Introduction to Mass Analyzers: Quadrupole vs. Time of Flight (TOF)

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Long Abstract

Mass spectrometry is an important analytical method in the clinical laboratory. It is important to understand the different types of mass analyzers available before a decision can be made on which is best suited for the needs of the clinical laboratory.

There are some important mass analyzer characteristics that should be considered when choosing a mass analyzer. The **mass resolving power** is the measure of the ability to distinguish two peaks of slightly different *m/z* where *m/z* is the mass of a given molecule (*m*) divided by the given molecule's charge (*z*). The **mass accuracy** is the ratio of the *m/z* measurement error to the true *m/z*. Mass accuracy is usually measured in ppm. The **mass range** is the range of *m/z's* that can be accurately determined by a given analyzer. The **linear dynamic range** is the range over which ion signal is linear with analyte concentration.

These characteristics vary between different analyzers. We will focus on the two most common types of analyzers in clinical mass spectrometry, quadruple and time of flight (TOF) analyzers in a comparative way.

Quadrupole mass filter

Quadrupole mass analyzers use fluctuating electrical fields to selectively stabilize or destabilize the paths of given ions passing through a radio frequency (RF) quadrupole field made between four parallel rods within the mass analyzer. Only ions in a given range of *m/z* ratio are passed through the system at any time. A quadrupole mass analyzer acts as a selective mass filter. This single quadruple variation can selectively and accurately separate and detect one selected type of ionized molecule at a time. To increase the selectivity of the detection a tandem triple quadruple mass analyzer system is used. A "triple quad" has three consecutive quadrupole stages, the first

acting as the initial mass filter to pass a particular incoming ion through just like in the single quadruple method. In a triple quad however, the selected ions enter the second quadrupole, which is a collision chamber, wherein that ion can be broken into smaller fragment ions. The third quadrupole also acts as a mass filter, to select a particular fragment ion from the collisions occurring in the second quadruple to the detector. This type of analysis can be highly sensitive and also highly specific. Quadruple mass analyzers are an excellent choice when developing mass spectrometry methods for which a focused analysis is important. That is, one already knows what one is looking for. This comes with a price. If a small molecule of clinical importance exists in a patient sample, but its mass was not looked for, it would go undetected. For example, if a mass spectrometry method using a quadruple mass analyzer was set up and validated for the quantification of morphine but a patient sample also had a quantity of codeine, we would not see it because we were not looking for it.

Time of flight (TOF)

The time of flight (TOF) analyzer utilizes an electric field to accelerate generated ions through the same electrical potential, and then measures the time each ion takes to reach the detector. If the ions all have the same charge, their kinetic energies will be identical, and therefore each ion's velocity will depend only on its particular mass. This equates to lighter ions reaching the detector first while heavier ions taking longer.

This type of mass analysis has very high mass resolving power. What this means in a clinical laboratory is we can tell the exact molecular formula of a particular ion. Since all ions entering the mass analyzer are subsequently massed and counted, we generate an entire small molecule profile of the clinical sample. This type of analysis allows for a retrospective look at potential small molecule analytes that may have existed in the patient specimen. Going back to the original question proposed above, if the patient specimen did in fact also contain codeine, we could specifically look at whether that ion was present after the mass analysis had taken place. TOF applications therefore are an excellent choice for broad spectrum drug/small molecule screening where an analyte which may exist in the patient sample is unknown to the clinician. This high mass resolving power comes at a price of lowered sensitivity that subsequently lowers the linear dynamic range of the mass analysis. This generally means TOF analyzers tend not to be good for quantitation of small molecules.

This presentation will describe further the benefits and drawbacks of each analyzer and the balancing act that must be made when only one type of mass spec can be purchased and used in the clinical laboratory.