/4$ probe at the higher power levels used, attesting to the robustness of the probe design. Given the relative simplicity of the design with only a transmission line, MAS module, one single fixed capacitor, and magic-angle adjustment in the magnet bore, expanding this to accommodate multiple MAS modules should be straightforward. Moreover, the design allows for remote tuning of the circuit outside the magnet bore.

4. Future design considerations

In this section several of the design considerations that will address the potential capabilities and limitations of the multiple sample probe are discussed. These include: spacing between modules, increased SNR, alternative probe designs, data acquisition, variable temperature capabilities, module size, nucleus selection, and a two-piece probe design.

4.1. Spacing between modules

There is sufficient space in the probe to accommodate seven transmission lines and therefore seven MAS modules, with all the transmission lines extending from the bottom of the magnet bore. As noted previously, all of the modules should be at $>80\%$ field, and ideally should be at $>95\%$ field at all times. If modules are placed 3 cm (center to center) apart, then 7 modules can be fit into 18 cm. If the spacing is closer to 2.5 cm, then all of the modules will be at $>95\%$ field at all times. The two-module prototype will be designed so that the spacing between the modules can be varied.

4.2. Increased SNR

We have found that the SNR can be increased by adding additional turns to the coil in the module. A diminishing

return between the number of coil turns and improved SNR will eventually occur, but the increased SNR from a nine turn coil compared to a six, seven, and eight turn coil suggests that more turns should be explored. At some point the increase in the number of turns will reduce the decoupling field strength to an unacceptable level, which will require the use of a more powerful amplifier.

4.3. Alternative probe designs

One potential alternative to our probe design is to utilize a sample changer that stores multiple rotors in the magnetic field and swaps samples from the MAS module for acquisition. The advantages of this design are that many samples could be stored in the field (possibly >10), and that only one MAS module is required. However, there are several disadvantages. First, the time to switch between samples is probably, at best, at least a minute, whereas the approach that we suggest requires less than a second. Second, the approach of storing the samples in the magnet requires that for each change, the sample spinning must be stopped, the rotor extracted, the next sample placed in the spinning module, the sample brought to the same spinning speed, and finally an acquisition taken. All this must happen flawlessly, and all within the confines of the magnet bore and also within $>80\%$ of static field strength (realistically, within 20 cm of the magnet center). Third, the circuit would probably have to be retuned for each sample, and changing observe nuclei would be difficult at best. Retuning the circuit will negate the benefit of keeping the sample at high field between acquisitions unless the tuning can be reliably returned to the values needed for that sample without pulsing. The only real advantage of the design which switches samples is that only one spinning module is required compared to multiple modules.

4.4. Data acquisition

Current NMR hardware and software are designed to acquire NMR data on only one sample at a time. In our probe, the data is acquired sequentially, which means that the data acquisition buffer must be switched between each sample. In theory, it should be possible to acquire data sequentially from multiple samples on most commercial spectrometers using solid-state switches and modified software. At this time, we have purchased the high-power solid-state switches necessary to switch between different probe circuits and we are working with Tecmag to implement the software switch between buffers.

4.5. Variable temperature capabilities

In general, although we state that the variable-temperature capabilities are compromised, it is necessary to qualify this statement. First, it should be possible to have some control of the temperature, especially from 0 to 80°C by controlling the temperature of the bearing gas. There is no

fundamental reason why there cannot be a temperature sensor of the bearing gas right before it enters the spinning module. Second, because the probe will be bottom loading, there is the possibility of mounting a variable-temperature stack for at least the top module, and in theory it could be expanded to incorporate other modules. Finally, we rarely use variable-temperature studies for pharmaceutical formulations, primarily because the stress testing is performed under rigidly controlled conditions of temperature and relative humidity that are usually much more extreme than ambient conditions.

4.6. Module size and nucleus selection

Because each module has its own tuning circuit, it should be possible to implement the probe with the capability to acquire different nuclei from each module, i.e., for a seven module system, three of the modules may be configured to acquire carbon, two nitrogen, and two silicon. X channel receiver switching would be performed after the signal has passed through the preamplifier. This would require separate preamplifiers for each channel, but the cost of a preamplifier is relatively modest compared to the ability to observe multiple nuclei. It would also be possible to change spinning modules to accommodate various sample sizes. The advantage of the coax probe design is that the tuning frequency range for both the X and H channels are relatively insensitive to coil size, thus changing from a 7 mm sample module to a 3.2 mm sample module should require minimal changes to the tuning elements. We are currently considering designs that will allow for easy switching of sample modules.

4.7. Two-piece probe design and top/bottom access

In our original prototype, the RF cables, tuning wands, and spinning gas for the top module exited the top of the magnet, and the elements for the bottom module exited the bottom of the magnet. With the current coax design, all of the cables, gas lines, and tuning elements emerge from the bottom of the probe. The only negative aspect of this design is that the probe is excessively long (~100 cm). This could cause a problem if the magnet legs are too short. In theory, the simplest solution is to add extensions to the magnet legs to raise them an additional 30–40 cm from their current height. Alternatively, the probe could have separate top and bottom sections, in which the top section contained the spinning modules and the bottom section contained the tuning elements. The only connections that are critical at the center conductor connections of the coax transmission lines. The advantage of this probe design is that each component would be short enough to be placed under the magnet and then the probe could be mated together, and that it would be possible to readily change probe heads to accommodate various experiments, such as different or custom spinning modules. It would also allow the module-containing probe section to be removed/

exchanged for maintenance and repair without causing significant downtime.

4.8. Other considerations

There are several other areas of development that must be pursued once a functional seven module probe is constructed: determining the speed of movement of the probe in the magnet, optimizing the order of acquisition from each module to maximize the number of acquisitions for each sample, and controlling the MAS rate for each module.

5. Conclusion

In this paper we demonstrated the ability to acquire CPMAS spectra of two samples simultaneously. We also showed a probe design that could be scaled to incorporate seven MAS modules, with the benefits of remote tuning outside the magnet bore and close (<3 cm) spacing. Although we have only shown applications of this probe design to pharmaceuticals, it could also benefit researchers in fields such as glasses, catalysis, and polymers.

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