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Updating ‘the Book’: modern methods for modern times

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Introduction

An accurate and complete understanding of the contents of any pharmaceutical or biopharmaceutical helps to ensure both drug efficacy and patient safety. This is no revelation. In fact, this was recognized almost 200 years ago when the first pharmacopeias formed, with the very aim of specifying the minimum level of testing that should be performed throughout the development and manufacture of drug substances (DS) and drug products (DP). The method of choice to communicate the chosen test methods and criteria to the industry was the monograph. Multiple monograph and general chapters and other technical content together form the basis of each pharmacopeia’s compendia, or ‘book’. The oldest, largest, and most widely adhered to pharmacopeia is that of the United States Pharmacopeia, or USP. Their ‘book’ is the USP-National Formulary (USP-NF) and is a combination of two compendia: the USP focuses on DS, dosages, compounded substances, dietary supplements, and ingredients, whereas the NF focuses on excipients. Ensuring that the almost 5,000 monographs within the USP-NF today are correct, up-to-date, and making use of the most appropriate and current existing technology involves the work of a large team comprising staff, advisory bodies, committees, expert panels,

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and councils. In this article we will explore the area of pharmacopeial monograph modernization, including thoughts and input from USP staff and industry experts, and consider relevant and upcoming chromatographic and spectroscopic techniques.

Why ion chromatography (IC)?

Improved analytical methods and techniques are always in need to ensure understanding of critical quality attributes and adherence to safety standards for pharmaceutical and biopharmaceutical products. Liquid chromatography techniques are widely used and are gaining more traction because of technical advancements and wider applicability accounting for improved reliability, accuracy, and environmental safety concerns. Examples of liquid chromatography techniques include high performance liquid chromatography (HPLC) and IC. Figure 1 shows examples of HPLC and IC systems.

In a broader sense, both HPLC and IC are essentially liquid chromatography techniques covering a range of detector options and pressure limits, and these techniques use the same mathematical models and calculations for establishing peak area and peak symmetry. However, the two techniques are quite different from each other in terms of the type of stationary phases, mobile phases, common detectors employed, etc. HPLC primarily utilizes absorbance detectors for analyzing the sample of interest, whereas IC relies on suppressed as well as non-suppressed conductivity detections for sample analysis. Another major difference between the two is the choice of mobile phases for analyzing the analytes of interests. For example, IC systems rarely use mobile phases containing organic solvents, whereas HPLC eluents comprise organic solvents such as acetonitrile, methanol, etc. Despite the similarities with HPLC, IC systems possess clear distinctions. For example, IC uses strong acids and bases as the mobile phases and such mobile phases are detrimental for HPLC systems on a long term basis. All parts of IC systems that are exposed to these mobile phases are designed with a special polymeric inert material, polyether ether ketone (PEEK), which can handle such corrosive mobile phases. Additionally, modern IC systems can even make eluents automatically, allowing the automatic production of high purity IC eluents.[1] This is made possible through precise control of the electric current applied to the electrolysis of water to generate hydroxide and hydronium ions. Eluent generation eliminates the need to manually prepare eluents from concentrated acids and bases. The only routine reagent then needed is deionized water. Consequently, the instrument pump seals and pistons only come into contact with deionized water instead of acids and bases which can precipitate. This extends the lifetime of pump seals and pistons, and significantly reduces the overall pump maintenance requirements.

Over several decades, IC has been successfully adopted for determining ionic species such as counterions, impurities, excipients, and others in drug products and drug substances.[2] Consequently, the interest in IC applications is constantly growing. The benefits of reproducibility, sensitivity, and reliability that are critically needed for the assessment of drug products and drug substances are increasingly being realized. Most frequently the analytes analyzed by IC include active pharmaceutical ingredients (APIs) or drug substances, counterions (anions or cations) of API,

Thermo Scientific™ Dionex™ ICS-6000 System

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Figure 1. Examples of liquid chromatography systems

impurities and degradants, excipients, simple sugars (e.g., monosaccharides), sialic acids, amino acids, antibiotics, glycans, and others. Most of these analytes are detectable either via suppressed or non-suppressed conductivity.[3-5] Other analytes may require absorbance (UV/Vis), pulsed amperometric detection (PAD), mass spectrometry (MS), fluorescence, or inductively coupled plasma-MS (ICP-MS).

The USP modernization initiative

The constant developments in IC technology expanding potential applications, and increased adoption, are recognized not only by the pharma and biopharma industry but also by the key regulatory agencies around the world. There have been an increasing number of monographs (~60 monographs) that now adopt IC-based methods. In the past 10 years, the USP has added two new general chapters on IC and its applications illustrating the growing acceptance of these instrumental methods.[6] Presently, there is an on-going USP initiative to modernize individual monographs (~1200 monographs) with modern techniques and procedures. The objective of this initiative is to modernize individual monographs by:

1. Replacing any outdated technology and methodology with more current procedures for that particular monograph
2. Adding critical identification tests to the monograph (e.g., impurities)
3. Deleting non-value-added tests, as needed
4. Eliminating/minimizing the use of class 2 solvents (such as chlorinated and mercuric solvents)
5. Deleting organoleptic tests (e.g., flame tests, odor tests) and replacing with instrumental methods of analysis

This USP monograph modernization initiative can be viewed simply using a Venn diagram (Figure 2) wherein the common processes are categorized into four major sections of a monograph: identification (indication of identity mainly for drug product), assay (indication of strength), organic impurities (indication of purity), and other (tests such as pH, performance tests, etc.).[7] These major sections clearly illustrate the goals and expectations from the USP modernization initiative.

There are certain requirements or guidelines to modernize these individual monographs including:

1. The compendium should contain only current as well as new monographs and general chapters in a timely manner, and all the monographs/general chapters that are no longer needed should be omitted.
2. Monographs and general chapters should be modernized and/or revised to reflect the “state of the industry” practices and ensure the availability of all the relevant reference standards.
3. Monographs should be suitable for intended use to ensure that all components are clear and complete. Additionally, all unnecessary tests should be removed, and there should be an appropriate selection of reference standards.

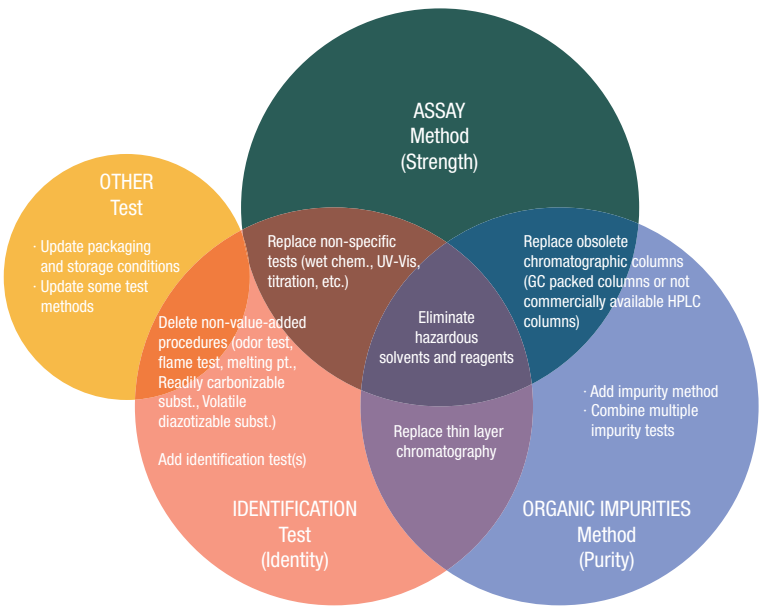

Figure 2. Monograph modernization prioritization scheme

The role of ion chromatography in monograph modernization

In light of the USP modernization initiative, we wanted to understand the pharma and biopharma segment's response towards the adoption of such compendial methods. Additionally, we were also curious to know if IC was considered as a strong tool within the modernization initiative and the status of the adoption of IC-focused compendial methods. Recently, we conducted a survey and the results indicated that 68% of respondents in the pharma and biopharma industry responded positively towards the related IC usage. The response included either they were currently using IC or are planning to use IC for their future needs (Figure 3).

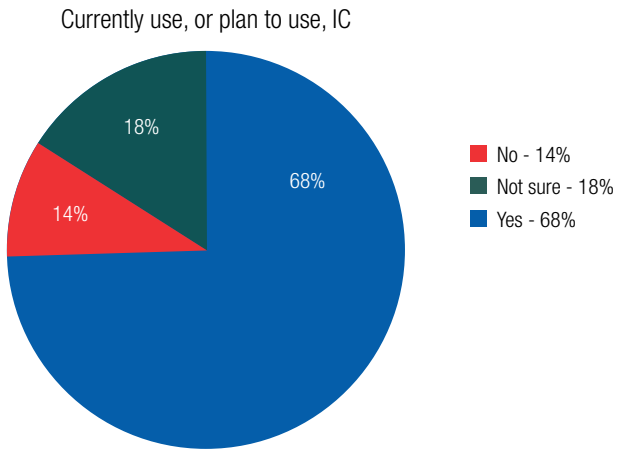

Figure 3. Response towards current use or plan to use IC

In follow-up questions on the usage of compendial monographs, more than 50% of participants responded that they were using compendial monographs either as complete or minimum standards for method developments (Figure 4).

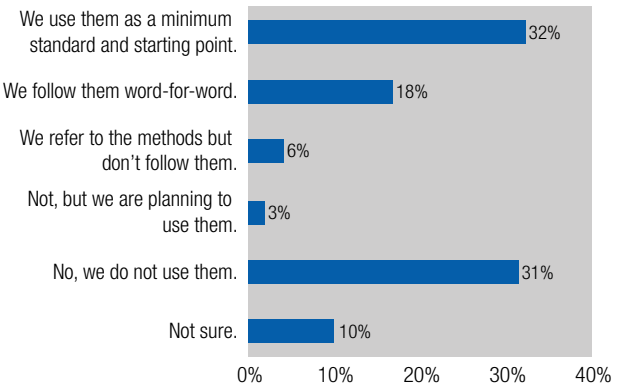

Figure 4. Response on the current usage of compendial monographs

These findings indicate the strong need to modernize the monographs where users can realize the technological advancements and related benefits that methods or procedures (such as IC) can offer to their sample analysis as well as meeting analytical needs. In the direction of the modernization initiative, IC has already been a well-established regulatory method for analyzing anions and cations for pharmaceutical and biopharmaceutical relevant drug substance and drug products. Additionally, IC offers several benefits including:

1. The ability to simultaneously detect multiple ions (cations or anions) that do not have chromophores in a single injection
2. A wide selection of stationary and mobile phases
3. Minimal to no sample preparation
4. Ease of interfacing with multiple detectors (e.g. MS)
5. Option for greater automation of IC methods compared to other chromatographic techniques
6. No handling of hazardous chemicals

All of these benefits can play a significant role in the modernization initiative and in future monograph simplification. For example, the analysis of a formulation sample containing a combination of sodium, potassium, magnesium, chloride, acetate, gluconate, and phosphate ions (Figure 5) would traditionally require separate techniques to quantify both cations and anions. Using the current monographs, flame photometry can analyze for sodium and potassium; atomic absorption can analyze for magnesium; chloride can be determined via titration with silver nitrate; acetate and gluconate ions can be determined via ion exclusion chromatography; and phosphate ions would require spectroscopic procedures (molybdate reaction). Thus, for all these ion analyses in a single formulation, a total of five techniques are recommended. However, all of the anions including chloride, acetate, gluconate, and phosphate can be determined via anionic IC in a single injection and all of the cations, namely sodium, potassium and magnesium, can be determined together in a single injection using cationic IC.

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Current Monograph Scenario	Techniques required for the complete ion analysis	Cations and Anions Present in a Formulation	Techniques required for the complete ion analysis	With the USP Modernization Initative
Flame photometry	←	Sodium (Cation)	→	Cationic IC
Flame photometry		Potassium (Cation)		Cationic IC
Atomic absorption		Magnesium (Cation)		Cationic IC
Titration with silver nitrate		Chloride (Anion)		Anionic IC
Ion exclusion chromatography		Acetate (Anion)		Anionic IC
Ion exclusion chromatography		Gluconate (Anion)		Anionic IC
Spectroscopic procedure		Phosphate (Anion)		Anionic IC
Total number of tests involved = 5				Total number of tests involved = 2

Figure 5. Example comparing current vs. modernized monograph scenario for complete ion analysis in a given formulation

Thus, the incorporation of IC offers a great potential to reduce the number of tests from five to two and to significantly simplify any such monograph. Such opportunities not only offer analysts a significant reduction in the number of tests but also introduce the reliability and reproducibility required in a modern GMP pharmaceutical laboratory, namely retention time reproducibility, time and cost savings, and an overall reduction in the laboratory inventory and related user training and system maintenance needs.

Conclusion

In summary, IC is well positioned to modernize pharmacopeial methods. It offers great benefits in the diverse applications of the modern pharmaceutical and biopharmaceutical laboratory in the development of methods for the drug products and drug substances of the future.

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