

Ion Mobility Spectrometry (IMS) Delivers Fast, Successful Method Validation for Cleaning Verification

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Purpose:

To develop a validated ion mobility spectrometry (IMS) cleaning verification method to determine the pharmaceutical active diphenhydramine HCl (DPH), and to illustrate the advantages of using IMS over HPLC.

Introduction:

IMS instrumentation is well-established in the security field where it has been widely used to detect explosives, narcotics, and chemical warfare agents. More recently, IMS has been applied with growing popularity to the determination of pharmaceutical actives. IMS uses few consumables, has sub-nanogram sensitivity, produces results within seconds, and is easy to operate. Its main advantages are speed – high throughput (60-120 samples per hour) – and sensitivity – picogram to nanogram (1 ppb to 1 ppm).

Case Study:

A major pharmaceutical manufacturer¹ was evaluating IMS to replace HPLC for cleaning validation. They challenged the IMS to meet the requirements for all the validation parameters in an established cleaning verification method that uses HPLC. They also compared the potential time and cost savings of switching to IMS.

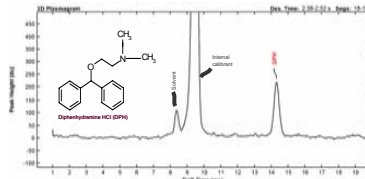
Reference:

1. K. Payne, W. Fawber, J. Faria, J. Buaron, R. DeBono, A. Mahmood, "IMS for Cleaning Validation," *Process Analytical Technologies Supplement to Spectroscopy*, Jan. 2005, 24

Experimental Method:

The data were obtained using an IONSCAN-LS[®] system from Smiths Detection. A robotic autosampler made 1- μ L injections of DPH standards, blanks, swab samples, and mock samples prepared in methanol/isopropanol (4%/96%) into the HPI injection port. The DPH molecular ion was detected at a flight time of 14.382 ms, corresponding to a reduced ion mobility (K_0) of 1.2285 cm²/Vs. Specificity was tested by running standards and comparing them with placebo blanks. The linear range was determined from a plot of the mean DPH signal amplitude vs. concentration for triplicate injections ranging from 20 – 150% of the chosen action level (0.135 μ g/mL). Six replicate injections at the limit of quantitation (LOQ) and at the action level were made to determine precision. To test the accuracy of the method, three stainless steel surfaces spiked with DPH at 75, 100, and 125% of the Acceptable Residual Limit (ARL) were swabbed, and extracts of the swabs were diluted and analyzed. For additional accuracy testing, 20 mock samples – each containing a known concentration of DPH at 75–125% of the action level – were assayed. For stability testing, standards were aged 48 hours.

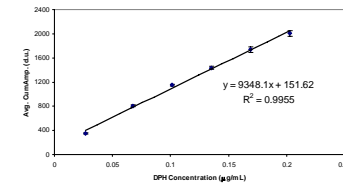
IMS Plasmagram for the Analysis of DPH



Analysis of DPH Standards

Concentration (μ g/mL)	% of Action Level	Mean Amplitude (d.u.)	RSD (%)
0.027	20	349	2.7
0.068	50	808	1.9
0.101	75	1149	1.1
0.135	100	1433	1.8
0.169	125	1739	2.8
0.203	150	2004	2.4

IMS Linearity Data for DPH



Results and Conclusion:

The IMS method met or exceeded all the validation criteria. Results for specificity, linearity, precision, accuracy, and stability are shown in the table. The LOD and LOQ were 0.009 μ g/mL and 0.022 μ g/mL, respectively. Each sample took 12 seconds to analyze. The cycle time of 60 seconds per sample (60 samples per hour) was limited by the autosampler.

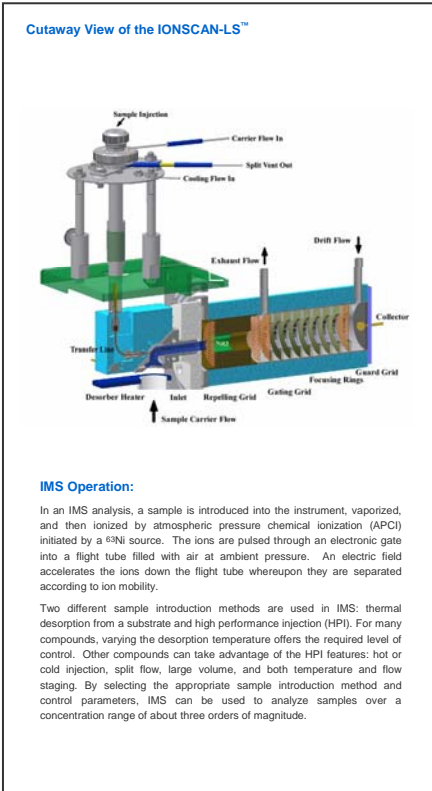
The time needed to complete the analyses for the validation tests using IMS was approximately 2.5 hours compared to 17.5 hours when using HPLC, a savings of nearly two working days.

Cleaning Validation Protocol Requirements and IMS Results

Requirement	IMS Result	Met?
Specificity Interference from swabs and excipients \leq 5%	No interference	Yes
Linear Range 20 to 150% of action level	20 to 150% of action level	Yes
Linearity $R^2 \geq 0.98$	$R^2 = 0.9955$	Yes
Precision at Action Level RSD \leq 5%	RSD = 1.8%	Yes
Precision at Limit of Quantitation (LOQ) RSD \leq 10%	RSD = 6.3%	Yes
Accuracy (swab recovery) Recovery \geq 70% RSD \leq 15%	Recovery = 95-102% RSD = 3.0 – 3.4%	Yes
Accuracy (mock samples) Recovery = 90-110%	Recovery = 93-105%	Yes
48-Hour Stability Recovery = 95 – 105%	Recovery = 100 – 101%	Yes

Time/Cost Comparison of IMS vs HPLC in Cleaning Validation Method

	HPLC	IMS
Consumables	Mobile phase: potassium phosphate pH 2.5 and acetonitrile (70:30) Flow rate: 1.2 mL/min – 1.2 L eluting solvent	< 2 L high purity N ₂
Equipment start-up	Prepare mobile phase = 60 min Establish mobile phase and column equilibration = 180 min Total = 240 min	None
Time per sample	9 minutes	1 minute
Cost per sample	High	Low
Additional costs	Waste solvent disposal	None
Total time for all analyses associated with method validation	17.5 hours	2.5 hours



IMS Operation:

In an IMS analysis, a sample is introduced into the instrument, vaporized, and then ionized by atmospheric pressure chemical ionization (APCI) initiated by a ⁹³N source. The ions are pulsed through an electronic gate into a flight tube filled with air at ambient pressure. An electric field accelerates the ions down the flight tube whereupon they are separated according to ion mobility.

Two different sample introduction methods are used in IMS: thermal desorption from a substrate and high performance injection (HPI). For many compounds, varying the desorption temperature offers the required level of control. Other compounds can take advantage of the HPI features: hot or cold injection, split flow, large volume, and both temperature and flow staging. By selecting the appropriate sample introduction method and control parameters, IMS can be used to analyze samples over a concentration range of about three orders of magnitude.

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