June 2006
Ion Mobility Spectrometry

Two analytical techniques have been newly promoted for pharmaceutical cleaning validation over the last five or so years. They are (1) ion mobility spectrometry, and (2) FTIR with a fiberoptic probe. The latter is certainly more an example of the combination of infrared analysis with a fiberoptic probe for sampling. This Cleaning Memo, however, will focus on the former technology, ion mobility spectrometry.

Furthermore, while I stated that the technology is being newly promoted for pharmaceutical cleaning validation over the last five years, the technology itself is over thirty years old. Most people who travel by air have probably encountered the technology in some way as they went through security screening. It is the technique used to analyze for explosives on computers, shoes, and other personal items. In that procedure, the item is wiped with a pad, and the pad put in an instrument which identifies the presence or absence of certain explosives.

What happens in the instrument itself? The sample is introduced into the instrument, and then the sample is volatilized. That volatile sample is ionized, usually with a radioactive nickel source. The ionized molecules then enter a "drift tube" where they are accelerated by an electrical field to a detector. The ionized molecules are captured by a detector. The measurement for ionized molecules is a function of the time of flight (TOF), which typically is in milliseconds (ms). The resultant "plasmagram" gives units as a function of time. One way to look at ion mobility spectrometry is to say it is like mass spectrometry without the vacuum and without any measure of charge to mass ratio (hence it is "time of flight" only). The TOF of a specific ionized molecule is relatively constant over a broad injection amount.

Sampling with ion mobility spectrometry can be with liquid samples (typical injections range from 1-10 µL). Liquid samples can be either rinse samples or desorbed swab samples. Another alternative is to use special sampling pads (such as those made of PTFE) to "swipe" the surface to be sampled, and then place the sampling pad directly into the instrument (similar to what is done in the airport). Note that the percent recovery from sampled surfaces is unclear using this special pad, as I have not specifically seen publications describing recoveries of representative materials from surfaces using this technique.

Two of the commercial instruments currently available are from Smith's Detection and from GE Sensing. Smith's Detection calls their technology IMS (for ion mobility spectrometry). This instrument has been on the market longest. GE Sensing calls its technology ITMS (for ion trap mobility spectrometry). The "trap" in the GE Sensing technology refers to a device which allows the instrument to measure and detect both positive and negative ions "simultaneously" (that is, in one run as the instrument automatically switches between the two modes). The GE Sensing instrument is also portable, in that it weighs 12 kg (as compared to 42 kg for the Smith's Detection unit) and has a backup battery to keep the instrument powered up during a physical transfer. One of the main advantages of ion mobility spectrometry is the speed of analysis. Sample throughput is typically on the order of one minute or less, so more samples can be processed in a given elapsed time (at least as compared to a typical HPLC analysis time of 10-30 minutes).

This shorter analysis time allow method development to occur in a shorter elapsed time. Note that it is still necessary to determine instrument parameters to optimize the measurement performance for a given molecule

in a typical method development process. However, since each result can be obtained in a shorter time, the overall elapsed time for method development can be shorter. It is also important during method development and validation to account for possible interferences of other molecules that might be present in the analyzed sample.

Should pharmaceutical manufacturers consider this technology? Certainly! Anything that can make cleaning validation more efficient should be considered. However, one concern is the way both Smith's Detection and GE Sensing are promoting the technology. The major promotional feature (quite rightly) is the speed of analysis. However, the benefit promoted by the two companies is that because the analysis time is short, cleaned equipment can be released much sooner for manufacture of the subsequent product – at least compared to the use of HPLC for analysis to release the "quarantined" equipment. While this shorter analysis time may be significant for method development and for shortening times in the analytical lab, I'm not sure that faster analytical method turnaround is a significant factor in speeding equipment release in cleaning validation, cleaning verification, or routine monitoring for most manufacturers.

The reasons are simple. In cleaning validation itself, the equipment is not going to be released until all the test data is evaluated. If bioburden is part of the requirement for a cleaning validation protocol (see last month's Cleaning Memo), then the time to get results back from the microbiological lab (several days) is going to be the limiting factor.

Well, what about once the cleaning process is validated? Isn't there an advantage there? My reply would be that under most conditions, if a pharmaceutical manufacturer is waiting on extensive analytical results following the cleaning process to release the equipment, then that manufacturer isn't take full advantage of the purpose of cleaning validation. As the PIC/S guidance (PI 006-2) says, the objective of cleaning validation is to confirm consistency so that "analytical monitoring may be omitted or reduced to a minimum in the routine phase". The FDA, in a CGMP Note (Second Quarter 2001), says that "Once cleaned by a validated procedure, a firm generally should not be expected to analytically examine equipment surfaces to demonstrate cleanliness…. Hand cleaning methods may be an exception to this general rule because of inherent variability in operator compliance and abilities. Usually, visual inspection of equipment surfaces, including hard to clean nooks and crannies, along with rinse water testing would suffice." So, once the process is validated, at most a reduced amount of analytical testing as a monitoring technique should be considered. If the only analytical sample taken is a final rinse water sample, then the time difference between HPLC and ion mobility spectrometry (among the other activities required to release the equipment) is probably not a significant factor in the time required for equipment release.

My input would be to evaluate the technology for possible advantages in your specific situation. However, unless you are one of the (what I think should be relatively rare) cases where release of equipment could be accelerated significantly by an extremely short analysis time, look beyond the marketing promotional emphasis for other possible advantages for your facility.

In the interest of full disclosure, I should state that I am not now nor have I been in the past a consultant to Smith's Detection or GE Sensing, although I did some training for Ionics on TOC before Ionics was part of GE. Furthermore, I am an owner of some GE stock (which I probably should have sold months ago).