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EQUIPMENT QUALIFICATION OF ION MOBILITY SPECTROMETRY AND METHOD DEVELOPMENT AND VALIDATION FOR PHARMACEUTICAL EQUIPMENT CLEANING VALIDATION

by

Amy Lee Heiser

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Science
Department of Chemistry
Advisor: Andre R. Venter, Ph.D.

Western Michigan University
Kalamazoo, Michigan
December 2012

EQUIPMENT QUALIFICATION OF ION MOBILITY SPECTROMETRY AND METHOD DEVELOPMENT AND VALIDATION FOR PHARMACEUTICAL EQUIPMENT CLEANING VALIDATION

Amy Lee Heiser, M.S.

Western Michigan University, 2012

Ion mobility spectrometry (IMS) instrumentation has been identified as a suitable technology for the detection and reporting of drug product and detergent residues from pharmaceutical manufacturing equipment. Ion mobility is not a new technology, but is entering the field of cleaning validation because of tightened requirements from the US Food and Drug Administration (FDA).

The purpose of this thesis is to outline a practical implementation of the analytical technique, Ion Mobility Spectrometry in a cleaning validation program. Ion Mobility Spectrometry (IMS) is fast and specific for the analysis of small organic molecules and has been gaining popularity in the pharmaceutical industry. The challenge in the implementation of any new analytical technique in a pharmaceutical laboratory is establishing suitable methodology and this thesis will outline the steps taken for developing and validating a method for detection of the antihistamine drug Loratadine. The author will also provide a detailed introduction to the requirements of equipment qualification, cleaning validation and analytical method validation programs in the pharmaceutical industry.

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ACKNOWLEDGMENTS

I would like to thank all those who have made this thesis possible at Perrigo Company and at Western Michigan University. A special thank you to Dr. Andre Venter who supported me throughout my graduate studies and who without his advise this thesis would not have been possible. I owe a heartfelt thank you to Dr. Sherine Obare who provided advice and encouragement during every step of the process and who fought for my success. I also want to thank Dr. John Miller for being a member of my thesis committee and for providing support along the way. Finally, I owe my biggest thank you to my husband for supporting me through this process and never losing faith in my ability to succeed.

Amy Lee Heiser

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CHAPTER 1

INTRODUCTION

The US Food and Drug Administration requires that all pharmaceutical manufacturing facilities maintain a cleaning validation program to demonstrate the cleanliness of the equipment used to manufacture drug products. The requirements of the cleaning validation program are outlined in the current Good Manufacturing Practices (cGMPs). The cGMPs are a compilation of regulations for the pharmaceutical industry as found in the Code of Federal Regulations (CFR). [3] The pharmaceutical firm is responsible for establishing a program which is supported with analytical data demonstrating that the equipment is essentially free of drug substance and detergent residue.

High Pressure Liquid Chromatography (HPLC) is a very common technique for analysis of small molecules used in the pharmaceutical industry. Another instrumentation technique gaining popularity in the industry is Ion Mobility Spectrometry (IMS), which is capable of quantifying many of the same analytes as HPLC, but in a fraction of the time. Speed of analysis is critical in all quality control laboratories, but specifically for cleaning validation due to the cost of leaving manufacturing equipment quarantined awaiting testing. This chapter will provide a brief introduction to IMS technology and cleaning validation as well

as the equipment qualification requirements for new instrumentation used for release of drug products or manufacturing equipment.

1.1 Ion Mobility Spectrometry

Ion mobility spectrometers separate ions based upon their mobility through a gas. The ions generated by the ion source are propelled through a drift tube by an applied electric field. Unlike mass spectrometry the drift tube in an IMS contains a neutral carrier gas, such as compressed air, which provides resistance for the moving ions. By this principle, analytes are separated by their size and shape, not only by their mass and charge. [1] Because separation of target analytes takes place in the gas phase, there is no need for complicated mobile phase or diluent preparation in the case of liquid chromatography or the associated costs of vacuum systems in the case of mass spectrometry.

There are five main stages in the analysis of compounds by ion mobility spectrometry. The first, sample preparation, involves solubilizing the analyte and/or applying the analyte directly onto the desorbing surface (i.e. using a Teflon substrate to swab a surface). Next, the analyte is volatilized to the gas phase and enters an ionization chamber. Ionization may take place according to several different mechanisms, dependent upon the ionization source. After ionization, the ions enter the separation stage, where the charged analytes travel through a drift tube at atmospheric pressure. There the ions are divided into packets based on size and shape and reach the Faraday plate for detection at

their respective drift times. The relative amount in each ion packet in arbitrary digital units (du) is plotted against the drift time for all analytes observed in a plasmagram as shown in Figure 1.1 in 2-dimensional and 3-dimensional plasmagrams.

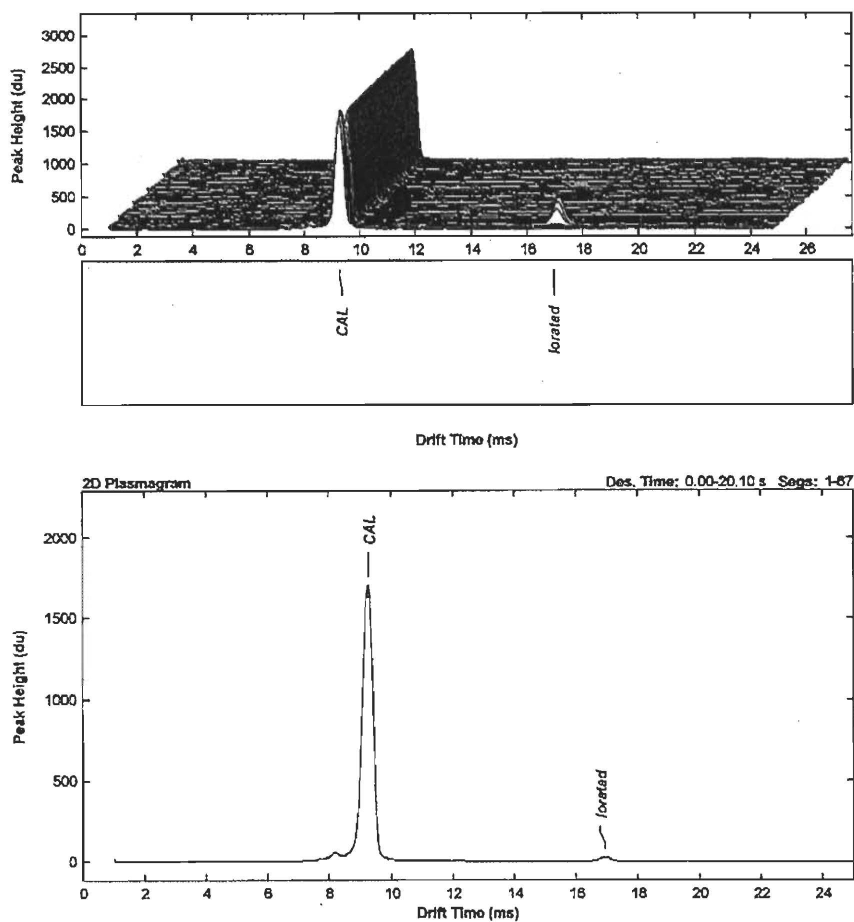

Figure 1.1 3-D and 2-D plasmagrams of loratadine

Ion mobility spectrometry first gained its popularity in the field of narcotics and explosives detection. [1] Since ion mobility is dependent upon shape and size, a specific ion's mobility is repeatable and unique. The detection level of IMS instrumentation is so low that the US armed forces, airport security and law

enforcement can use a small handheld device and know immediately whether trace amounts of narcotics or explosives are present. [8] IMS units used for security purposes come in all different shapes and sizes including whole body scanners which use a puff of air to dislodge any trace residue from a person's clothing, hair or skin. These devices use a library of reduced mobility values to quickly identify compounds without the need for a laboratory and authentic standards. These scanners do not provide quantification of key analytes, but they are convenient and relatively inexpensive to use.

Another important sector for IMS instrumentation is the field of pharmaceutical cleaning validation. [7] IMS instrumentation applied on a production line can provide a limits-based value for a specific drug within a moment of sample collection. Similar to narcotics, prescription and over-the-counter pharmaceuticals are volatile and ionizable compounds, easily detectable by IMS technology.

1.2 Equipment Qualification and Calibration in a cGMP Laboratory

All equipment utilized in an analytical or quality control laboratory for generation of data to be used for release of drug products or substances must meet cGMP requirements. The cGMPs are a compilation of regulations made by the US FDA and included in the code of federal regulations under Title 21. [3] The cGMP specific to laboratory control of instruments states "The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in

accordance with an established written program containing specific directions, schedules, limits for accuracy and precision and provisions for remedial action in the event accuracy and/or precision limits are not met."[4] The programs developed across the industry to meet these requirements vary greatly, and many professional groups within the pharmaceutical industry have developed suggested guides to harmonize the process. The product of one such group is an article by Sigvardson et.al [5], which highlights the major requirements of an equipment qualification program and also provides examples of tests that are generally included for some common types of equipment. Because Ion Mobility is a relatively new technique to the pharmaceutical industry, many of the testing parameters referenced in this thesis were provided by the instrument vendor [2], or developed by the Author.

Some pharmaceutical firms may require a Design Qualification (DQ) in order to purchase the instrument. The DQ will outline what function the instrument will perform within the firm. [4] Although the DQ is not a cGMP regulatory requirement, it is a worthwhile process to ensure the targeted instrument meets the firms needs for the required task. Once the instrument is purchased, there are three main qualification steps, the instrument qualification (IQ), operational qualification (OQ) and the performance qualification (PQ, or also referred to as the performance verification or PV). When a software or computer system is purchased with the instrument, a computer system validation (CSV) is also be required.

1.3 Pharmaceutical Cleaning Validation

In order to prevent carryover, contamination and adulteration of drug substances and products between batches, the maintenance of a validated cleaning program is a critical requirement of the US government's current Good Manufacturing Practices (cGMPs). [3] The FDA requires all firms to have an established cleaning validation program supported by written cleaning procedures, protocols and reports to show the robustness of the program. Although there is no one way to design a validation program, the FDA expects a pharmaceutical firm to have met a few basic requirements, such as written procedures (including standard operating procedures or SOPs) detailing the cleaning method for each potential scenario as well as a general procedure for validating the cleaning process. [4]

A validation protocol and report shall be written for each validation study and approved by management. Within the validation protocol, a pharmaceutical firm will document the cleaning method employed for the type of equipment or equipment chain being qualified, limits for the acceptable detergent and drug substance residue, the sampling procedures, the analytical methodology which will be used for testing residues, and finally the sensitivity of the analytical methodology or limit of detection (LOD). The validation report shall clearly state results of the executed protocol and the validation status of the cleaning process.

The microbiological burden requirement for a cleaning validation program will not be discussed in this thesis.[4]

1.3.1 Establishment of Limits for Drug Substances and Detergents

The acceptable limits for detergent and drug substance shall ensure the efficacy and safety of the firm's product to prevent cross contamination, and must consider the sensitivity of the analytical method. [4] The limit must not only consider the maximum therapeutic dose of the active ingredient and the toxicity of a detergent component, but should also take into account any known by-products and reactants. For example, when cleaning acetylsalicylic acid, known by its common name as Aspirin, with a basic detergent, it is possible that degradation may occur and the analytical method must also be sensitive to its known degradent, salicylic acid.

Chemical and detergent limits can be calculated either for an individual piece of equipment, or for a train of equipment utilized in the manufacturing process. Since most detergents have many proprietary ingredients, a method utilizing total organic carbon or conductivity is often employed and a limit such as 10 ppm may be acceptable. [9] Not only is it difficult to develop a method for unknown ingredients, but it is also unlikely that a highly water-soluble detergent would leave residue when properly rinsed. In cases where a toxic detergent component is known or the detergent is not highly water-soluble, a more stringent limit shall be applied. [4]

1.4 Analytical Method Development and Validation

Analytical methods should meet the criteria outlined in the International Conference on Harmonization (ICH) Guidelines to be considered fully validated for testing of cleaning validation samples. The degree of validation required is dependent on whether the method will be used for quantitative or limits-based determination. [6] Limits-based methods are commonly used for cleaning validation because they provide assurance that residue is below a certain level without the need for exact known quantities. A quantitative method for reporting of residue levels has been outlined in this thesis; therefore the analytical method must be accurate, precise, and linear over the desired range of analysis. The linear range must span the limit of quantification (LOQ) through the residue limit, and a low detection level (LOD) must be established. The validation shall also include a recovery study to show that the swab and solvent combination effectively remove at least 50% of analyte spiked onto a surface representative of that used for pharmaceutical manufacturing equipment. Pharmaceutical equipment surfaces may include a number of materials of construction including stainless steel, rolled steel, anodized aluminum, polypropylene, high-density polyethylene and many others.

The most acceptable methods of sampling from equipment surfaces are direct surface sampling and rinse sampling. In most cases a direct surface sampling is desired because the method does not rely solely on the solubility of the analyte, and the limit of detection is typically lower. [9] One advantage to rinse

sampling is the ability for larger areas to be sampled and for use in difficult to reach areas such as tubing or pumps. [6] Direct surface sampling techniques typically employ a swab that is free of contaminants, detergents and glue, which may interfere with the analysis. A swab must also be made of a material that is resistant to many common solvents such as acetone, 2-propanol, methanol and acetonitrile. During the method development process, a blank swab sample is extracted and analyzed to ensure that the extraction technique does not cause interference of the analyte.

With some IMS instruments, a Teflon substrate or wipe may be used instead of a swab which can be placed directly onto the desorption chamber, thus avoiding any extraction and dilution which lowers the detection level of the method. This type of sampling is ideal for organizations with instrumentation close to the production floor, further reducing the down time of the equipment being cleaned. This type of sampling however is still subject to similar method validation criteria and should be able to remove at least 50% of the residue from an equipment surface.

1.5 Conclusion

This thesis reports the process and steps taken to fully validate IMS instrumentation for use in a pharmaceutical laboratory. Additionally, the method validation process and results are provided for the drug product loratadine.

Finally in the concluding Chapter 5, the Author discusses recommendations for future method validation of cleaning methods.

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CHAPTER 2

SMITHS DETECTION IONSCAN-LS

2.1 Introduction

Although there are many manufacturers of IMS instrumentation, the IONSCAN-LS by Smith's detection was selected in part because of its equipment qualification package and 21 CFR Part 11 compliant software, IM-Station. The IONSCAL-LS differs from the IONSCAN used by security personnel primarily because it is equipped with an autosampler and High performance injector (HPI), in addition to its capability for direct analysis of a Teflon wipe.

2.2 Sample Introduction in the IONSCAN-LS

The IONSCAN-LS autosampler is capable of holding up to 120 vials for automatic analysis. The autosampler deposits analyte to one of two locations, (1) the Teflon substrate for direct desorption or (2) to the high performance injector (HPI) capable of heat and pressure ramping. When using direct desorption, the autosampler deposits an aliquot of analyte directly onto the Teflon substrate and the analytes are desorbed into the reaction chamber with temperatures above the melting point of the analyte. The HPI can operate in either hot or cold injection mode depending upon the complexity of the matrix and the tendency of the analyte to degrade with heat. The HPI can also be used in split mode if the analyte concentration is too high. The split mode is also

useful if components are present in the solution that must be removed before or after desorption of the analyte of the interest. Whether the analyte is desorbed from the substrate or injected by the HPI, the volatilized analyte enters the reaction chamber to undergo ionization. [1]

2.3 Ionization in the IONSCAN-LS

The IONSCAN-LS utilizes a 555 MBq ^{63}Ni radiation source, which emits low energy β-particles. Atmospheric pressure chemical ionization (APCI) is the primarily mechanism responsible for the ionization of analytes in the IONSCAN-LS, and both the positive ion mode and negative ion mode will be discussed in this chapter. Regardless of the mode selected, the β-particles in the ionization chamber first collide with nitrogen and oxygen to create the reactant ions in equations 1 and 2 to support the subsequent steps of the ionization reactions. [1]

$$N_2 + e^- \rightarrow N^+_2 + 2e \qquad \text{(Eq 1)}$$

$$O_2 + e^- \rightarrow O^-_2 \qquad \text{(Eq 2)}$$

2.3.1 Positive Ion Chemistry

Positive ion chemistry is most commonly used for small pharmaceutical molecules due to their tendency to have functional groups with high proton affinity, see Figure 2.1 for a list of functional groups according to the their proton affinity.

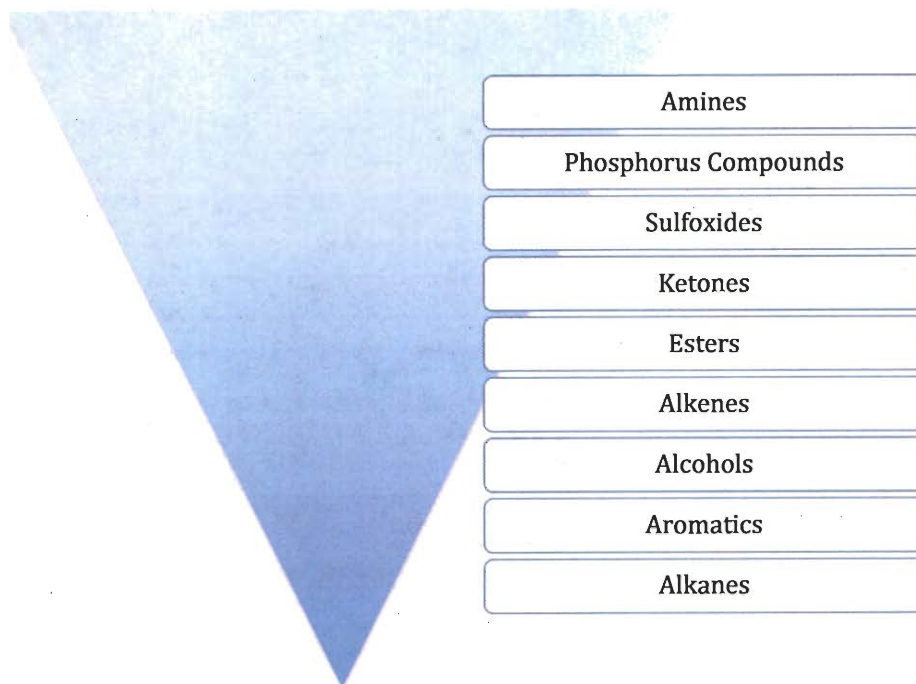

Figure 2.1. List of functional groups from high proton affinity (top) to low proton affinity (bottom) [1]

When undergoing positive ion chemistry, the product ions in Equation 1 interact with the water in the atmosphere to form water clusters according to the reaction scheme in Equations 3, 4, 5 and 6 as described by Eiceman and Karpas. [2] The IONSCAN-LS utilizes a Drierite cartridge to reduce the atmospheric moisture concentration to less than 10 ppm water in the ionization chamber. The degree of proton hydration can vary with the moisture level in the chamber, so the Drierite serves the critical purpose of maintaining a relatively constant moisture environment. [1] The hydrated proton from Equation 6 now acts as the primary reactant ion for subsequent reactions.

$$N^{+}_{2} + 2N_2 \rightarrow N^{+}_{4} + N_2 \quad \text{(Eq 3)}$$

$$N^{+}_{4} + H_2O \rightarrow 2N_2 + H_2O \quad \text{(Eq 4)}$$

$$H_2O^{+} + H_2O \rightarrow H_3O^{+} + OH \quad \text{(Eq 5)}$$

$$H_3O^{+} + H_2O + N_2 \leftrightarrow H^{+}(H_2O)_2 + N_2 \quad \text{(Eq 6)}$$

The IONSCAN-LS continually emits nicotinamide as an internal calibrant in the drift gas when operating in positive mode, which also acts as a reactant ion. The constant presence of nicotinamide in the positive mode means that it is continually undergoing proton transfer from the hydrated proton and is responsible for the peak seen in the plasmagrams of Figure 1.1 around 9.5 ms. After the desorption of the analyte(s), a shift of intensity in the 3-D plasmagram can be seen from the nicotinamide peak to a new peak representing the analyte of interest. The reaction of proton transfer to the analyte of interest is illustrated in equations 7 and 8, where N is nicotinamide and M is the analyte of interest. [1]

$$H^{+}(H_2O)_n + N \rightarrow NH^{+} + nH_2O \quad \text{(Eq 7)}$$

$$NH^{+} + M \rightarrow MH^{+} + N \quad \text{(Eq 8)}$$

Although the most abundant product will be the desired MH^+ ion, other reactions do take place in the reaction chamber and an analyst must be cognizant of the possibility of the confounding product ions in Equations 9 and 10. Cluster ion formation is demonstrated in equation 9, where Q is any other adduct including water. Dimerization is also possible and may occur when an excess of analyte is present according to equation 10. [1]

$$MH^+ + nQ \rightarrow Q_nMH^+ \qquad \text{(Eq 9)}$$

$$MH^+ + M \rightarrow M_2H^+ \qquad \text{(Eq 10)}$$

2.3.2 Negative Ion Chemistry

When the IONSCAN-LS is switched into negative ion mode, nicotinamide is no longer introduced through the drift gas, and a new reactant compound is introduced into the reaction chamber. A reactant ion other than the O_2^- generated in Equation 2 may be preferential either to reduce the number of interfering product reactions or to shift the drift time of certain analytes to aid in separation. In the case of explosives and drug substance detection, Cl^- is considered a preferable reactant ion to O_2^- because the Cl^- ion provides for greater sensitivity of compounds with aliphatic or aromatic groups. [2] Hexachloroethane was used as the Cl^- source in all negative ion mode experiments in this thesis. The introduction of hexachloroethane into the reaction

chamber replaces the product of Equation 2 with that of Equation 11. The primary chloride reactant ions generated by the IONSCAN-LS is then according to Equation 12. [1]

$$C_2Cl_6 + e^- \rightarrow Cl^- \quad \text{(Eq 11)}$$

$$nH_2O + Cl^- \rightarrow Cl^-(H_2O)_n \quad \text{(Eq 12)}$$

The product ion formation is shown in equations 13 through 16, where M is the analyte of interest. The most prevalent product ions are expected to be those generated in Equation 15. As with positive ion mode, the analyst must always be conscience of the other product ions that may form in the reaction chamber.

$$Cl^-(H_2O)_n + M \rightarrow Cl\,(H_2O)_n + M^- \quad \text{(Eq 13)}$$

$$Cl^-(H_2O)_n + M \rightarrow Cl\,(H_2O)_n + (M\text{-}H)^- \quad \text{(Eq 14)}$$

$$Cl^-(H_2O)_n + M \rightarrow M\,Cl^-(H_2O)_n \quad \text{(Eq 15)}$$

$$M\,Cl^-(H_2O)_n + M \rightarrow M_2\,(H_2O)_n^- \quad \text{(Eq 16)}$$

2.4 Separation by Ion Mobility

The product analyte ions enter the drift region via an electronic shutter gate, which allows a small portion of the population to enter the drift tube every 20-30 milliseconds. Once inside the drift tube, the ions are subject to an applied electric field, which can be switched from positive to negative polarity as necessary. While in positive polarity, positively charged ions are accelerated though the drift tube while neutral molecules and negative ions are exhausted from the instrument. A drift gas is applied in the opposite direction of ion movement through the tube, creating a buffering effect for the fast moving ions as shown in Figure 2.2. With all conditions held constant in the drift tube, ions are separated according to a characteristic mobility.

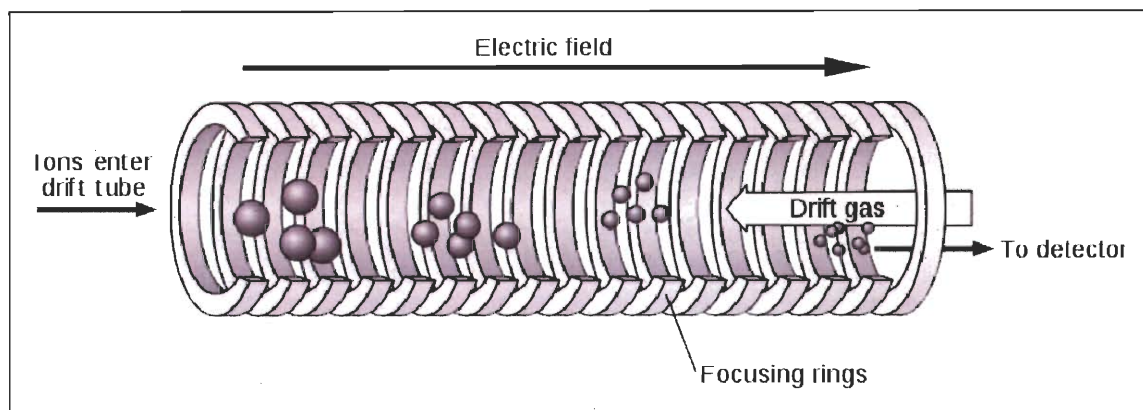

Figure 2.2 Schematic of a drift region in an ion mobility spectrometer [3]

The mobility constant (K) for an ion packet of similar mass and charge is proportional to the velocity of the ion through the drift chamber (v) and the electric field (E) according to Equation 17, where v is in cm/s and E is in cm/V.

$$K = \frac{v}{E} \tag{17}$$

The velocity of an ion packet through the drift chamber is dependent upon such conditions such as temperature and pressure. In order to account for day-to-day or instrument-to-instrument variability, the reduced ion mobility (K_0) for a given ion packet is normalized where temperature (T) has units of Kelvin and pressure (P) is expressed as Torr according to Equation 18. The use of an internal calibrant, allows the IONSCAN-LS to correct for these day-to-day differences by correcting the ion mobility of the analyte with the known reduced mobility of the calibrant.

$$K_0 = K\frac{273}{T}\frac{P}{760} \tag{18}$$

A number of models have been developed to describe the mobility of ions through a drift chamber, and the limitations of many are discussed by Eiceman and Karpas. [2] These models aim to explain the relationship between the applied electric field, drift gas density, an ion's reduced mass and collision cross-section, as well as the electrostatic interactions taking place within the drift tube. Lawrence describes the relationship between reduced mobility and the molecular weight of closely related opiates, suggesting that reduced mobility may be estimated using the appropriate model. [4] Since many of these factors are held constant within the IONSCAN-LS, the most critical factor affecting mobility is an

ion's collision cross section, used to describe the effective space an ion occupies while travelling through the drift region. Even ions of the same mass, may exhibit different mobilities because of their 3-dimensional structure and collision cross section. [5] For this reason, Ion mobility spectrometry pairs well with mass spectrometry in detection and identification of molecules with similar masses.

2.5 Data Generation

The IONSCAN-LS detector uses a simple collector plate to measure the voltage output from the impacting ions and plot the charge density of each ion packet in digital units (du) against the drift time in milliseconds (ms) on a 2-dimensional plasmagram. Each 2-D plasmagram, or segment is made up of approximately 15 co-added scans and the shutter gate mechanism allows for the generation of a new scan every 20 ms. The IONSCAN-LS software stacks the segments into a 3-D plasmagram, with drift time in the x-dimension and segment number in the z-dimension. When using direct desorption from the substrate or the HPI for a hot injection, it can be expected that the analyte will be completely exhausted in the early segments allowing for a short analysis time. When using cold HPI injection however, it is possible that analytes will desorb at different rates, allowing separation of peaks in the x and z-dimension. As part of method development, the analysis time must be set long enough to ensure complete desorption from the substrate or the HPI to reduce the likelihood of carryover into the next injection. [1]

Data generated from the plasmagrams can be reported in two ways by the IM-Station software; the maximum amplitude (MaxA) represents the peak height in du of largest detected segments, and the cumulative amplitude (CumA) is the summation of height in du from all detected segments of the injection. As a part of method development, both MaxA and CumA values should be collected and upon finalization of the validation parameters, either CumA or MaxA can be selected as the best reporting method. [1]

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CHAPTER 3

IONSCAN-LS EQUIPMENT QUALIFICATION

3.1 Introduction

This chapter will outline some of the general requirements for an equipment qualification and the steps taken to confirm the suitability of the IONSCAN-LS for use in cleaning validation. This includes the IQ, OQ and PQ testing as provided by the vendor and agreed upon by the firm, an annual calibration program, daily confirmation tests, and the generation of documents and processes for use of the instrument. All results and information for the qualification was documented in a formally written report and generated in accordance with an approved protocol.

The instrument calibration procedure outlined in this chapter was developed for initial qualification and for the annual calibration to fulfill the requirements of the equipment qualification lifecycle. The calibration procedure has two parts, negative ion mode and positive ion mode. Acetaminophen and dextromethorphan HBr were selected as calibration analytes because they are actively being controlled in the cleaning validation program and they have shown suitable responses when analyzed by the IONSCAN-LS. Some of the calibration procedures and acceptance criteria have been adopted from those provided by

the vendor while others were determined based upon repeat analysis and expected variability.

3.2 Experimental

The IQ was designed by the vendor to ensure the lab has sufficient power and space to install and operate the instrument efficiently. In addition to the vendor's requirements, a logbook was created for documenting calibrations, maintenance activities and other noteworthy information. Because the IONSCAN-LS houses a regulated radiation source ^{63}Ni, the instrument was enrolled in a program for testing and monitoring the radiation emitted by the source.

The instrument OQ and PQ are related in that they ensure the validity of the data generated by the instrument using a series of tests and measurements. The vendor's OQ evaluated the instrument's moving parts by measuring the alignment of the desorber, the autosampler syringe target positions and the autosampler slide tray positioning. The PQ includes analyzing blanks to measure the instrument noise and the internal calibrant / reactant responses to ensure they were within the recommended range. Using trinitrotoluene (TNT) and diazepam standards, the vendor established limit of detection, linearity, repeatability and other analytical parameters against agreed upon acceptance criteria.

The PQ should also demonstrate that the instrument is capable of performing the tasks for which it is intended; therefore the Author included the annual calibration procedure as a part of the PQ documentation for the IONSCAN-LS. The calibration method utilizes analytes which may also be analyzed as a part of cleaning validation testing. In this way, the PQ demonstrates that the instrument is able and ready to perform cleaning validation testing. An additional document generated during this stage of the qualification is a method for general use of the instrument and a maintenance procedure outlining what OQ testing should be repeated in the case of a part change or repair.

The CSV portion of the qualification program ensures that the data is generated, stored and processed according to the current guidance's and requirements. Parts of the CSV include safe guards to ensure no data is lost or deleted. The computer systems validation ultimately ensures the efficacy of the data generated by the instrument, but a more detailed explanation will not be discussed further in this thesis.

3.2.1 Instrument Control Parameters

The instrument conditions and control parameters utilized by the IM-Station software to control the IONSCAN-LS, autosampler, and HPI are discussed in this chapter. All injections utilize the autosampler for delivery to the HPI in positive ion mode analysis and delivery onto the Teflon substrate for

negative ion mode analysis. The calibration methods were developed using the same principles outlined in Chapter 4 with help from the vendor to ensure the parameters and criteria are a suitable replacement for the calibration program suggested by Smiths Detection.

3.2.1.1 Negative Ion Mode

In negative ion mode, the control parameters were optimized for analysis of acetaminophen drug substance. The Teflon substrate was utilized for negative ion mode, therefore the desorption temperature and analysis time was adjusted to ensure complete desorption of the analyte from the substrate. The detection algorithm includes the expected full width at half max based upon the peak shape consistently generated. The selected parameters and settings are listed in the following text:

Table 3.1 - Miscellaneous Parameters

Drift heater	111 °C
Inlet heater	205 °C
Desorber heater	200 °C
Calibrant block heater	60 °C
Drift flow	351 cc / min
Analysis Delay following start of desorption	0.025 seconds (s)
Scan period	20 milliseconds (ms)
Shutter grid width	0.200 ms
Number of co-added scans per segment	15
Analysis duration	20 s
Number of segments per analysis	67
Sampling period	50 μs
Number of sample points per scan	379

Table 3.2 - Detection Algorithm Parameters

Calibrant K_o	1.6520
Calibrant FWHM	300 µs
Calibrant amplitude threshold	75 du
Acetaminophen K_o	1.4220
Acetaminophen FWHM	303 µs
Acetaminophen amplitude threshold	40 du

Table 3.3 - Auto Sampler Parameters

Number of rinses	8
Rinse volume	5.0 µL
Number of sample rinses	3
Number of sample pumps	4
Sample fill rate	40
Sample dispense rate	100
Post fill air volume	1.0 µL
Pre-dispense delay	0 s
Post-dispense delay	6 s
Dispense to target	Substrate
Minimum substrate cool time	10 s
Rinse solvent	Acetone

3.2.1.2 Positive Ion Mode

In positive ion mode, the control parameters were optimized for analysis of dextromethorphan HBr drug substance. The HPI substrate was utilized for positive ion mode in hot injection mode. The detection algorithm includes the expected full width at half max based upon the peak shape consistently generated. The selected parameters and settings are listed in the following text:

Table 3.4 - Miscellaneous Parameters

Drift heater	237 °C
Inlet heater	290 °C
Desorber heater	285 °C
Calibrant block heater	70 °C
Drift flow	300 cc / min
Analysis Delay following start of desorption	0.025 seconds (s)
Scan period	20 milliseconds (ms)
Shutter grid width	0.200 ms
Number of co-added scans per segment	8
Analysis duration	10 s
Number of segments per analysis	63
Sampling period	50 μs
Number of sample points per scan	379

Table 3.5 - Detection Algorithm

Calibrant K_o	1.8600
Calibrant FWHM	350 μs
Calibrant amplitude threshold	500 du
Dextromethorphan HBr K_o	1.1992
Dextromethorphan HBr FWHM	413 μs
Dextromethorphan HBr amplitude threshold	30 du

Table 3.6 - Auto Sampler Parameters

Number of rinses	5
Rinse volume	5.0 μL
Number of sample rinses	0
Number of sample pumps	4
Sample fill rate	40
Sample dispense rate	100
Post fill air volume	1.0 μL
Pre-dispense delay	15 s
Post-dispense delay	-1 s
Dispense to target	HPI (Hot)
Minimum substrate cool time	0 s
Rinse solvent	Isopropanol

3.3 Parameters of Analysis and Acceptance Criteria

The parameters of analysis for the qualification and calibration method were selected to test the instrument performance for suitability of use and include functional tests for all segments of the instrument. The acceptance criteria for the calibration were adapted from vendor recommended criteria to account for the variability of the instrument and measurable range of the specific analytes. [1]

Table 3.7 - Negative Ion Mode

Parameter of Calibration	Procedure	Acceptance Criteria
Noise Check	Measure the Root Mean Squared (RMS) amplitude and peak noise for the last of three subsequent blank analyses	RMS amplitude < 3 du. Peak noise < 15 du.
Calibrant Ion Check	Measure the reduced ion mobility (K_o), full width at half max (FWHM) and amplitude of the calibrant ion in a blank analysis	K_o between 1.6470 and 1.6570 FWHM between 250 and 400 µs Max peak Amplitude > 200 du
Reactant Ion Check	Measure the amplitude of the reactant ion at the beginning and end of a blank analysis	Initial reactant amplitude > 600 du Final reactant amplitude > 200 du
Carryover Check	Measure the amount of carry over from a concentrated acetaminophen standard (0.78 µg / mL acetaminophen) in the last of three acetone injections	Average of three carryover checks have < 2% carryover
Limit of Detection Check	Measure the response of three subsequent injections of dilute acetaminophen (0.06 µg / mL)	Acetaminophen is detected in all three injections
Detector Linearity Check	Measure the response of 7 standards from 0.11 µg / mL to 0.78 µg / mL acetaminophen	Correlation Coefficient ≥ 0.98
Peak Profile Check	Measure desorption time at maximum amplitude and the total number of segments for	Desorption time at max amplitude between 0 and 2.5 seconds

	the last of three injections of to 0.56 µg / mL acetaminophen	Number of detected segments between 20 and 50
Injector Repeatability Check	Measure the amplitude of six subsequent injections of to 0.67 µg / mL acetaminophen and calculate the relative standard deviation	% RSD < 8%

Table 3.8 - Positive Ion Mode

Parameter of Calibration	Procedure	Acceptance Criteria
Noise Check	Measure the RMS amplitude and peak noise for the last of three subsequent blank analyses	RMS amplitude < 3 du Peak noise < 15 du
Calibrant Ion Check	Measure the reduced ion mobility (K_o), full width at half max (FWHM) and amplitude of the calibrant ion in a blank analysis	K_o between 1.8550 and 1.8650 FWHM between 300 and 480 µs Max peak Amplitude > 600 du
HPI Injector Leak Check	Record the actual standby carrier flow and pressure when set at 25 mL / min	Carrier Flow between 23 and 27 mL / min Injector Pressure within 2 psi of set point
Carryover Check	Measure the amount of carry over from a concentrated standard (3.3 µg / mL dextromethorphan HBr) in the last of three isopropanol injections	Average of three carryover checks have < 2% carryover
Limit of Detection Check	Measure the response of three subsequent injections of dilute dextromethorphan HBr (0.4 µg / mL)	Dextromethorphan HBr is detected in all three injections
Detector Linearity Check	Measure the response of 7 standards from 0.8 µg / mL to 3.3 µg / mL dextromethorphan HBr	Correlation Coefficient ≥ 0.98
Peak Profile Check	Measure desorption time at maximum amplitude and the total number of segments for the last of three injections of to 2.5 µg / mL dextromethorphan HBr	Desorption time at max amplitude between 0.5 and 3.0 seconds Number of detected segments between 5 and 30
Injector Repeatability Check	Measure the amplitude of six subsequent injections of to 2.9	% RSD < 5%

	µg / mL dextromethorphan HBr	

3.4 Preparation and Analysis

The concentrations were selected based upon method development to determine the range of analysis and the solvent types were selected based on analyte solubility and to achieve minimal carryover of analyte. The following concentrations of dextromethorphan HBr were prepared in HPLC grade isopropanol (Fisher Scientific, Waltham, MA): 0.4, 0.8, 1.2, 1.6, 2.0, 2.5, 2.9 and 3.3 µg / mL dextromethorphan. The following concentrations of Acetaminophen were prepared in pesticide grade acetone (Fisher Scientific): 0.06, 0.11, 0.22, 0.34, 0.45, 0.56, 0.67 and 0.78 µg / mL acetaminophen.

3.5 Results and Discussion

The results of the PQ demonstrate that the instrument is accurate and precise over the range of analysis for TNT and Diazepam. Additionally, the tests in the IQ and OQ show that the functional parts of the instrument are operating correctly. The initial calibration results demonstrate that the IONSCAN LS is accurate and precise over the range of analysis for two compounds that are likely to be analyzed in a cleaning validation program. The results of the calibration are summarized in tabular form in sections 3.5.1 and 3.5.2. Utilizing quadratic calibration curves, both acetaminophen and dextromethorphan HBr have

correlation coefficients greater than 0.99. See Figures 3.1 and 3.2 for plots of the quadratic fit.

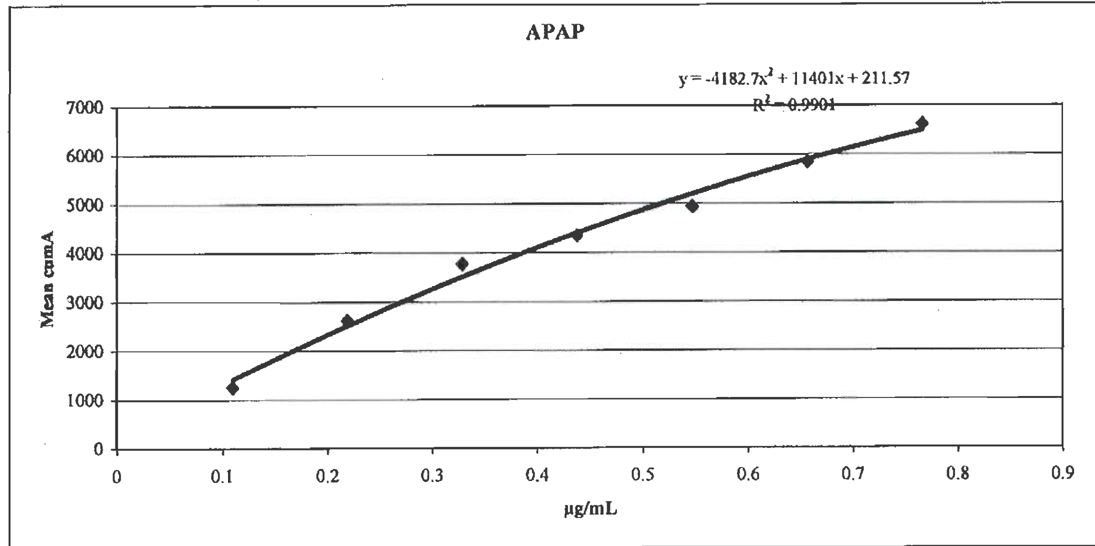

Figure 3.1 Acetaminophen calibration curve in negative ion mode

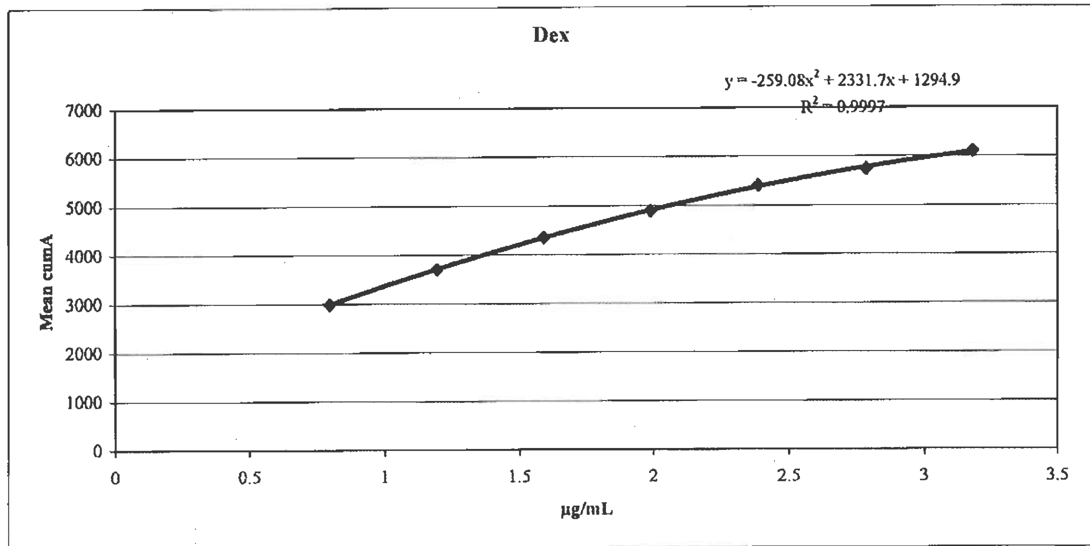

Figure 3.2 Dextromethorphan calibration curve in positive ion mode

The desorption profiles of relatively high concentrations of acetaminophen and dextromethorphan show that the temperature and analysis time is sufficient to completely desorb the analytes. See Figures 3.3 and 3.4 respectively.

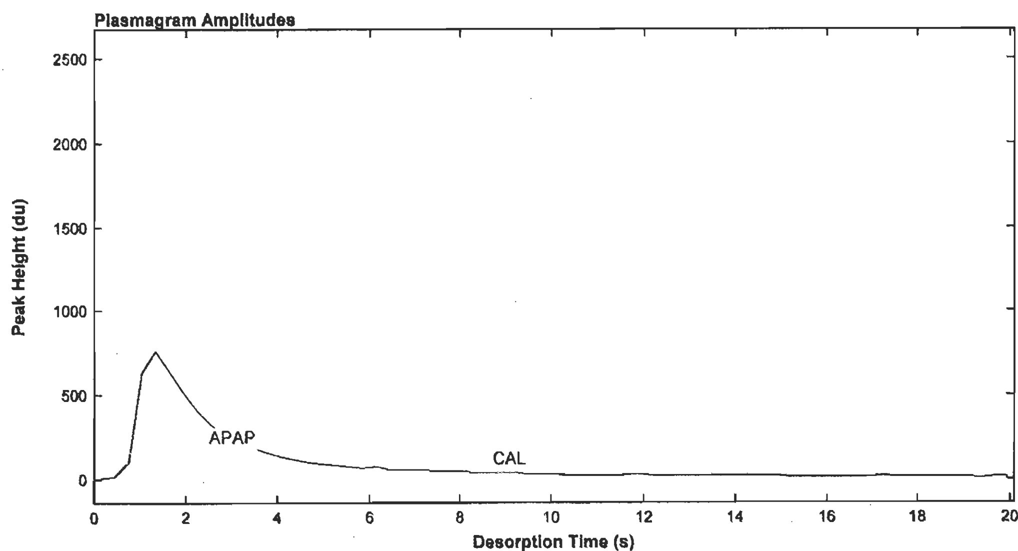

Figure 3.3 Desorption profile of acetaminophen in positive ion mode

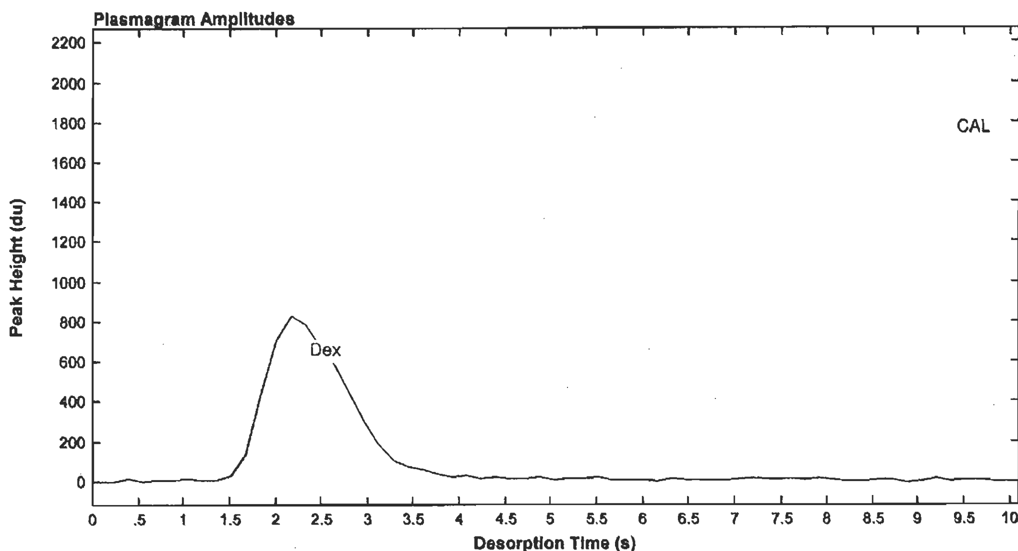

Figure 3.4 Desorption profile of dextromethorphan in positive ion mode

Table 3.9 - Negative Ion Mode Results

Parameter of Calibration	Procedure	Acceptance Criteria
Noise Check	Measure the Root Mean Squared (RMS) amplitude and peak noise for the last of three subsequent blank analyses	RMS amplitude: 0.9 du Peak noise: 5.4 du
Calibrant Ion Check	Measure the reduced ion mobility (K_o), full width at half max (FWHM) and amplitude of the calibrant ion in a blank analysis	K_o: 1.6520 FWHM: 322 µs Max peak Amplitude: 870.2 du
Reactant Ion Check	Measure the amplitude of the reactant ion at the beginning and end of a blank analysis	Initial reactant amplitude: 1889.3 du Final reactant amplitude: 1914.4 du
Carryover Check	Measure the amount of carry over from a concentrated acetaminophen standard (0.78 µg / mL acetaminophen) in the last of three acetone injections	Average of three carryover checks: 0%
Limit of Detection Check	Measure the response of three subsequent injections of dilute acetaminophen (0.06 µg / mL)	Acetaminophen was detected in all three injections
Detector Linearity Check	Measure the response of 7 standards from 0.11 µg / mL to 0.78 µg / mL acetaminophen	Correlation Coefficient: 0.99
Peak Profile Check	Measure desorption time at maximum amplitude and the total number of segments for the last of three injections of to 0.56 µg / mL acetaminophen	Desorption time at max amplitude: 1.2 seconds Number of detected segments: 25 segments
Injector Repeatability Check	Measure the amplitude of six subsequent injections of to 0.67 µg / mL acetaminophen and calculate the relative standard deviation	% RSD: 5%

Table 3.10 - Positive Ion Mode Results

Parameter of Calibration	Procedure	Acceptance Criteria
Noise Check	Measure the RMS amplitude and peak noise for the last of three subsequent blank analyses	RMS amplitude: 2.1 du Peak noise: 14.8 du
Calibrant Ion Check	Measure the reduced ion mobility (K_o), full width at half max (FWHM) and amplitude of the calibrant ion in a blank analysis	K_o: 1.8600 FWHM: 355 µs Max peak Amplitude: 1859.1 du
HPI Injector Leak Check	Record the actual standby carrier flow and pressure when set at 25 mL / min and 41 psi	Carrier Flow: 25 mL / min Injector Pressure: 41 psi
Carryover Check	Measure the amount of carry over from a concentrated standard (3.3 µg / mL dextromethorphan HBr) in the last of three isopropanol injections	Average of three carryover checks: 0%
Limit of Detection Check	Measure the response of three subsequent injections of dilute dextromethorphan HBr (0.4 µg / mL)	Dextromethorphan HBr was detected in all three injections
Detector Linearity Check	Measure the response of 7 standards from 0.8 µg / mL to 3.3 µg / mL dextromethorphan HBr	Correlation Coefficient: 1.00
Peak Profile Check	Measure desorption time at maximum amplitude and the total number of segments for the last of three injections of to 2.5 µg / mL dextromethorphan HBr	Desorption time at max amplitude: 2.1 seconds Number of detected segments: 16 segments
Injector Repeatability Check	Measure the amplitude of six subsequent injections of to 2.9 µg / mL dextromethorphan HBr	% RSD < 3%

3.6 Conclusions

The IQ / OQ / PQ protocol and initial calibration were performed successfully and a report was written and approved. At this point, the instrument would be considered suitable for generation of cGMP data like method validation and cleaning validation data. The calibration procedure is suitable for use during annual calibration.

3.7 References

1. IONSCAN-LS User Guide **2005**, Smiths Detection.

CHAPTER 4

METHOD DEVELOPMENT AND VALIDATION

4.1 Introduction

The first step in analytical method development is the identification of the proper technique for quantification of the analyte of interest. HPLC is a very common technique for analysis of small molecules used in the pharmaceutical industry because many absorb in the UV range. However, most HPLC methods require complicated mobile phase preparation or lengthy analysis times due to the complicated matrix of the drug product and detergents. Although IMS is not suitable for replacing all HPLC methods, there is a potential benefit of significant reduction in sample / solution preparation and analysis time for those that are suitable for IMS.

The main goal in transitioning from HPLC to IMS methodology for the analysis of cleaning validation samples is the reduction of per sample analysis time. After a cleaning event, a piece of equipment will remain quarantined until the results of the swab or rinse sample are received from the laboratory. For example, the laboratory may receive 18 swab samples from an equipment train where loratadine and detergent xyz has been used. Until those 18 swab samples have been tested and the equipment deemed clean by the laboratory

(i.e. levels of loratadine and detergent xyz below the determined limit), the equipment train cannot be utilized for further production. The approximate time required for the analysis of 18 loratadine swab samples by an IMS and HPLC procedure has been detailed down in Table 4.1. Based upon the estimated times in Table 4.1, the equipment turn over time may reduced by as much as 3 hours if the IMS procedure is utilized. The time savings will vary by product since HPLC analysis times vary greatly from analyte to analyte. Acetaminophen, for example may have an analysis time of less than 2 minutes and famotidine may require up to 10 minutes per sample. When selecting products for the switch from HPLC to IMS, it should be determined whether the sample analysis time warrants the cost of method development and validation by IMS. Based upon the information in Table 4.1 loratadine was identified as a suitable product for transfer from HPLC to IMS methodology.

Table 4.1 – Example analysis time comparison for HPLC vs IMS of 18 swab samples submitted for cleaning validation

Procedural Step for Analysis	Time required for 18 swab samples by HPLC	Time required for 18 swab samples by IMS
Preparation of Mobile Phase / sample diluent	Up to 1 hour	Not Required
Instrument Equilibration	Up to 30 minutes	Up to 30 minutes
Standard preparation	10 minutes	20 minutes
Standards and system suitability check analysis time	42 minutes (7 injections at 6 minutes per standard)	5 minutes (5 injections at 1 minute per standard)
Sample analysis time	108 minutes (18 injections at 6 minutes per sample)	18 minutes (18 injections at 1 minute per sample)
Total Analysis Time	**Minimum of 4 hours**	**Minimum of 1 hour**

4.2 Experimental

Once loratadine was selected as the analyte, the structure was evaluated for its ability to volatilize and ionize. As seen in Figure 4.1, loratadine includes two amine groups and a ketone, all with high proton affinity, making it a good candidate for positive ion mode analysis. Additionally, the low molecular weight of 383 g/mol means that it is likely that the desorber will volatilize the molecule. For initial test injections, several solvents were selected based on the solubility of loratadine. Because of the sensitivity of the instrument and potential for carryover, a concentration of less than 10 µg/mL was prepared in each of the following solvents: acetone, isopropanol, methanol and ethanol. The 10 µg/mL solutions were injected directly onto the Teflon substrate to be desorbed with a temperature that is greater than the melting point of loratadine and which can completely desorb the analyte (280 °C was selected as a default from the equipment qualification procedure) and an inlet temperature 5-10 °C greater than the desorber temperature to prevent condensation of the analyte in the inlet.

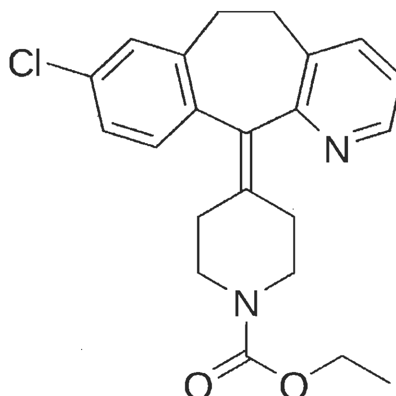

Figure 4.1 2D structure of loratadine [4]

The IONSCAN-LS User Guide recommends that the selected solvent be deposited in the middle of the Teflon substrate and allowed to evaporate prior to desorption of the analyte. These steps ensure even desorption and reduce the potential for solvent interactions in the reaction chamber. Although acetone and isopropanol gave suitable result in test injections, isopropanol was selected because it can be purchased at a lower cost than the pesticide grade acetone.

The drug product was injected early in the development process to determine if use of the HPI is necessary. The Teflon substrate is the ideal injection location because it is faster and easier to use than the HPI, but if analysis of the drug product resulted in carryover of matrix components or interference with the loratadine peak, the HPI would be necessary. In substrate test injections of the drug product, the loratadine peak showed good resolution

from the matrix components and no interference from the detergent, therefore development work with the HPI was not completed. An example of HPI method validation for a cleaning method is described in the work of Baert et.al.[2] where the HPI was optimized to achieve good peak shape for the analyte compound talarozole with a K_o value of 1.072 in the presence of other similarly structured compounds.

4.2.1 Signal Optimization

The loratadine peak was programed into the software and the peak signal was optimized from the starting conditions from the calibration procedure for Dextromethorphan HBr in order to meet the following criteria: [1]

1. The peak shape should be sharp with a single maxima in the 2D plasmagram
    a. The peak must have a width of less than 1.5 times the full width of the peak at half the max height (FWHM).
2. The peak should have a consistent drift time with a variability of less than 50 μs from the programmed mobility.
3. The analyte should be completely desorbed from the substrate within the analysis time, and will ideally have a desorption profile without excessive tailing. See Figure 4.2 for example desorption profiles.
    a. There must be no carryover from injection to injection.

b. The start and end of analyte signal must be visible in the desorption profile.

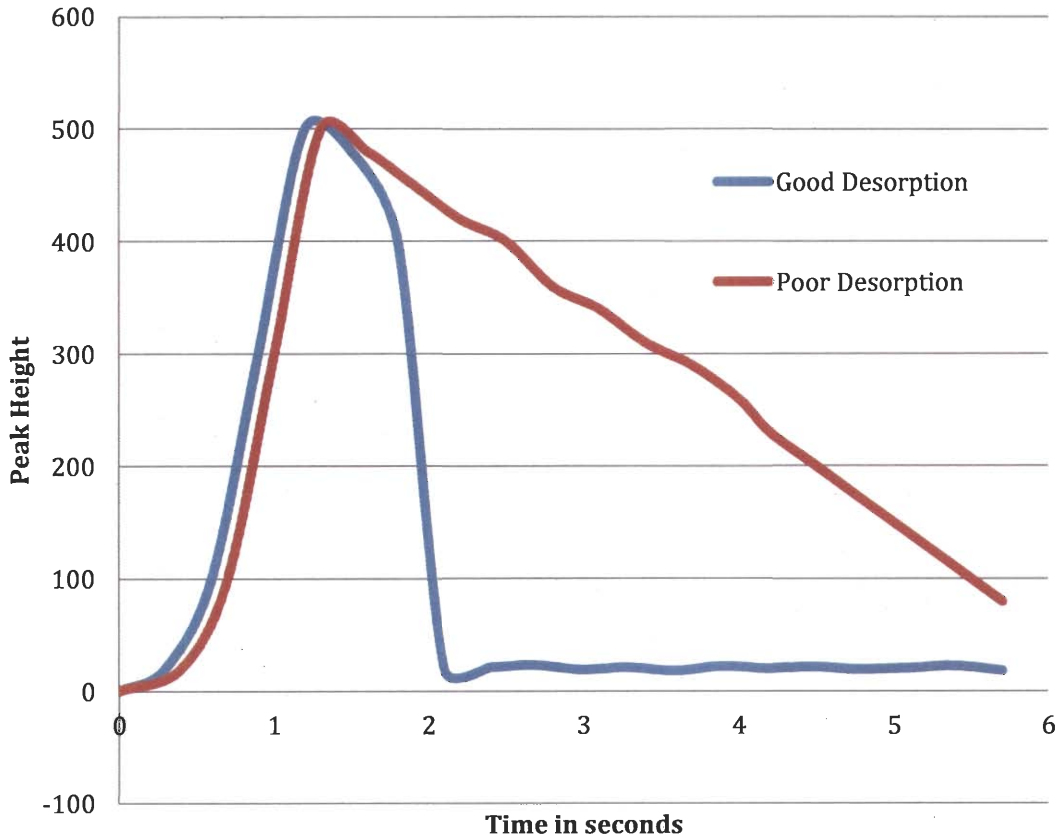

Figure 4.2 Example desorption profile showing good and poor peak shape

In positive ion mode, many of the analytes with similar molecular weights will respond well to similar instrument conditions. For this reason, the optimization of control parameters was minimal from those described in section 3.2.1.2 for the calibration procedure. The duration of analysis was increased to 20 seconds in order to prevent carryover from the drug product matrix and detergent. To allow for evaporation of the isopropanol from the substrate, a post-

dispense delay of 5 seconds was used and proved adequate for all replicates of the 1 μL injection. The number and volume of sample and rinse injections was adjusted slightly to further reduce the possibility of carryover and to improve variability between injections. The optimized control parameters for loratadine are included in section 4.2.5.

4.2.2 Establishment of Linearity and the Limit of Quantification

As discussed in previous chapters, the IMS technology tends to have a short linear range. To overcome this obstacle and have a method that covers the necessary range of analysis for loratadine, a quadratic fit was utilized for the linearity data. For this reason, at least four of the standard concentrations are injected during every analysis to provide a calibration curve for the determination of sample concentration. To ensure the suitability of the quadratic curve during each analysis, a calibration check near the middle of the range is injected after every 10 samples and must meet the acceptance criteria: the calibration check response must be not more than 10% different from the empirical result calculated by the calibration curve. See figure 4.3 for the quadratic plot of the linearity standards.

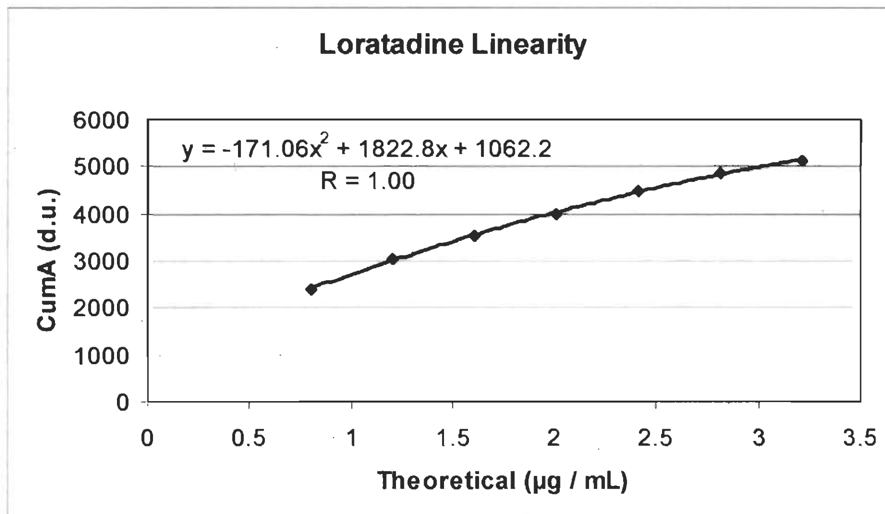

Figure 4.3 Linearity plot of loratadine using quadratic fit

The target range of analysis for all cleaning methods should cover at least 50 – 150% of the cleaning limit. The limit determined for the loratadine equipment was 2.0 µg/mL, taking into account the swab area and dilution volume. Standard concentrations between 0.8 and 3.2 µg/mL loratadine showed adequate correlation using a quadratic fit to meet the correlation coefficient acceptance criteria of not less than 0.98. The limit of quantification was determined to be 0.8 µg/mL loratadine and the 2D plasmagram in figure 4.4 shows that the peak is clearly observable from the baseline.

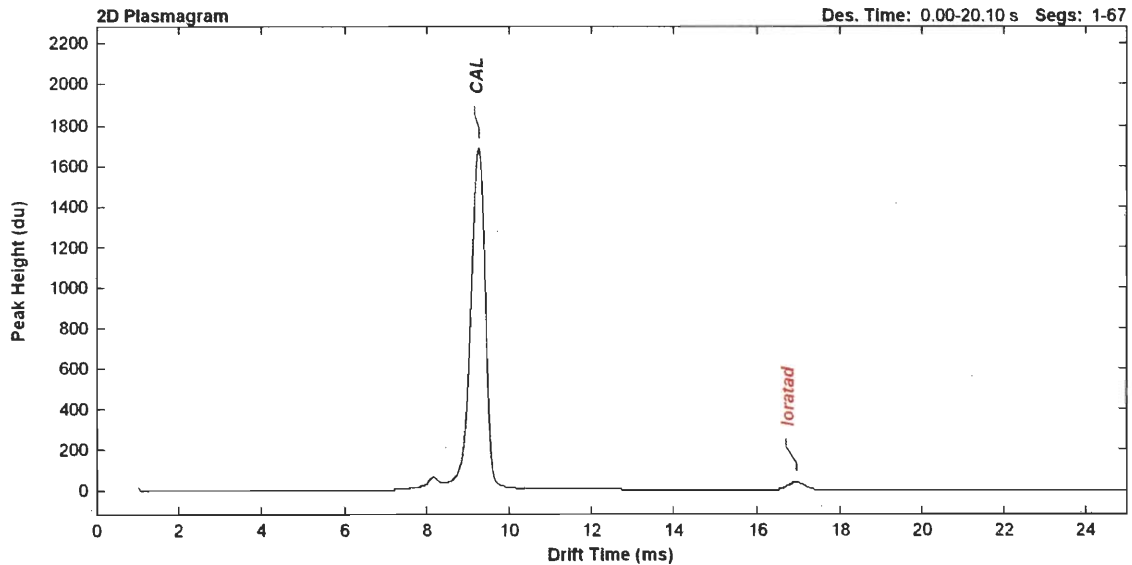

Figure 4.4 2D plasmagram of 0.8 µg/mL loratadine

4.2.3 Recovery of Analyte from a Surface

To show recovery from all equipment surface types, the product was spiked onto small representative surfaces at 100% of the cleaning limit. A swab was dipped into a solvent and using a systematic technique, the prescribed surface area was swabbed. (Surface area for swabbing was described as a part of the cleaning limit determination in Section 1.3.1 p14). The swab solvent was isopropanol because it is also used as the sample diluent and readily evaporates from the equipment surface. If recovery studies are not successful with the sample diluent, other solvents may be explored.

The technique used for swabbing the spiked analyte is critical for the successful recovery of the analyte and for this reason the technique should be

standardized between the groups in the lab and those performing the equipment swabbing in the production facility. The type of swab is also a critical parameter in recovery studies, and they must be free of all detergents and glues that can cause interference with the analyte. For all experiments in this thesis, large Absorbond Sampling Swabs (Part number TX716) from Texwipe were used.

4.2.4 Specificity in the Presence of Drug Product Excipients and Detergent

For the method to be specific for loratadine, the specificity study must show that the analyte is quantifiable in the presence of the drug product matrix and all potential detergents that will be used to clean a specific piece of equipment. Swab samples were prepared with drug product at the cleaning validation validation limit and the detergent at a level that is likely to be present. Because the limit of the detergents can be high enough to cause excessive carryover in the IMS, the visual appearance threshold is used to determine the concentration of each detergent in the spiked sample. The visual appearance threshold is the concentration of detergent that is visible on a piece of equipment in ambient lighting conditions. The rationale for using this threshold is that the equipment will fail visual inspection if present above this threshold and the swab will not be submitted to the laboratory for analysis. As seen in Figure 4.4 the method is specific for loratadine in the presence of three detergents. None of the detergents used for cleaning the pharmaceutical equipment show significant response in the 3D plasmagram when spiked at the threshold limit (Loratadine concentration at 1 μg/mL).

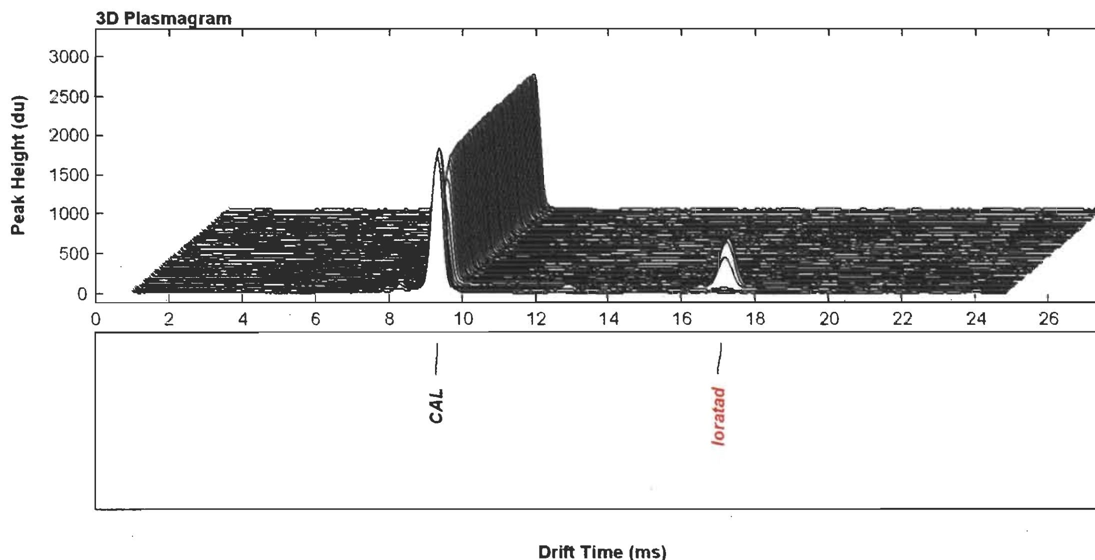

Figure 4.5 3D plasmagram of loratadine in the presence of drug product excipients and three detergents.

4.2.5 Control Parameters for Analysis of Loratadine

The following control parameters were optimized during method development and used for all method validation parameters. Based upon method development, all results were reported using Cumulative Amplitude measurements.

Table 4.2 - Miscellaneous Parameters

Drift heater	237 °C
Inlet heater	290 °C
Desorber heater	280 °C
Calibrant block heater	70 °C
Drift flow	300 cc / min
Analysis Delay following start of desorption	0.025 seconds (s)
Scan period	20 milliseconds (ms)

Shutter grid width	0.200 ms
Number of co-added scans per segment	8
Analysis duration	20 s
Number of segments per analysis	67
Sampling period	50 μs
Number of sample points per scan	479

Table 4.3 - Detection Algorithm

Calibrant K_o	1.8600
Calibrant FWHM	350 μs
Calibrant amplitude threshold	500 du
Loratadine K_o	1.1992
Loratadine FWHM	533 μs
Loratadine amplitude threshold	20 du

Table 4.4 - Auto Sampler Parameters

Number of rinses	4
Rinse volume	5.0 μL
Number of sample rinses	0
Number of sample pumps	4
Sample fill rate	30
Sample dispense rate	100
Post fill air volume	1.0 μL
Pre-dispense delay	15 s
Post-dispense delay	5 s
Dispense to target	Substrate
Minimum substrate cool time	10 s
Rinse Solvent	Isopropanol

4.3 Method Validation

Utilizing the control parameters in section 4.2.5, the method was validated according the method validation protocol in section 4.3.1.

Table 4.5 - Method Validation Protocol

Parameter	Procedure	Acceptance Criteria
Limit of Detection (LOD)	Inject loratadine at 0.4 µg / mL	The active peak is visually resolved from the baseline.
Limit of Quantitation (LOQ)	Inject loratadine six times at 0.8 µg / mL	% RSD of the six replicates is < 5.0%. The average percent of theoretical input of the six injections must be between 85 % and 115 %.
Linearity	Inject loratadine at the following concentrations: 0.8, 1.2, 1.6, 2.0, 2.4, 2.8 and 3.2 µg / mL	The correlation coefficient is > 0.98. % RSD for the six replicate injections of each standard concentration is < 5 %.
Accuracy and repeatability	Prepare triplicate swab samples at 50%, 100% and 150% of the cleaning limit and inject.	Percent recovery of each must be between 85 % and 115 %. % RSD of the nine percent recoveries must not exceed 5 %.
Intermediate Precision	Three analysts prepare three swab samples at a concentration of 2 µg / mL loratadine on three different days.	% RSD of the nine intermediate precision percent of theoretical input results is < 5 %.
Stability of Solution (Sample and Standard)	Prepare three swab samples and analyze in duplicate every 24 hours against a freshly prepared standard calibration curve. Analyze the initial standard solutions every 24 against a freshly prepared standard calibration curve.	Average percent difference between the initial and various stability time point solutions is < 2 %.
Recovery of product from a surface	Recover finished product spiked at 100% of the cleaning limit from representative equipment surfaces and repeat six times. Swab each of the six replicates using a swab dipped in isopropanol.	% Recovery of the six recovery samples is > 50 % % RSD of six recovery sample results is < 25 %.

Parameter	Procedure	Acceptance Criteria
Specificity	Prepare and inject product at 100% of the cleaning limit with each detergent spiked at the visual appearance threshold. Prepare a swab blank sample for comparison purposes.	There should be no significant interference from the detergent matrix and the sample preparation components.
System Suitability	Utilize the results from all parameters of the validation	The % difference for each check standard must be less than 10 %. Correlation Coefficient is > 0.98 for each calibration curve.

Table 4.6 - Method Validation Results

Parameter	Result
LOD	LOD = 0.4 µg / mL
LOQ	LOQ = 0.8 µg / mL % RSD_6 = 1.7 Average Empirical Input = 101 %
Linearity	Correlation Coefficient = 1.00
Accuracy and Repeatability	% of theoretical input = 96, 102, 99, 92, 94, 98, 89, 94, 90 %. % RSD_9 = 5 %
Intermediate Precision	% RSD_9 = 4 %
Stability of Solution	The standard solution did not meet acceptance criteria. The standards must be prepared fresh for use.
	The swab sample is stable for < 48 hours.
Recovery of product from a surface	% RSD_6 = 5 % % Recovery Avg_6 = 81 %
Specificity	The detergents and product matrix components did not interfere with the ability to detect and quantify loratadine swab samples. The empirical result of loratadine in the combination samples closely matched the result of the product sample.

4.4 Conclusions

A quantitative method has been developed and validated to meet ICH requirements for the following parameters: System Suitability, Limit of Detection (LOD), Limit of Quantification (LOQ), Linearity, Accuracy (Including recovery from the equipment surface), Precision, Stability of Solution and Specificity. [3] To show specificity of the method, the analyte was quantitative recovered in the presence of the drug product matrix (placebo) as well as the detergent used for cleaning the equipment. The method validation results reported in this thesis demonstrate that the IONSCAN-LS from Smiths Detection is suitable for the determination of residual loratadine in swab samples for the purpose of cleaning validation.

4.5 References

1. IONSCAN-LS User Guide. **2005**, Smiths Detection.
2. Baert, B.; Boonen, J.; Thierens, C.; Spiegeleer, B. D., Ion mobility spectrometry of talarozole, a new azole drug in cleaning quality control. *Int J. Ion Mobil. Spec.* **2011**, 14, 109-116.
3. ICH Quality Guidelines for Analytical Validation. (1996). Validation of Analytical Procedures: Methodology. Retrieved October 14, 2012 from www.ich.org
4. Wikipedia Commons. (2009). 2D Structure of Loratadine. Retrieved October 13, 2012 from www.wikipedia.com

CHAPTER 5

RECOMENDATIONS

Based upon the work completed in this thesis, the Author recommends the use of the limits-based approach of method validation IMS analysis, because the required validation parameters is reduced to limit of detection determination, calculation of recovery from the surface and swab and specificity in the presence of the placebo or detergent. Linearity may still be completed, but is not a requirement and the quadratic fit utilized for loratadine analysis would not be necessary. By injecting several limit standards during each run, the residue results can be reported as less than the limit standard with a response immediately greater than the swab residue response. This approach would provide a pharmaceutical firm with semi-quantitative swab residue results for tracking and trending purposes, and would greatly reduce the amount of method validation work required.