



ENC 2001

Frequently Asked Questions:

- 1) Do I need to position my sample management/separation system as close to the NMR magnet as possible?

There are certainly advantages to maintaining a reasonable distance between the magnet/probe and the sample management system. However, these constraints are significantly relaxed at the capillary scale, primarily due to the excellent fluidic integrity that is maintained using a capillary (50 μm i.d./360 μm o.d.) feed line. A fundamental limit in conventional systems is the amount of peak broadening (sample dilution/mixing) that occurs in the transport tubing. This limitation often requires that the sample handler and magnet/probe be positioned to within 1-2 meters of one another, and even then with measurable degradation in peak integrity. In stark contrast, at the capillary scale, the effect of 5 meters of capillary is virtually unnoticeable in terms of peak broadening.

- 2) Is it cost-effective to exclusively run deuterated solvents in this capillary NMR flow system?

Yes! A 24 hour run of non-deuterated acetonitrile in a conventional scale NMR flow system (1 mL/min) is approximately \$16/day (prices based on Aldrich 2000 catalog), with 720 mL of total solvent consumed. A 24 hour run of deuterated acetonitrile in a capillary NMR flow system (5 $\mu\text{L}/\text{min}$) is approximately \$10/day, with about 3.5 mL of solvent used.

- 3) Isn't the achievable S/N in NMR directly related to sample volume? Isn't "bigger" better?

The S/N in NMR is actually directly related to the quantity of sample (mass, moles, or number of spins) being investigated. The real challenge to NMR optimization is effective management of the sample while balancing the tradeoffs in design to provide the most efficient means of NMR analysis. In many cases, intelligent sample preparation (for example, preconcentration) can provide a higher concentration of sample for NMR detection using a smaller RF coil that is of greater mass sensitivity, resulting in an effective increase in S/N. In other cases, the simple ability to accomplish useful NMR with a 100-fold reduction in solvent consumption justifies the move to the capillary scale. In chromatographically-intensive applications, the ability to maintain excellent fluidic integrity with NMR provides additional incentive to move to the capillary regime.

- 4) Why should I consider using such a small sample?

There are many reasons, some of which are related to ability to maintain excellent fluidic performance, or reduce the cost of solvent consumption while simultaneously utilizing NMR-compatible deuterated solvents, as described above. Other reasons include:

- a) Reduction or elimination of the need for solvent suppression via the use of a deuterated solvent stream. Due to the cost effectiveness of using deuterated solvents at the capillary size scale, solvent exchange (protonated-to-deuterated) can be readily accomplished using (LC) techniques, thereby reducing sample preparation.
- b) Trace Analysis. Some applications (such as natural products) require trace analysis, as little sample is available to investigate. Other applications (e.g. metabolic or

degradation studies) benefit from LC pre-concentration for maximum mass sensitivity and minimal NMR acquisition time. In such applications, conversion of the sample from a low mass, large volume (low concentration) sample to a low mass, small volume (high concentration) sample provides NMR S/N enhancement.

- c) Efficient utilization of sample. Some applications (e.g. combinatorial chemistry/drug discovery) start with a relatively large quantity of sample that must be sequentially analyzed by multiple groups using a wide array of analytical techniques. This typically requires that the sample be prepared for NMR, analyzed using NMR, and then restored to its original condition for subsequent analysis by different research groups. Some combi-chem users have identified an opportunity for extraction and NMR analysis of a relatively small volume (several microliters) of the sample that is considered to be essentially disposable, that is, so small an amount that it does not require reconstitution to its original state for analysis by another group. This saves time, money, and effort.

5) Do I need to worry about solvent or sample compatibility?

MRM probes utilize a completely fused silica transport system, that is, all wetted surfaces are fused silica. While no sample transport medium is 100% compatible with all known chemicals, fused silica provides one of the most robust and workable solutions for most samples and solvents encountered in NMR analysis, including DMSO.

6) Is the flowcell interchangeable?

No, and it is not necessary. Due to the flow-through design of the MRM flowcell, clogging or permanent damage will be infrequent, and the NMR specs will be stable for a long time. Improper sample handling can, of course, lead to irrecoverable conditions, such as letting the probe dry out while it contains sample. MRM offers a return-to-factory service policy. In most cases, the probe can be returned with new flowcell within 5-working days (USA; 10-working days international) from the time the probe is received by MRM.

7) How long does it take from the time of order to get a MRM probe?

Typical lead time from the time of order to the time of delivery is 3 months. Installation can typically be completed within 2 weeks of probe delivery.

8) What nuclei are currently offered?

MRM probes are currently ^1H detect with ^2H lock.

9) Does MRM plan to offer carbon indirect detection?

^{13}C indirect detection will be incorporated into MRM's probe offering later in 2001. We have a prototype, and the time frame for product delivery will be based on the interest level expressed by prospective users at ENC. Buyers of our proton probe will be considered preferred customers for an indirect probe.

10) Do I need to purchase a Waters CapLC system?

For direct liquid introduction, it is not necessary to purchase a CapLC. MRM probes are generically compatible with any capillary-scale flow injection device, including syringe

pumps fitted with injection loops. However, the degree of control, functionality, repeatability, and reliability will obviously be highly dependent upon the particular means of sample management chosen. We strongly recommend the Waters CapLC for direct sample introduction as well as for chromatography applications. For capillary LC-NMR, MRM has aligned strategically and exclusively with Waters Corporation. We believe that the Waters CapLC is the highest quality, highest performance capillary LC available, and therefore the best choice for achieving success in LC-NMR when using MRM probes.

11) Will my current liquid handler work with a MRM probe?

MRM probes are fully compatible with any *capillary-scale* liquid handler. However, it must be emphasized that many liquid handlers currently used in NMR are not targeted for capillary-scale applications. The most significant differences include the way the sample is placed in-line with the solvent stream for injection, the achievable flow rates, and the pressure capabilities, accuracy, and precision of the pumps. It should also be noted that many conventional-scale systems claim to be capillary-scale compatible via stream splitting (of the solvent) to achieve lower flow rates. In such systems the amount of waste obviously increases greatly, and flow rate accuracy and reliability is often compromised.

12) Is the MRM probe compatible with my Bruker/Varian/JEOL spectrometer?

MRM probes are compatible with all three of the major NMR spectroscopy systems.

13) Is the MRM probe intended for flow injection or capillary LC?

While specifically designed for capillary LC-NMR, the MRM probe can be used in flow injection applications as well as capillary LC applications.

14) Is the MRM probe difficult to shim?

No. In fact, you'll find that it is generally easier and more straightforward to shim a MRM probe than other conventional NMR probes.

15) What frequencies are offered?

MRM currently offers 300 – 600 MHz ¹H frequencies.

16) Will I need to do anything special to my spectrometer to accommodate a MRM probe?

Nothing beyond what is typical of a new probe. Shim settings, power settings, heater control settings, etc. should be tailored to the values MRM provides with the probe. JEOL and more recent Bruker spectrometer systems may require a special hardware key for probe recognition by the spectrometer. (This key is supplied by MRM).

17) What about automation/control by my NMR spectrometer?

The CapLC has computer-controlled programming and sample injection. Automated stopped-flow is not yet available but is under active development, along with coordinated triggering of the CapLC and NMR console.