A OVERVIEW OF THE METHODOLOGIES FOR THE FAST MEASUREMENT OF ONCOLOGY DRUGS USING LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY

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Abstract: *Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has revolutionized pharmaceutical analysis over the past ten years thanks to significant advancements in its sensitivity and affordability. As a result, LC-MS/MS is now widely used in pharmaceutical research and manufacturing to identify pharmaceutical compounds, such as anticancer drugs. Small molecule cancer medications are now being quantified using LC-MS/MS in a variety of biological matrices to enhance preclinical and clinical pharmacokinetic investigations in the research and development of oncology treatments. The most advanced LC-MS/MS will be discussed in this mini-review article along with how it is used to quickly quantify small molecule anticancer medicines. Additionally, efforts have been made in this study to cover a number of crucial elements in the development of quick LC-MS/MS techniques, such as matrix effect assessment, chromatographic separation, and sample preparation.*

Keywords: *LC-MS/MS, rapid; oncology drugs*

Introduction

Liquid chromatography-tandem mass spectrometry has revolutionized pharmaceutical analysis over the past ten years thanks to significant advancements in its sensitivity and affordability. As a result, LC-MS/MS is now widely used in pharmaceutical research and manufacturing to identify pharmaceutical compounds, such as anticancer drugs. Small molecule cancer medications are now being quantified using LC-MS/MS in a variety of biological matrices to enhance preclinical and clinical pharmacokinetic investigations in the research and development of oncology treatments. The most advanced LC-MS/MS will be discussed in this mini-review article along with how it is used to quickly quantify small molecule anticancer medicines. Additionally, efforts have been made in this study to cover a number of crucial elements in the development of quick LC-MS/MS techniques, such as matrix effect assessment, chromatographic separation, and sample preparation.

Method of Literature Search

The National University of Singapore's subscription to the PubMed and Web of Science databases was used to perform the literature search. The search terms "rapid" or "fast" AND "LC-MS/MS" AND "cancer" AND the title or abstract phrase "LC-MS/MS" The publications were then evaluated for their applicability to LC-MS/MS-based fast quantification of anticancer medications. There were no time restrictions in place, and all items found were current as of May 30, 2018. It has also been studied additional pertinent material that was referenced in the retrieved publications. Only articles in the English language are included in the review's purview.

Results and Discussion

The search technique presented has led to the discovery of 72 publications that are

pertinent to the quick measurement of anticancer medicines using LC-MS/MS techniques. Based on the number of analytes, each of them has been divided into two groups.

LC-MS/MS is currently a particularly potent and well-established analytical technique for achieving rapid quantitation of anticancer drugs/metabolites in a very small volume of biological samples without time-consuming chromatographic separation and difficult sample preparation prior to mass signal detection. This is due to its unprecedented selectivity and steadily rising sensitivity. The following is a further explanation of some factors to take into account while designing an LC-MS/MS for quick quantification of anticancer medications.

Sample Preparation

The first crucial step in attaining high sensitivity and specificity of quick LC-MS/MS systems is efficient sample preparation to prevent excessive signal suppression caused by the matrix effect. We want to separate the target drugs/metabolites via sample preparation from the numerous biological matrices that comprise a range of endogenous components such proteins, carbohydrates, salts, and lipids, among others. Before injecting the biological samples into the MS/MS analyzer for quantification of the target analyte(s), there are generally three sample preparation processes. These sample preparation processes may be carried out using protein precipitation (PPT), solid-phase extraction (SPE), or liquid-liquid extraction (LLE). According to the findings of all 72 studies examined here, PPT accounted for 50% of them, followed by LLE (32.4%) and SPE (17.6%).

Chromatographic Separation

Since 1952, when Archer J.P. Martin and Richard L.M. Synge shared the Nobel Prize in Chemistry for their suggested idea of partition chromatography, chromatography has unquestionably been the most significant analytical approach for the identification and quantification of a drug and its metabolites. Various chromatographic methods and columns have been created based on the idea in order to separate substances with almost any variation in the partition coefficients between the mobile and stationary phases. Liquid chromatography has been extensively employed in the pharmaceutical business since the second half of the 20th century for drug bioanalysis in preclinical investigations and clinical trials. Numerous analytical techniques for using liquid chromatography in conjunction with a UV detector to identify different substances have been reported. However, owing to the low selectivity of UV detection—a frequently utilized analytical method for pharmaceutical analysis in the last century—this analytical procedure employed for quantifying analytes in biological samples is highly laborious and time-consuming. Sample preparation for analyses using liquid chromatography with UV detection is typically very difficult for analytical scientists because endogenous substances and concurrently administered drugs must be eliminated as much as possible through sample preparation to minimize background interference in the analysis. The typical chromatographic run time is lengthy, averaging between 30 and 60 minutes. This is due to the fact that, before being detected and measured, the target drugs/metabolites must be chromatographically separated from both endogenous and exogenous interfering

substances. With the invention of the LC-MS/MS in the middle of the 20th century, pharmaceutical analysis underwent a dramatic transformation. Due to the better selectivity of MS/MS, LC-MS/MS is able to separate the analyte(s) from the matrix components even when additional endogenous compounds and spiked internal standards are present, in contrast to most LC-UV analytical techniques. To develop and validate LC-MS/MS techniques for the quick identification of anticancer drugs/metabolites, the potential issue of detrimental ion suppression or enhancement from the co-eluting peaks must still be resolved. This will be covered in more detail in the next section of the review.

The basis for attaining a quick measurement of analytes in varied biological matrices is laid by the extraordinarily high selectivity and steadily rising sensitivity of MS/MS. Tables 1 and 2 provide an overview of the run time (RT), or the entire amount of time required to complete a chromatographic separation, reported in the 72 studies. Figures 3 and 4, respectively, showed how they were distributed. According to Figure 3, the quickest run times for the detection of one analyte are 36% and 28% (both shaded) for RT 1.5 3.0 min and 3.1 4.0, respectively. These two RTs add out to a cumulative proportion of 64%. Therefore, it makes sense to describe quick quantification of one drug in biological matrices as having a run duration of less than 4 minutes. On the other hand, based on Figure 4, which shows that the two highest percentages of the quickest run times are 39% and 38% (both are shaded) for RT 4.1 5.0 min and 5.1 6.0, respectively, a run time of 6 min might be characterized as rapid quantification of 2 analytes. For the chromatographic separation of analytes, up to 92% of the articles mentioned in Table 2 reported an RT of 6 min or above. When two medicines or metabolites are included, the run times for achieving quick analysis are 4 and 6 minutes, respectively.

The frequent usage of gradient elution mode to ensure effective separation of pharmaceuticals from other drugs or their own metabolites may be used to explain the lengthier run time for the detection of 2 drugs/metabolites. Since the column must be re-equilibrated to the initial gradient settings before satisfactory retention can be attained in the following runs, gradient elution often requires a longer period in the elution of chemicals. However, using an ultra-high performance liquid chromatography (UPLC) machine helps get around the problem of the longer run time of gradient elution mode. A quicker chromatographic analysis is achieved by using sub-2 m particles in UPLC as opposed to the normal particle sizes of 3-5 m employed in traditional HPLC columns. As a consequence, the time it takes for the mobile phase to re-equilibrate is reduced. Multiple analyte determination using UPLC and gradient elution is effective. According to Table 2, this represents 36.6% of all research. Contrarily, as indicated in Table 1, gradient elution for UPLC is only used in 6.1% of all investigations for the analysis of a single analyte. For instance, Bouchet et al. published a well-validated UPLC-MS/MS approach for the rapid, simultaneous detection of nine tyrosine kinase inhibitors that required just 4 minutes of run time. Similar to this, Merienne et al. used another UPLC-MS/MS approach to accomplish high throughput routine detection of 17 tyrosine kinase inhibitors.

Additionally, UPLC separation in gradient mode results in chromatographic bands that are more regularly spaced out and enhances the peak morphologies of the later-eluting substances.

Unlike HPLC-UV approaches, LC-MS/MS analysis does not need a baseline chromatographic separation to elute the target analytes from other interfering substances during method development. This is particularly true for the identification of one medication while its metabolites display various mass transitions. The separation of a parent drug and its metabolites, particularly its phase II conjugated metabolites, is typically required when a drug and its metabolites are determined simultaneously because they may have similar fragmentation profiles to the parent drug, which could result in inaccurate measurement of the analyte.

Regarding the papers listed in Table 2, some authors merely stated the stationary phase and mobile phase conditions employed without going into detail about the chromatographic separation optimization, whereas the majority reported a multi-factorial optimization on LC column selection (C8 or C18), mobile phase components and ratios, as well as the mobile phase flow rates. Most of these optimizations were empirical, and no theoretical justification was provided. However, a study team in the US put up a theory-driven, effective plan to boost the analysis's speed and resolution using a fast gradient LC-MS/MS technique. In a gradient elution of a combination of five structurally similar compounds, they methodically investigated the impact of gradient duration, beginning and end eluent strength (% organic), and flow rate on the separation resolution and peak capacity. Additionally, it was shown via experimentation that speeding up the flow rate in a fast gradient approach enhances the system's resolution and peak capacity. The linear-solvent-strength (LSS) gradient theory may be used to provide a solid mathematical justification for the outcomes. This confirms our earlier observation that UPLC-coupled gradient elution is an effective method for the quick (6 min) simultaneous measurement of numerous analytes. Even though stable isotopically labelled (SIL) analogues of the analytes are favored in order to get superior quantitative findings, as many as 74.3 of the internal standards from 72 articles are structural counterparts. First, they are not commercially available, and second, they are too pricey.

Matrix Effects

Although MS/MS has been shown to have greater selectivity and sensitivity, the biological matrix residues often have a major impact on the signal. The interference of exogenous compounds during sample preparation (such as polymers from polypropylene tubes) or endogenous substances from the biological matrix (such as human plasma) during LC-MS/MS technique development might result in ion suppression or enhancement. "Matrix effects" refer to the modification of ionization efficiency caused by the presence of co-eluting chemicals. Although these effects cannot be seen in the chromatogram, they negatively affect the method's precision and sensitivity. Therefore, in accordance with the European Medicine Agency (EMA) and United States Food and Drug Administration (FDA) recommendations, an evaluation of matrix effects is required to guarantee that the accuracy, selectivity, and sensitivity of LC-MS/MS studies are

not jeopardized. The scientists performed a number of tests to investigate the mechanism of matrix effects and came to the conclusion that one potential cause was the outcome of rivalry between non-volatile matrix elements and analyte ions for access to the droplet surface for transfer to the gas phase. Therefore, the development and validation of a sensitive and reliable analytical technique for the identification of anticancer drugs/metabolites in biological matrices depends on the use of appropriate methodologies for the assessment of matrix effects.

There are typically two ways to evaluate matrix effects. The first technique is the post-extraction addition technique, and the second is the post-column infusion technique. In a 2003 research publication, Matuszewski et al. discussed approaches for evaluating the matrix impact in quantitative bioanalytical techniques based on LC-MS/MS. By comparing the MS/MS response (peak areas or peak heights) of an analyte at any given concentration spiked post-extraction into a biological fluid extract to the MS/MS response (A) of the same analyte present in the "neat" mobile phase, the matrix effect during the validation of analytical methods in biological fluids may be best examined. The following is an expression for the matrix effect (%) equation:

$$\mathbf{ME\ (\%) = B/A \times 100.} \qquad \mathbf{(1)}$$

A number of 100% means that there was no absolute matrix effect and that the reactions in the "neat" mobile phase and the plasma extracts were identical. Ionization augmentation is indicated by a number more than 100%, while ionization suppression is shown by a value less than 100%. The post-extraction addition method is a quantitative but static method that only offers details on matrix effects at the moment of analyte elution. The post-column infusion method for calculating matrix effects is a more dynamic approach.

Conclusions and Perspectives

Both preclinical research and clinical trials benefit greatly from the use of rapid liquid chromatography-tandem mass spectrometry. The test run durations of quick LC-MS/MS techniques for a single analyte and multiple analytes were determined to be 4 and 6 min, respectively, based on the articles published in English. Assay run durations for quick analysis of anticancer drugs/metabolites might be further decreased to speed up drug development with the advancement of UPLC systems and the availability of additional isotopically-labelled internal standards.

PPT is the most extensively utilized method when compared to SPE and LLE for the production of biological samples since it is the most straightforward sample preparation technique and can concurrently measure both hydrophilic and lipophilic substances. In light of availability and cost, structural analogs are mostly utilized as internal standards. Future work should focus on codifying the guidelines for choosing acceptable internal standards, which are now mostly decided by trial and error.

In order to assist early phase clinical studies and identify possible drug-drug interactions, LC-MS/MS has been frequently employed to examine the pharmacokinetics of cancer medications. Because of its superior sensitivity and specificity, LC-MS/MS is an effective technique for clinical therapeutic monitoring of cancer medicines.

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