Analysis of Biofluids by NIMS

Monday, March 30th, 2009

Prof. Gary Siuzdak and co-workers at the Scripps Research Institute along with collaborators at Pfizer have just published a paper in *Analytical Chemistry* describing nanostructure initiated mass spectrometry (NIMS) in tissue and biofluid analysis. They first reported the NIMS technique in a 2007 *Nature* paper and presented it as a complementary ionization technique to MALDI. NIMS differs from MALDI in that instead of a crystalline matrix, it uses “initiator” molecules trapped on a nanostructured surface. The initiator that has been found to be the most useful to date is a fluorous siloxane. MALDI can techniques can suffer from signal suppression of low molecular weight entities from the matrix which is why it is best suited for proteins and peptides. NIMS, on the other hand, uses higher molecular weight initiator which does not suppress signal of lower molecular weight analytes, thereby making it more conducive to metabolite studies. This is exactly what this most current paper describes.

The researchers used NIMS to detect various drugs and their metabolites in both tissue, in this case brain tissue, and in biofluids such as urine, blood, and plasma. There were several advantages found using NIMS compared to other methods including little to no sample preparation, greater sensitivity, and full scale MS-only mode detection, as opposed to MS/MS. Even greater sensitivity may be gained using NIMS in MS/MS mode, but MS mode could provide information about the drug, its metabolites, and changes to endogenous metabolites that would otherwise be nondistinguishable. For example, the authors point out that while autoradiography is the current gold standard in drug distribution, it only tells you where the radioisotope is, it does not provide structural information that NIMS provides.

As for biofluids, the authors directly spotted the fluids on the NIMS surface, dried them down, then analyzed. They could increase sensitivity by conducting an on-target extraction. Essentially using the fluorous siloxane as a liquid phase version of reverse phase chromatography. Spotting a urine sample containing diazepam then subjecting to directly to NIMS analysis could not detect diazepam. Spotting, then washing with 80% methanol, however, resulted in a on-target enrichment of the organic metabolites and provided a observable signal for diazepam.
The on-target extraction could probably be made even more sensitive if coupled with fluorous tagging. This would require a fluorous tagging strategy thus adding a step to the analysis, but could be very useful for analytes in very low concentrations. The Siuzdak group has already demonstrated this approach using a DIOS surface, so it will be interesting to see if they apply the same strategy to NIMS. They have also previously used the NIMS surface in what they call a Nimzyme application where a fluorous tagged enzyme substrate is immobilized on the NIMS surface then subjected to enzymatic reaction. The product of the enzyme reaction could then be analyzed after washing the NIMS surface clean of any non-fluorous materials.

The simplicity and sensitivity of NIMS certainly seems to make it an ideal method for the study of small molecules in biological samples and it’ll be interesting to see how it develops over the next few years.

Tags: biofluids analysis, diazepam, NIMS, Nimzyme, Siuzdak
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