Clinica Chimica Acta 450 (2015) 298–303

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Impact of automation on mass spectrometry

Yan Victoria Zhang [a,*], Alan Rockwood [b,c]

[a] Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY 14642, United States
[b] Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT 84112, United States
[c] ARUP Laboratories, Salt Lake City, UT 84108, United States

ARTICLE INFO

Article history:
Received 21 June 2015
Received in revised form 13 August 2015
Accepted 30 August 2015
Available online 2 September 2015

Keywords:
Mass spectrometry
Liquid chromatography
Clinical practices
Automation
Routine clinical laboratories
High throughput

ABSTRACT

Mass spectrometry coupled to liquid chromatography (LC–MS and LC–MS/MS) is an analytical technique that has rapidly grown in popularity in clinical practice. In contrast to traditional technology, mass spectrometry is superior in many respects including resolution, specificity, multiplex capability and has the ability to measure analytes in various matrices. Despite these advantages, LC–MS/MS remains high cost, labor intensive and has limited throughput. This specialized technology requires highly trained personnel and therefore has largely been limited to large institutions, academic organizations and reference laboratories. Advances in automation will be paramount to break through this bottleneck and increase its appeal for routine use. This article reviews these challenges, shares perspectives on essential features for LC–MS/MS total automation and proposes a step-wise and incremental approach to achieve total automation through reducing human intervention, increasing throughput and eventually integrating the LC–MS/MS system into the automated clinical laboratory operations.

Contents

1. Introduction

Mass spectrometry (MS) has been proven to be a very powerful analytical platform and has been applied in several clinical fields over the last few decades. MS was first used in diagnosing inborn errors of metabolism [1–3] and then became the technology of choice for forensic and clinical toxicology [4,5]. The combination of liquid chromatography and tandem mass spectrometry (LC–MS/MS) provided even faster growth when soft ionization techniques became available [6]. LC–MS/MS is now commonly used in many clinical specialties such as endocrinology [7], immunosuppressant and therapeutic drug monitoring [8], small molecule and peptide and protein marker analysis [9–12]. Recently, MS has

* Corresponding author at: University of Rochester Medical Center, 601 Elmwood Avenue Box 608, Rochester, NY 14642, United States.
E-mail address: victoria_zhang@urmc.rochester.edu (Y.V. Zhang).

http://dx.doi.org/10.1016/j.cca.2015.08.027
0009-8981/

shown great progress in microorganism identification [13], initiating the exploration of a new clinical area.

The expansion of MS in clinical practice is mainly due to its several advantages over traditional immunoassay, ultraviolet or florescence-based technologies. MS itself is a high resolution technique with high specificity that allows positive identification of compounds of interest [14]. It is able to detect several or even hundreds of analytes simultaneously. MS is also compatible with samples in a variety of matrices including serum, plasma, urine and saliva. In addition, most MS-based assays do not rely on raising antibodies and therefore the method development time has been greatly reduced.

While MS is making its way into many clinical laboratories, it is still limited to specialty laboratories and many challenges that prevent it from being implemented routinely. The overall workflow is labor intensive and manual process-driven; it requires highly trained technical staff to perform daily operations, regular troubleshooting and assay development and validation [15–18]. Limited access to those expertise and extensive technical training requirement has hindered the further growth and implementation of this platform [19–21]. The throughput is lower than other chemistry or immunoassay analyzers in clinical laboratories, which provides less desirable productivity and turnaround time for many clinical applications [21,22].

In the near term, MS will remain a specialty instrument. We believe, however, that automation on many important external features will be essential enabling this platform to be more applicable in the routine clinical use. The ideal mass spectrometer will be accessible to those who desire its use without the requirement of becoming an expert in its technical aspects.

This article will explore the desirable automation features for MS. Recent developments in these areas and the practical interim steps that clinical laboratories can take to improve the efficiency and productivity of the platform to achieve the ultimate goal of developing MS into a total automation, high throughput, continuous and random access platform.

2. Current status of LC–MS/MS workflow

A typically LC–MS/MS workflow includes sample receiving/acquisition, sample preparation, LC–MS/MS analysis, data review and results reporting steps (Fig. 1). Though LC–MS/MS analysis itself is fairly automated, the overall workflow requires manual processes which are labor-intensive and time consuming.

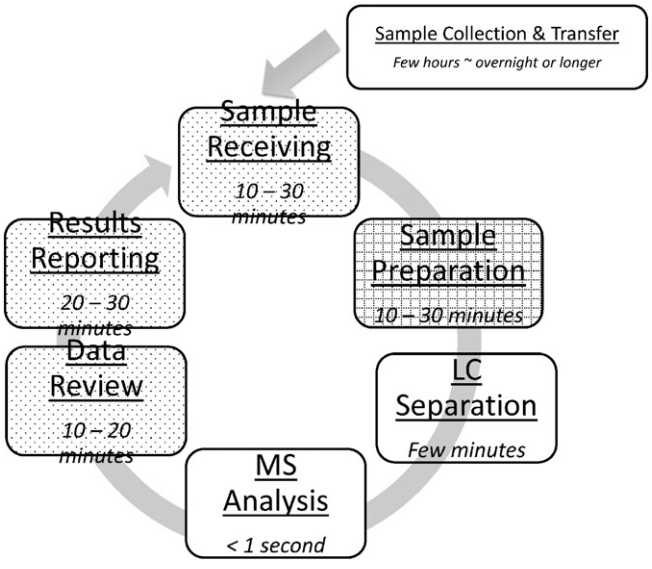

Fig. 1. Current LC–MS/MS platform workflow and typical time requirement for each step. Sample receiving includes sample identification, centrifugation, de-capping, aliquoting and re-labeling steps. Time estimate is based on one batch sample for one 96 well plate. Blank box: automated process; dotted line: semi-automated process; dots: manual process.

The sample receiving and acquisition step includes retrieving or obtaining samples from the central processing site or another part of the core laboratory, sample identification against a working or sample list, centrifugation if necessary, decapping, aliquoting and re-labeling steps. Those steps are typically processed manually. Samples are processed in batches to increase productivity. Processing samples for a typical 96-well plate, the sample receiving step can take 10 to 30 min depending on the specific processes involved.

Sample preparation involves a single or multiple steps for samples to be LC–MS/MS compatible. For instance, whole blood samples require lysis of the cells to release the analyte before further clean up. Other body fluid samples such as serum or plasma may be treated with protein precipitation to remove large molecules in the sample. Liquid–liquid extraction or solid phase extraction (SPE) can be used alone or combined with other methods such as protein precipitation to make samples compatible with mass spectrometric analysis. Those steps can be manual or semi-automated with liquid handlers or SPE handlers. The time required for one batch (96 well plate) is at the scale of 10 to 30 min. Liquid handler can reduce human involvement, but cannot significantly reduce the overall time requirement for this step.

Although being the essence of the platform, LC separation and MS analysis is not the labor-intensive step or mostly the rate-limiting step in the entire workflow. The LC separation takes a few minutes to typically less than 10 min and the MS analysis is as fast as a fraction of a second for most instruments and most applications. However, before LC–MS/MS analysis, sample information typically needs to be manually entered to the MS analytical software to create a work list.

After analysis, the results are reviewed by the staff for any adjustments or reintegration of chromatograms or other data review required before the results are transferred into the laboratory information system and then reported to electronic health record. Data review and results reporting can take another 10–20 min for one batch of samples.

Current MS practice does not necessarily fit the overall workflow in a clinical laboratory. It is labor intensive, has limited throughput, suffers from a lack of robustness, and has no random access. As a result, MS requires a high level of human capital besides its high capital expenses and is under pressure to become more automated with high throughput to reduce overall cost [23].

3. Key features for future automated LC–MS/MS workflow

Higher level of automation will reduce the barriers of entry, increase scalability and enable the LC–MS/MS platform to be accessible and implemented in routine clinical laboratories. Automated mass spectrometry platform can in the future either be a standalone floor model (Fig. 2A) or integrated into the core laboratory function as one of the automated platform along with chemistry analyzers, hematology analyzers, coagulation analyzers and others (Fig. 2B). In either case, key features include automated pre-analytical process, bar coding system, a bi-directional interface, an automated sample preparation system, and advanced software for data review process.

By being part of the core laboratory automation system, the MS platform can take advantage of the existing pre-analytical module for sample login, de-capping, sample sorting, and aliquoting. Those aliquots are then delivered (often through a conveyor belt) to the designated analyzer (Fig. 2B). A standalone MS platform must include the bar coding system and interface to get access to patient information and tests that are requested. A standalone MS platform may still need manually aliquot as do most standalone chemistry analyzers.

MS samples will need to be prepared with an automated liquid handler or similar means with the designated sample preparation method. The treated samples will then be subjected to the chromatographic separation and MS/MS analysis. Results will be processed by the software and reported directly to the LIS. Any abnormal samples or results will