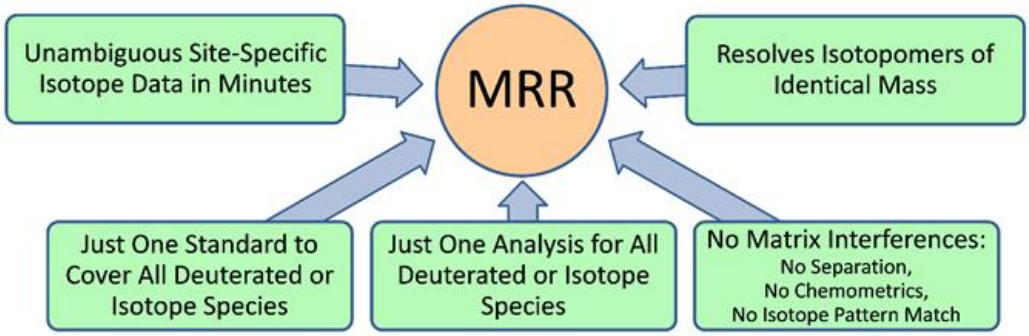
Rapid and Direct Site-Specific Deuteration Monitoring



OVERVIEW

Site-specific deuteration monitoring in pharmaceutical and chemical substances is a challenging task for conventional analytical techniques including mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. For example, MS cannot distinguish between the deuterated isotopomers of identical mass; whereas NMR requires large sample quantities and complex, time-consuming data analysis methods.

BrightSpec's Molecular Rotational Resonance (MRR) technology can provide unambiguous, quantitative, and site-specific isotope or deuteration data in minutes, with little sample required, and with just one measurement. There is no need for creating or purchasing deuterated standards – just one fully protonated or any other available isotopologue standard will do the job. Furthermore, no chemical separation, isotope pattern matching, or chemometrics are required for MRR analysis.

WHY MRR FOR DEUTERATION OR ISOTOPE ANALYSIS?

MRR identifies the species or fragments based on differences in their molecular rotational moments of inertia, i.e. their corresponding 3-dimensional mass distributions. As such, MRR brings a much higher level of sensitivity to isotope analysis compared to MS. For example, MRR can easily distinguish not only between the isotopologues of different masses but also between the isotopomers of ***identical*** mass (Figure 1).

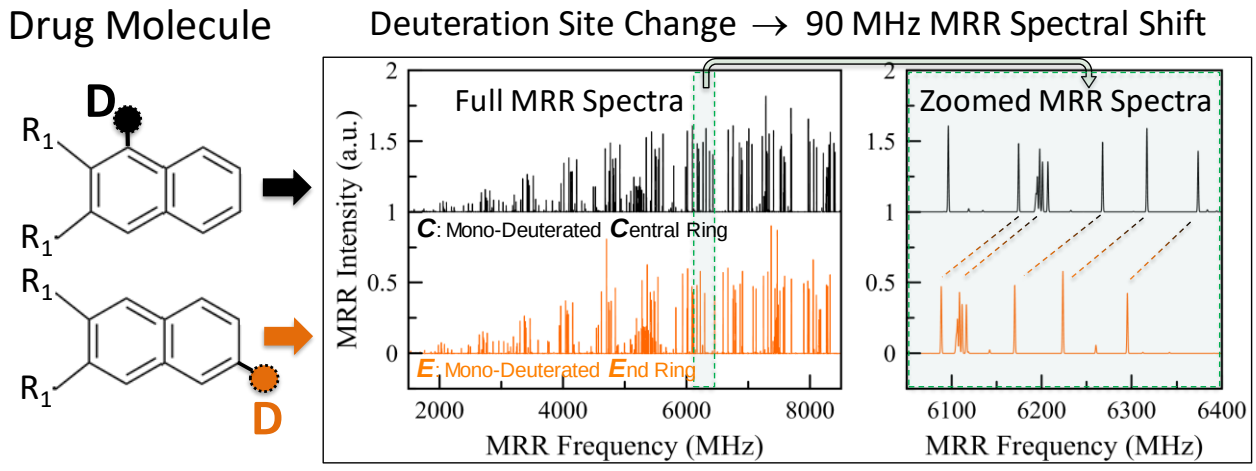


***Figure 1**. MRR spectra of two isotopomers of identical mass generated by a method demonstrated by Neill et al.[1] Top Spectrum (Black): Drug molecule monodeuterated at its central ring. Bottom Spectrum (Orange): Drug molecule monodeuterated at its end ring.*

MRR ANALYSIS EXAMPLE: DEUTERATION REACTION PROGRESS MONITORING

Three real-world deuterated drug candidate samples were taken out of a pharmaceutical reactor and analyzed with MRR at different stages of the deuteration reaction. 'Sample-1' represents the starting material, i.e. the unreacted or fully protonated molecule. Samples 2 and 3 were taken out of the reactor 8 and 24 hours after the deuteration reaction start, respectively. The reference spectra of all H/D species were obtained by measuring the broadband MRR spectrum of fully protonated drug followed by the extraction of the individual spectra of the remaining isotopologues directly from the reaction mixture using a method demonstrated by Neill et al.[1] (data not shown).

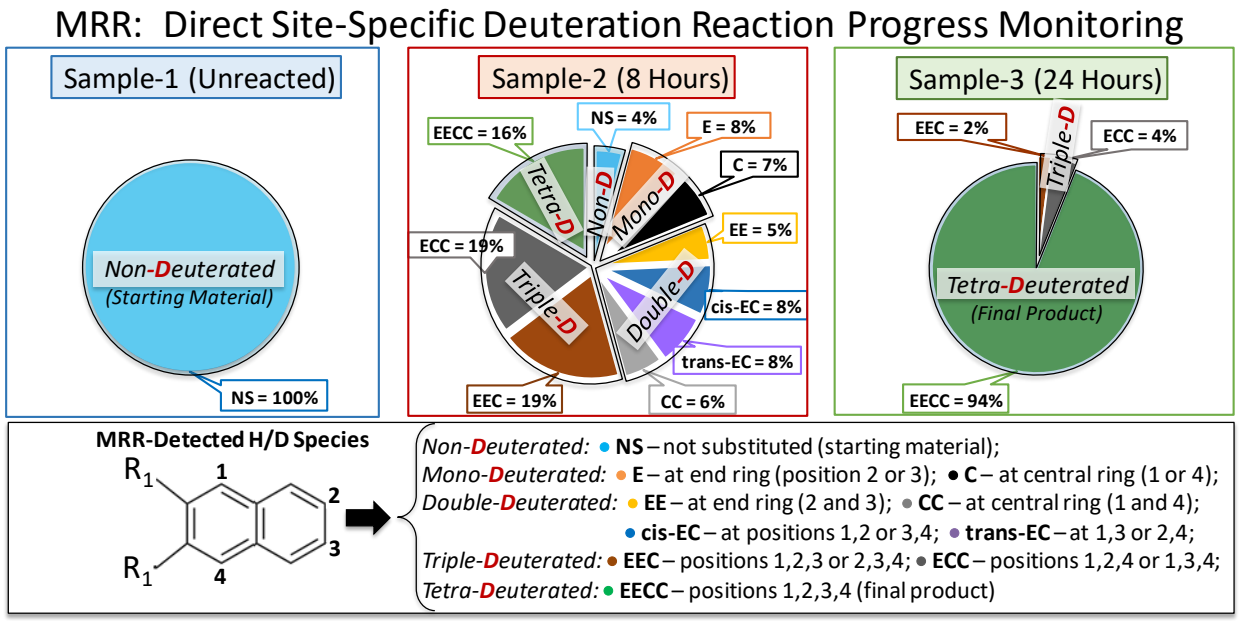


***Figure 2**. Direct site-specific monitoring of an active pharmaceutical ingredient deuteration reaction progress by MRR. All 10 possible H/D isotopic species can be monitored in a single measurement, and with just one reference standard. Please see text for detail.*

Figure 2 data confirmed that sample-1 (starting material) is an essentially pure protonated drug. In sample-2, MRR detected all ten possible H/D isotopologues to directly indicate that 8 hours are not enough for the deuteration reaction to conclude. In contrast, the sample-3 data confirmed that the deuteration reaction is essentially complete in 24 hours to yield the 94%-pure final product, i.e. the tetra-deuterated drug.

CONCLUDING REMARKS

This white paper demonstrates that MRR can address several major analysis challenges of deuterated substances, such as availability of deuterated reference standards and obtaining reliable site-specific deuteration data rapidly when there is little sample available. Furthermore, MRR is online-capable.[1] Finally, MRR's quantitative analysis methods are chemometrics-free, making the technique easy to develop, maintain and transfer. As a result, the addition of MRR to the CMC toolbox can not only accelerate the development of new deuterated pharmaceuticals but also ease their manufacture and/or development of the relevant QbD-based quality control strategies.

REFERENCES

1. J.L. Neill et al., Org. Proc. Res. Dev., *'Online Stereochemical Process Monitoring by MRR Spectroscopy'*, **2019**, *23 (5)*, pp. 1046-1051.

FOR MORE INFORMATION:

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