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Quantitative determination of residual active pharmaceutical ingredients and intermediates on equipment surfaces by ion mobility spectrometry

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ABSTRACT

Ion mobility spectrometry (IMS) is an analytical technique that separates ions based on their gas phase mobility at atmospheric pressure. Since gas phase ion mobility is a function of the shape and structure of the ion, this technique has the potential to provide unique specificity and selectivity. Furthermore, IMS is very sensitive (subnanogram detection limits for many small molecules), and a single analysis is typically completed within 1 min. In principle, these features of IMS should make it an ideal choice for use in cleaning verification analysis of pharmaceutical manufacturing equipment. This report describes the successful development and validation of three different equipment cleaning verification methods using IMS. The methods were developed for a specific intermediate (Compound A) in the synthetic route for a drug substance as well as for final drug substances (active pharmaceutical ingredients Compounds B and C). The cleaning verification methods were validated with respect to specificity, linearity, precision, accuracy, stability, and limit-of-quantitation. In all cases, the limits-of-quantitation were determined to be at the nanogram or sub-nanogram level. Both swab and rinse samples collected from the equipment surfaces were successfully analyzed and manufacturing equipment down-time was significantly minimized due to the reduction in cleaning verification analysis time (for example, the total analysis time for more than 30 samples using IMS was reduced to less than 2 h).

1. Introduction

Verification of cleaning processes is a critical task in pharmaceutical manufacturing in order to prevent cross-contamination of drug substance and/or drug product. Regulatory authorities require written procedures on how to conduct, validate and monitor cleaning processes [1–5]. To evaluate the effectiveness of equipment cleaning, validated methods for analyzing residues or contaminants from the manufacturing equipment surfaces are required [1–5]. Two fundamental approaches are generally employed to verify cleaning processes. The first approach termed "*ex situ*", employs methods designed to analyze for residues from samples collected (e.g., swabs or solvent rinses of the equipment surfaces) after equipment cleaning [6–38]. The second approach termed "*in situ*" employs automated methods executed by directly analyzing the equipment surfaces after cleaning [39–42]. Although the *in situ* approach has great potential, further studies need to be conducted to implement accurate, robust, and cost effective *in situ* analytical techniques/methods for cleaning validation/verification analysis. Currently, the most common practice in the pharmaceutical industry is *ex situ* analyses of swab or rinse samples. Analytical methods used for *ex situ* cleaning verification must provide adequate sensitivity for monitored chemical substances and must demonstrate that the residues or contaminants can be recovered from the equipment surfaces at target threshold levels with sufficient accuracy and precision [1–5].

The purpose of cleaning validation/verification analysis is to determine whether or not the target residues or contaminants in the samples are below certain acceptance limits. The acceptance limits are determined based on toxicity data, pharmacological dose, and ICH guidances on impurities and may depend on the type of equipment and the nature of the drug substance. The analytical methods can be specific or non-specific. Some examples of specific methods include high performance liquid chromatography (HPLC) [8,9,17,18,20,21,24,28–30,33], gas chromatography (GC) [16,22], ion chromatography (IC) [12,31], micellar electrokinetic chromatography (MEK) [35], and mass spectrometry (MS) [13,38]. Examples of non-specific methods include total organic carbon (TOC) [14,23,43–46], conductivity [44–46], gravimetric [46], and pH [7,44–46] analysis. Although UV [11,44] and atomic absorption [44] methods are specific to some degree, they are more susceptible to interferences especially when compared to methods that utilize chromatography and/or mass spectrometry.

Recently IMS has garnered increased attention for cleaning validation analysis due to its speed, sensitivity and specificity [47–57].

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IMS separates chemical compounds based on their gas phase ion mobility at atmospheric pressure. Samples are introduced into the instrument either by thermal desorption (for example, rapid heating and vaporization from a Teflon substrate), or by high performance injection (HPI), where samples are injected into a glass liner and vaporized by the HPI injector. The vaporized sample molecules are then selectively ionized by an internal ionizing source (*e.g.*, ^{63}Ni). The resulting ions are pulsed into a drift region by an electronic shutter, where they are separated according to their gas phase mobility. The signal intensity (ion current) versus drift time is recorded and a so-called "plasmagram" is generated. IMS is able to routinely achieve subnanogram sensitivity for certain compounds such as nitro-organic explosives [58]. Consequently, this technique has been applied to detect explosives and drugs by military and security organizations for several decades [58]. Because the separation is based on the gas phase ion mobility which is related to the geometry (size and structure) of the ions, IMS can be highly specific and selective. A major advantage of IMS for cleaning validation/verification is that analysis results are obtained within 1 min of injection. This greatly reduces sample turnaround times and therefore reduces the time needed for executing cleaning validation/verification processes. There are, however, limitations on using the IMS technique. Compounds must be readily vaporized and ionized in order to obtain a good signal, and must also be thermally stable. Fortuitously, most pharmaceutical compounds and their intermediates and/or contaminants have low molecular weights (generally below 1000 Da) that allow vaporization without thermolysis and contain functional groups that facilitate ionization.

In this report, the development of three IMS methods designed to evaluate cleaning processes for a synthetic drug substance intermediate (Compound A) and two final drug substances (Compounds B and C) are presented. These methods were validated with respect to specificity, linearity, precision, accuracy, stability, and limit-of-quantitation, and used to analyze swab and rinse samples collected from equipment surfaces after cleaning.

2. Experimental

2.1. Materials and reagents

Acetonitrile (ACN), and isopropyl alcohol (IPA) were purchased from EMD Chemicals, Inc. (Gibbstown, NJ). An in-house deionized water system was used to clean the plates for the recovery tests. Active pharmaceutical ingredients (API) and intermediates were synthesized by Boehringer-Ingelheim Pharmaceuticals, Inc. (Ridgefield, CT). Sunsorb Wipes (swabs) and Whatman 2 μm PTFE 46.2 mm filters (Teflon substrate) were purchased from VWR (West Chester, PA).

2.2. Equipment

IMS analyses were performed using an IONSCAN®-LS from Smiths Detection (Warren, NJ). IM station software (version 5.389) was used for data acquisition and processing. The instrument was programmed to use either positive or negative ionization mode depending on the structures of the analytes. Compounds A and C were analyzed in the positive ionization mode while Compound B was analyzed in the negative ionization mode. For the thermal desorption method the sample was deposited onto the Teflon substrate. For the HPI method, the sample was injected into a glass liner inside the high performance injection (HPI) injector. Instrument parameters for analysis are given in Table 1a. The method for Compound C used the HPI sample introduction approach which required additional settings (Table 1b).

Table 1a
Instrument parameters for analysis of Compounds A, B, and C.

Instrument parameters	Compound A	Compound B	Compound C
Ionization mode	Positive	Negative	Positive
Sample volume	1 μL	1 μL	1 μL
Post-dispense delay	7 s	7 s	7 s
Inlet temperature	280 °C	240 °C	280 °C
Desorber temperature	280 °C	232 °C	260 °C
Drift heater temperature	233 °C	111 °C	233 °C
Drift flow rate	300 mL/min with air	351 mL/min with air	300 mL/min with air
Scan Period	30 ms	30 ms	35 ms
Analysis duration	10 s	12 s	20 s

Table 1b
HPI parameters for analysis of Compound C.

HPI injection mode	HPI cold
Carrier flow	25.0 mL/min
Initial temperature	50 °C
Final temperature	280 °C
Delay time	2 s
Multi-stage temperature ramp	No

2.3. Preparation of standards

The stock solutions for Compounds A and B (approximately 100 μg/mL and 50 μg/mL, respectively) were prepared using IPA. Appropriate dilutions were made in IPA to obtain calibration solutions ranging from 0.1 to 1.0 μg/mL and 1.1 to 11.0 μg/mL for Compounds A and B, respectively.

The stock solution for Compound C (approximately 100 μg/mL) was prepared using methanol. Appropriate dilutions were made in methanol to obtain the calibration solutions ranging from 1.1 to 9.1 μg/mL.

2.4. Recovery of samples from steel, hastelloy, and glass plates

2.4.1. Plate preparation for recovery testing

Three 10 × 10 cm steel plates, three 10 × 10 cm hastelloy plates and three 10 × 10 cm glass plates were washed with water, ultrasonicated in acetonitrile followed by isopropanol (IPA) for Compounds A and B or methanol (Compound C) for 5 min each. After ultrasonication, the plates were allowed to air dry in a hood.

2.4.2. Spike solution preparation

The spike solutions were prepared at the acceptance levels for the cleaning processes. For Compound A, the acceptance level was either 0.166 μg/cm^2 or 4.76 μg/cm^2 depending on the equipment type. For Compounds B and C, the acceptance level was 0.444 μg/cm^2. The high level spike solution (approximately 476 μg/mL) for Compound A was prepared using IPA. The solution was then further diluted with IPA to make the low level spike solution (approximately 16.6 μg/mL). The spike solutions (approximately 44.4 μg/mL) for Compounds B and C were made with IPA and methanol, respectively.

2.4.3. Spike recovery test

Steel, hastelloy, and glass plates (10 cm × 10 cm) were spiked with 1 mL of Compound A, Compound B, or Compound C spike solutions. The spiked plates were allowed to dry in the hood. The Sunsorb Wipes were cut into 6 cm × 6 cm pads, folded and put into 20 mL trace clean vials. To each vial, 1.0 mL IPA (for Compounds A and B) or methanol (for Compound C) was added. The vials were vortexed to moisten the swabs evenly. Each soaked swab was firmly passed over the surface of one spiked plate horizontally, flipped, firmly passed over the surface vertically, and then transferred back to the vial. The swabs in the vials were dried under an air stream for

10 min, followed by addition of 10 mL of IPA (for Compounds A and B) or 10 mL of methanol (for Compound C) to each vial. The vials were vortexed and ultrasonicated for 5 min. The IPA or methanol extraction solutions were diluted into the calibration curve range as necessary and analyzed by IMS. Three replicate samples per level and per surface were prepared as described above.

2.5. Sample preparation for cleaning verification analysis

Each swab sample from the cleaning process was placed into a separate trace clean vial and dried under a stream of air for 10 min. Ten mL of IPA (for Compounds A and B) or 10 mL of methanol (for Compound C) was then added to each vial. The vials were vortexed and ultrasonicated for 5 min and the extraction solutions were analyzed by IMS. For rinse samples, 10 mL of IPA (for Compounds A and B) or 10 mL of methanol (for Compound C) was added into each sample container. The containers were shaken and ultrasonicated as needed to completely dissolve the samples before the analysis by IMS. Dilutions of the IPA or methanol solutions were prepared and analyzed in those cases where the analyte signal due to the sample exceeded the analyte signal of the highest standard.

3. Results and discussion

3.1. Development of the IMS methods

The first step in the development of an IMS method is to assess the molecular structure of each analyte in order to select the ionization mode and sample introduction process most likely to afford the required sensitivities based on the predetermined acceptance levels. Compounds A and C each contain multiple reduced nitrogen atoms (*i.e.,* amine, amide) which suggests, due to the relatively high proton affinities of these functional groups, that positive ionization is the appropriate mode. Although Compound B does not contain any high proton affinity functional groups it does contain a nitrile group with a relatively high electron affinity which suggests

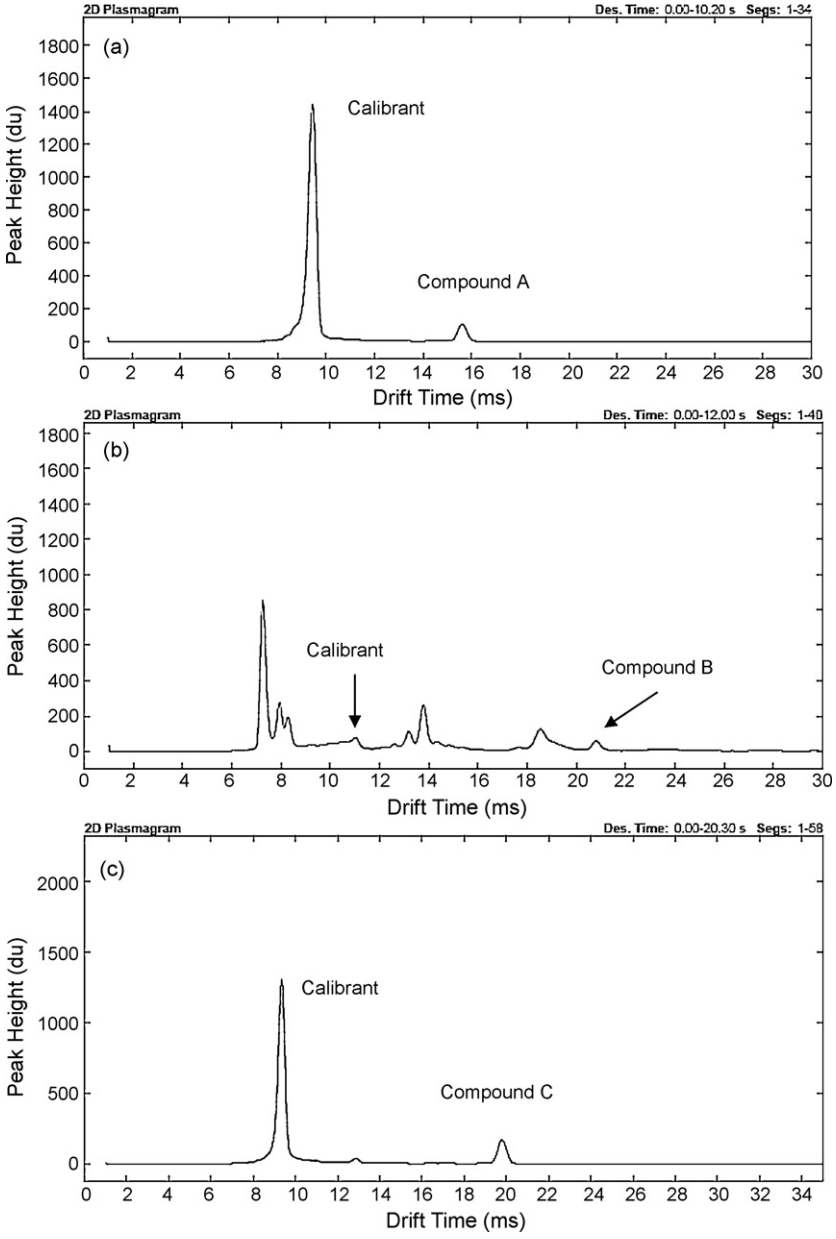

Fig. 1. (a) Representative plasmagram for Compound A standard using positive ionization mode. (b) Representative plasmagram for Compound B standard using negative ionization mode. (c) Representative plasmagram for Compound C standard using positive ionization mode.

that negative ionization would be effective. As already discussed above, there are two approaches for sample introduction into the IMS system: thermal desorption and high performance injection (HPI). Although thermal desorption is usually preferred for cleaning verification studies because of its relative simplicity, the two approaches differ with regard to solvent compatibility. Polar solvents such as water or methanol which have difficulty effectively wetting the surface of the Teflon substrate are not recommended for use with the thermal desorption approach. On the other hand, the HPI method tolerates polar solvents. HPI also has the capability to improve the separation of interferences by multi-stage vaporization and can allow large volume injection for dilute samples or, conversely, split injection for samples that are more concentrated. Compounds A and B were determined to have adequate solubility in IPA, which is compatible with thermal desorption. An attempt was made to develop a simple thermal desorption method for Compound C which has limited solubility in non-polar solvents. A stock solution of Compound C was first prepared by dissolving it in methanol followed by dilution of the stock solution with a relatively non-polar solvent (either acetone or IPA). Unfortunately, this "mixed-solvent" approach also did not work effectively with thermal desorption and ultimately Compound C required the development of an HPI method.

With the thermal desorption approach, inlet temperature, desorber temperature, and post-dispense delay are among the most critical parameters that need to be optimized in order to obtain good desorption profiles and the desired sensitivity. With HPI, there are a few more parameters and settings that require optimization during method development. There are two types of injection modes in HPI methods, HPI cold injection and HPI hot injection. In HPI cold injection mode, solvent vaporization occurs first followed by sample vaporization. This injection mode is used for compounds with different volatility to reduce the competition for charge and therefore improve sensitivity and precision. On the other hand, sample vaporization occurs immediately upon injection in HPI hot injection mode. This hot injection mode is particularly suitable for "sticky" compounds that give a broad or long-tailed desorption profile. This was not a problem for Compound C and thus, an HPI cold injection method was employed. Initial temperature, final temperature, and carrier gas flow are key settings when developing a method utilizing HPI. For Compound C, these parameters were optimized in order to obtain the best signal-to-noise and a good desorption profile. An advantage of IMS for cleaning validation/verification method development relative to other analytical techniques such as HPLC is that the instrument parameters can be varied and reequilibrated within minutes regardless of the sample introduction technique used. Fig. 1a–c shows representative plasmagrams of Compound A, B, and C standards after optimization of the method parameters.

The IMS instrument software automatically calculates the analyte peak heights based on the observed maximum amplitude (MaxA) or cumulative amplitude (CumA) of the plasmagrams. The optimum amplitude is entirely compound dependent and is empirically determined at the time of method development and validation. Analytical parameters (such as linearity, accuracy, and precision) are initially calculated using both MaxA and CumA to determine which is the best type of amplitude value to use for a given analyte. The results shown in Table 2 and 3 are results using the optimum amplitudes as noted.

3.2. Specificity

Swab blanks (*i.e.*, without analytes) were prepared following the sample preparation procedure described in Section 2.5 and analyzed by the developed IMS methods. Swab blanks are especially important when using negative ionization methods because there are more interferences observed in that mode. No interference was observed in the same drift time range as the analytes (Fig. 2a–c).

3.3. Linearity

The linearity for each of the three methods was evaluated by analyzing standard solutions at five different concentration levels ranging from 0.1 to 1.0 μg/mL, 1.1 to 11.0 μg/mL, and 1.1 to 9.1 μg/mL for Compounds A, B and C, respectively. The calibration curves were constructed by plotting either the maximum amplitude (MaxA) or cumulative amplitude (CumA) in digital units (d.u.) of all segments against the corresponding concentration injected. Table 2 shows the slopes, intercepts and correlation coefficients (r) for Compounds A, B, and C.

3.4. Limit-of-quantitation (LOQ)

Initial estimates of LOQ were based on extrapolating from the observed standard signal-to-noise ratios down to 10:1 as recommended by the IMS instrument manufacturer. In practice, we found these estimates to be too optimistic since, for example, in all three cases the analyte could not be detected at the estimated LOQ level. A robust LOQ is important since the purpose of cleaning verification analysis is to ensure that residues and/or contaminants are below a certain pre-determined acceptance level. Consequently, we chose to define LOQ more conservatively, specifically, by choosing a concentration well below the acceptance level and testing the precision of that standard concentration by making six replicate injections. For Compound A, six injections of the 0.10 μg/mL lowest standard solution gave a precision of 15.5% relative standard deviation (RSD) using the CumA response. Since this RSD value is lower than the arbitrarily chosen acceptance criteria for the precision at the LOQ concentration of ≤25%, the LOQ level for compound A was set to 0.10 μg/mL (corresponding to 0.10 ng injected). The LOQ for Compound B was determined to be 50% of the lowest standard concentration or 0.54 μg/mL (corresponding to 0.54 ng injected) based on the RSD (12.0%) calculated from six injections of that standard concentration using the CumA response. The LOQ value for Compound C was the lowest standard concentration (1.1 μg/mL, corresponding to 1.1 ng injected) using the MaxA response with an RSD of 9.4% for six injections. The LOQs determined above are at least four times lower than the concentrations at the lower acceptance level for each compound (1.66 μg/mL for Compound A and 4.44 μg/mL for Compounds B and C).

Table 2
Linear regression data for Compounds A, B, and C analysis.

Statistical parameters	Compound A (CumA)	Compound B (CumA)	Compound C (MaxA)
Concentration range (μg/mL)	0.1–1.0	1.1–11.0	1.1–9.1
Regression (slope/intercept)	2243.1/103.7	486.9/149.5	27.3/−3.5
Correlation coefficient (r)	0.9956	0.9916	0.9907
LOQ (ng)	0.10	0.54	1.1

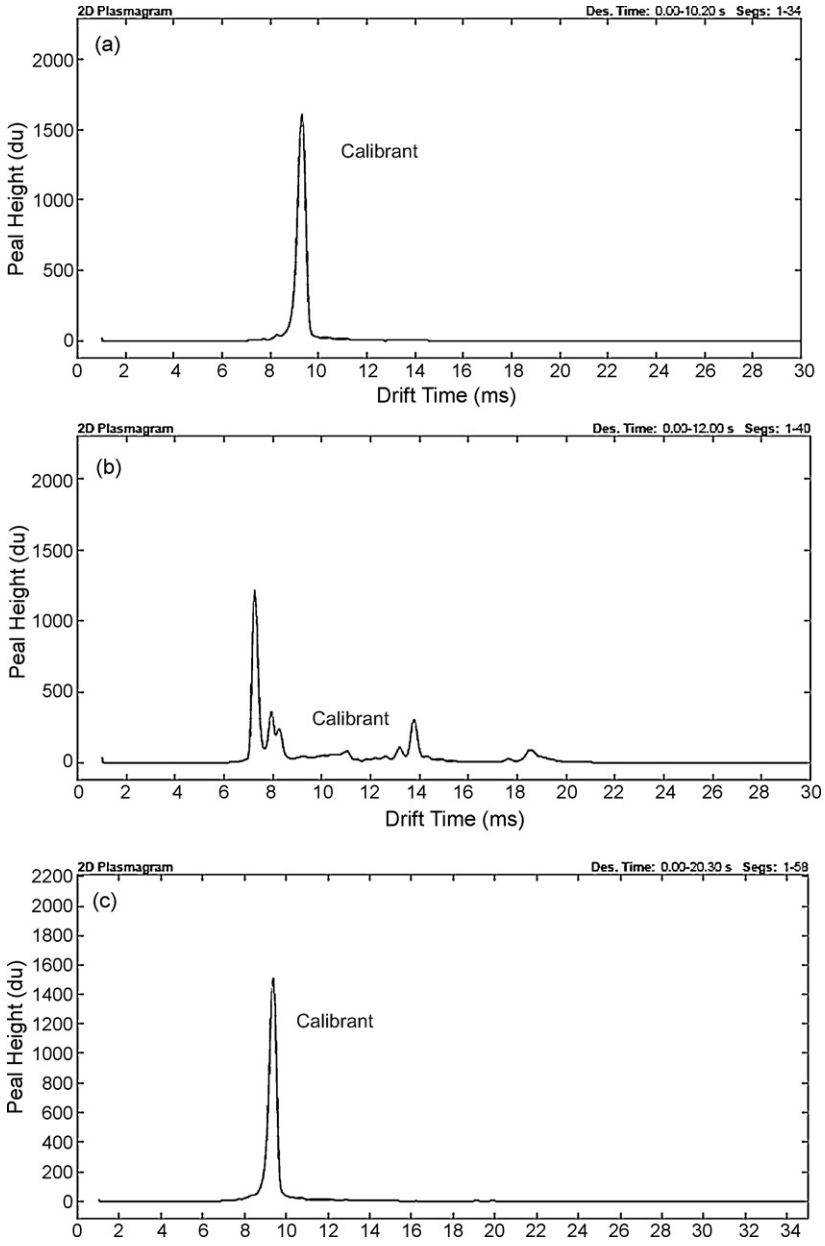

Fig. 2. (a) Swab blank for Compound A method. (b) Swab blank for Compound B method. (c) Swab blank for Compound C method.

3.5. Repeatability and intra-assay precision

Repeatability was determined by analyzing five replicate injections of a standard at the mid-range concentration level in the calibration curves. The average response and RSD were calculated and data are tabulated in Table 3a. The intra-assay precision expressed as RSD was evaluated by analyzing triplicate recovery samples on different surfaces at different spike levels. Results are reported in Table 3b.

Table 3a
Repeatability.

Injection replicate	Compound A CumA (d.u.)	Compound B CumA (d.u.)	Compound C MaxA (d.u.)
1	1323	6320	257
2	1272	6398	289
3	1291	6598	289
4	1209	6598	299
5	1323	6769	294
Average	1283.6	6536.6	285.6
RSD	3.7%	2.7%	5.8%

3.6. Accuracy

The accuracy of the methods was reported as percent recovery for Compound A, B or C from at least two different surfaces determined by spiking Compound A, B or C standards at the acceptance

Table 3b
Intra-assay precision.

Compound ID	Spike level ($\mu g/cm^2$)	%RSD on steel plate	%RSD on hastelloy plate	%RSD on glass plate
Compound A	0.166	6.8	9.3	NA*
Compound A	4.76	7.0	6.1	NA*
Compound B	0.444	10.8	5.8	10.8
Compound C	0.444	4.7	3.5	NA*

*Not validated for this surface.

Table 4
Recovery of Compounds A, B and C from different surfaces.

Compound	Spike level (μg/cm^2)	Surface	Recovery-1	Recovery-2	Recovery-3	Mean
Compound A	0.166	Steel	62.1	71.1	66.4	66.5
Compound A	0.166	Hastelloy	61.6	73.8	65.4	66.9
Compound A	4.76	Steel	84.2	76.2	73.7	78.0
Compound A	4.76	Hastelloy	78.0	71.6	80.7	76.8
Compound B	0.444	Steel	87.6	72.1	74.3	78.0
Compound B	0.444	Hastelloy	97.0	106.3	108.2	103.8
Compound B	0.444	Glass	87.8	97.2	78.3	87.8
Compound C	0.444	Steel	91.8	88.2	82.8	87.6
Compound C	0.444	Hastelloy	100.2	102.2	107.5	103.3

concentration levels on the surfaces. Triplicate analyses were performed at each spike level and on each surface. Recovery results are presented in Table 4. The recovery of the compounds from the surfaces is dependent on the swab technique which includes the type of swab, the solvents used to moisten the swabs, and the number of swabs used. When the average recovery is less than 80%, this usually means the swab technique needs to be optimized. Alternatively, to save time and to simplify the swab procedure, a correction factor based conservatively on the lowest recovery value can be applied for the calculations made in the sample analysis.

3.7. Stability

The stability of Compound A, B, and C standards and swab sample extraction solutions was evaluated by analyzing samples stored at room temperature for 24 h. Table 5 shows the recovery of standards and samples from their initial values calculated from IMS data. Standard and sample solutions are considered stable if the recovery from the initial concentration is more than 95%. As shown in Table 5, standard solutions for all three compounds and sample solutions for Compounds A and C were determined to be stable for at least 24 h. On the other hand, Compound B in the extracted sample solution was found to be only 84% of its initial value after 24 h. Therefore, extracted sample solutions for Compound B need to be analyzed on the same day they are prepared.

3.8. Analysis of swab samples from the cleaning process

Rinse and swab samples were collected after the cleaning process from different equipment and analyzed using the three validated IMS methods for Compounds A, B, and C. The results (Tables 6a–6c) show that most of the residues remaining on the surface of the equipment were below the acceptance level (μg/container results were converted to μg/cm^2 by chemical engineering stuff). Furthermore, with a run time of less than 1 min per injection, the total analysis time for 31 Compound A samples was less than 2 h and analysis of Compound B and C (approximately 30 samples in total) was even faster. Thus, we have found that a 24 h sample turn around time is easily achievable by implementing the use of IMS technology in lieu of a more conventional approach for cleaning verification analysis.

Table 5
Stability of standards and samples.

Compound	% of initial value for standard after 24 h	% of initial value for sample after 24 h
Compound A	103.7	95.3
Compound B	99.0	84.3
Compound C	117.5	111.7

Table 6a
Sample analysis results for Compound A.

Sample ID	Results (μg/mL)	Results (μg/container)
Swab samples, drying tray D-03, 1-12, 14-24	None detected	None detected
Rinse sample, R-07	0.11	1.1
Rinse sample, R-08	0.20	2.0
Swab sample, addition funnel AF-1	None detected	None detected
Swab sample, centrifuge F-13	None detected	None detected
Swab samples, D-03 vacuum oven chambers	None detected	None detected
Swab sample, drying tray D-03-13	0.49	4.9

Table 6b
Sample analysis results for Compound B.

Sample ID	Results (μg/mL)	Results (μg/container)
Rinse sample, R-06 reactor system	24.4*	244
Rinse sample, PDLEVAL0184-01	None detected	None detected
Rinse sample, PDLEVAL0184-02	53.3*	533
Swab sample, Seitz Filter F-9	None detected	None detected
Swab sample, sparkler filter F-11	None detected	None detected
Swab samples, drying tray-DP-63-1-5,7	None detected	None detected
Swab sample, centrifuge RC-50VXRF-13	None detected	None detected
Swab sample, funnel AF-2	None detected	None detected

*Dilution was made because the sample concentration is out of the linearity range.

Table 6c
Sample analysis results for Compound C.

Sample ID	Results (μg/mL)	Results (μg/container)
Rinse sample, PDL-EVAL0175-37 (Blank)	None detected	None detected
Rinse sample, PDL-EVAL0175-37-1 (R-10)	10.29*	102.9
Swab sample, PDL-EVAL0175 (Glatt Sieve)	1.10	11.0
Swab sample, DP-63 Yamato oven	Less than LOQ	Less than 11
Swab sample, DP-63-4 drying tray	Less than LOQ	Less than 11
Swab sample, DP-63-7 drying tray	Less than LOQ	Less than 11
Swab sample, DP-63-8 drying tray	Less than LOQ	Less than 11
Swab sample, 1450D/01 drying tray	Less than LOQ	Less than 11
Swab sample, 1450D/02 drying tray	Less than LOQ	Less than 11
Swab sample, 1450D/06-9 drying trays, etc.	None detected	None detected

*Dilution was made because the sample concentration is out of the linearity range.

4. Conclusion

Three IMS cleaning verification methods have been developed and found to be suitable for quantitative determination of Compound A, B, and C residues in rinse and swab samples collected from the equipment surfaces. IMS allowed the analysis of more than thirty samples to be completed within 2 h which in turn makes routine 24 h sample turnaround time a reality. This is especially important in a manufacturing environment where it is important to minimize equipment idle time as much as possible. The use of

IMS achieved nanogram to subnanogram LOQ levels for all three compounds without the requirement for a UV chromophore or for chromatographic separation. In conclusion, these features of IMS make it an ideal alternative and potentially even the analytical technique of choice for routine cleaning validation/verification analysis.

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