IMS for Drugmaking

Ion mobility spectrometry can improve pharmaceutical companies' production efficiency.

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Trace analysis is critical in pharmaceutical manufacturing, particularly in the equipment-cleaning steps during drug development. In the early drug-development stages, many cleaning-validation samples are analyzed while the manufacturing process is being developed. Each manufacturing batch run requires equipment that is clean.

In the later drug-development stages, when process validation is being completed, time is precious. This is the point where the product will be transferred to the commercial production facility, and the impact on the manufacture of commercial products must be minimized. The process is validated when the robustness of the formulation and manufacturing process has been demonstrated. For each day a pharmaceutical company delays the launch of a product, patients are deprived of lifesaving drugs and losses of a million dollars or more are realized.

Cleaning validation is performed to ensure that active pharmaceutical ingredients (APIs) and other production materials that come in contact with equipment surfaces are not contaminated or adulterated. Throughout all stages of development, every piece of manufacturing equipment must be verified as clean before it can be used. In cleaning validation, equipment surfaces (e.g., stainless steel, glass, rubber, and Teflon) are sampled after cleaning and the samples analyzed for traces of residual contaminants, including APIs and cleaning agents. The analyses must be quantitative, and pass–fail levels are determined according to Food and Drug Administration guidelines and specific company policy. Analysis of the verification samples can be a bottleneck that can extend equipment downtime. These analyses need an instrument that is selective, sensitive, and reliable; one that's easy to use; and one that's fast. Ion mobility spectrometry (IMS) offers all of these features.

IMS has been in development since the 1970s and came of age in trace determination for security by the early 1990s. Since then, its high sensitivity, rapid results, ease of use, and remarkable time and cost savings have been tapped for pharmaceutical analyses. It operates at atmospheric pressure, requires few consumables, has subnanogram sensitivity, produces results within seconds, and is easy to use.

IMS IMAGE COURTESY OF SMITHS DETECTION

The IONSCAN-LS IMS shown above has been designed for the pharmaceutical industry and is fully 21 *CFR* Part 11 compliant. Analytes are introduced into the IONSCAN-LS by thermal desorption, either from a Teflon substrate or by high-performance injection.

The IONSCAN-LS is well suited to pharmaceutical applications, with its control software affording easy access to method development and an autosampler to maximize speed and uniformity. With the IONSCAN-LS, IMS detection is optimized through a series of user-controlled injector and detector variables. The ability to program these variables opens up the widest possible scope of APIs. Once optimized to discern the particular API of interest, the set of parameters is saved as a method. The operator need only select the method to perform the analysis.

Process Validation

In order to obtain a robust pharmaceutical formulation and manufacturing process, the process itself has to be optimized, critical factors identified, and endpoint ranges for all critical factors defined and justified. Developing and validating this process is a challenging operation, with many steps and many batches run. Every step for every batch in the process has to be validated. Cleaning validation supports this process validation by verifying every piece of equipment as clean for every step. The time needed for cleaning the equipment and analyzing the samples taken from the cleaned equipment is significant, as the equipment is quarantined while the cleaning procedure is carried out.

After the manufacturing process is validated, the cleaning procedure must be validated. Then, during commercial manufacturing of the drug, cleaning validation does not have to be performed every time the equipment is cleaned in the process—it is used as a spot check. Each company has an ongoing monitoring program of the effectiveness of the cleaning method that sets a schedule for this commercial cleaning validation, typically performing it every 10–30 batches.

R&D in the pharmaceutical manufacturing industry has many unique challenges, among them 21 *CFR* Part 11, the defining regulation for electronic data collection within the industry. Driven by the need for effective medicines and operating under strict regulatory demands, new-product development can take 15 years and hundreds of millions of dollars (estimates range from about $800 million to $1.7 billion). Adding to the huge time and

money investment required to develop a drug is the fact that only about 10% of new drugs that enter clinical development ever make it to market.

Wyeth Research has developed and implemented a new R&D model that maximizes efficiency in the drug development process. At the core of this model is the development goal of 12 new drugs a year, of which 2 will be submitted for regulatory approval. To accomplish this, Wyeth has had to dramatically increase efficiency in all areas of its product validation processes.

The Wyeth model demands quantum leaps rather than incremental change from the previously used R&D methods. The new model lists four paths to accomplish this. Three of the four paths are business solutions dealing with company objectives, departmental re-alignment, and employee compensation. The fourth path includes the identification of new technologies to dramatically increase efficiencies. IMS is one of the new technologies that fits this path and allows streamlining within the process.

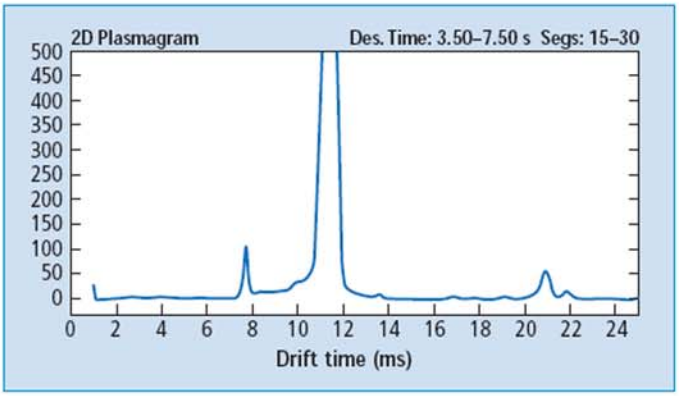

Figure 1. Ion mobility spectrum of Wyeth Research drug product Y.

Case Study: IMS Analysis of a Product

Recently, Wyeth Research's drug product Y was analyzed using the IONSCAN-LS's high-performance injection (HPI) feature. As shown in Figure 1, the plasmagram of drug product Y gave rise to a characteristic peak (Y) used for identification and quantitation. The plasmagram also shows, from left, the calibrant peak, a peak associated with the solvent, and a secondary peak associated with drug product Y.

Using HPI, the sample throughput rate for the analysis was 54 samples per hour; the sample size was 4 µL. Values obtained for the limit of detection (LOD) and limit of quantitation (LOQ) were 0.06 µg/mL and 0.18 µg/mL, respectively. Figure 2 shows representative data on linearity (correlation coefficient, R^2) and precision (relative standard deviation, RSD) obtained.

The IONSCAN-LS reduces downtime to the barest minimum. Time savings equate to cost savings in all areas of pharmaceutical manufacturing.

Cleaning Validation

Among the analytical methods widely used for cleaning validation in pharmaceutical manufacturing are total organic carbon (TOC) and high-pressure liquid chromatography (HPLC). Several pharmaceutical companies are now also using the IONSCAN-LS IMS.

IMS versus TOC. TOC is a fast and simple method. Its main drawback is that is can give false positive results because it finds all organic carbon and cannot distinguish between excipients or cleaning residue and the API. This lack of selectivity means that all organic carbon will be counted as the API and evaluated against the acceptance criteria, which were predetermined on the basis of the toxicity of the API. As a result, TOC can steal time by requiring unnecessary recleaning and reanalysis, when in fact the equipment actually is clean. These false indications are nonexistent in IMS, which gives quantitative, selective results.

IMS versus HPLC. HPLC is a selective analytical method, but it is not fast. In a typical analysis, the HPLC run time is about 10–25 min versus an IMS run time of about 30–45 s. With IMS, cost savings are realized in two areas. First, costs of consumables (solvents and column materials) needed in HPLC are nonexistent in IMS. More dramatically, cost savings are found in the IMS's speed. Speed of analysis means getting back into production or into the next process step faster. With the IMS's speed, production equipment can be verified as clean within hours rather than days.

In general, cleaning validation takes about two days using HPLC, whereas it takes only about 4 h using IMS.

In the pharmaceutical companies surveyed using the IONSCAN-LS IMS, downtime has been reduced dramatically. During the early part of development, many cleaning samples must be taken from each piece of equipment in each step of the manufacturing process. As an example, consider the analysis of 200 such samples.

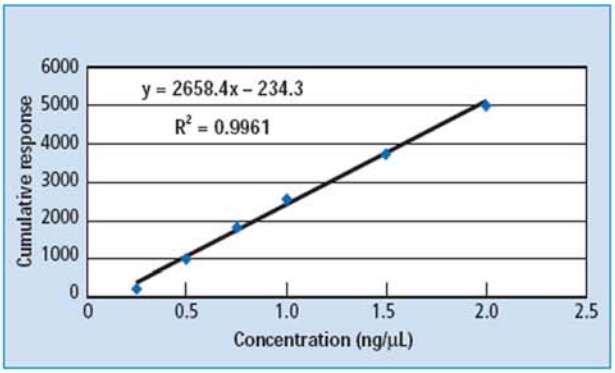

Figure 2. IMS concentration versus IMS response curve for Wyeth Research drug product Y.

A typical HPLC analysis is about 20 min per sample, compared with ≥1 min for IMS; for 200 samples, that is a time savings of ≥60 h.

Wyeth Research is developing and validating IMS methods for cleaning validation and is now implementing those methods on the IONSCAN-LS IMS for several products at multiple manufacturing sites.

Acknowledgments

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References

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