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Summary of Effective Nanoparticle Liquid Chromatography Technologies for Bio analysis

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Abstract

Particularly in proteomics, nano liquid chromatography-mass spectrometry (nLC-MS) is frequently the tool of choice for the examination of very small samples. Although extremely powerful on its own, nLC-MS frequently depends on procedures for sample preparation that are done beforehand. It is possible to handle priceless samples effectively thanks to online upfront devices that are immediately connected to the nLC-MS analysis system. This paper examines upfront on-line interactions, specifically based on the use of solid phase extraction columns, for getting high sensitivity, high selectivity, and high robustness, with a focus on nLC-MS-based systems. Also covered are methods for obtaining quick sample preparation and little sample loss based on on-line reactions, such as on-line enzymatic digestion systems. The emphasis is on papers released between 2016 and mid-2020.

Keywords: Mass spectrometry; Liquid chromatography; Sample preparation; Online

Introduction

A frequently used tool in bioanalysis is liquid chromatography combined with mass spectrometry (LC-MS). A miniaturising of the chromatographic system is frequently required due to the growing need for small sample analyses, such as those involving blood drops or samples of only a few cells [1]. Additionally, a sample preparation prior to LC-MS is frequently required when analysing a complicated bio sample (which may include a low concentration of the analytes of interest). Automation of the sample preparation process can ensure more throughput and fewer human errors. These automation systems can be classified as "online" or "offline," respectively. Off-line methods require transfer procedures, such as robotic pipetting from one vial to another, because the sample preparation process and LC-MS are not directly connected in a fluidic system. Completely autonomous robotic systems could be expensive and difficult. Additionally, sample loss owing to adsorption on single-use parts is a possibility, and it can be challenging to use full samples in vial to vial transfer procedures. Alternative systems might therefore be needed, particularly for determining ultra-trace levels of a substance. One method involves the use of on-line systems, in which one or more sample preparation processes are immediately connected to the LC-MS system via a fluidic system. As the idea of online sample preparation grows, this review's emphasis is on publications that were published between 2016 and mid-2020. As a preferred instrument for the analysis of very small samples, particularly in proteomics, nano liquid chromatography-mass spectrometry (nLC-MS) (column inner diameter (ID) 100 m) is the focus of our attention. The reader is referred to [2] for more information on stationary phases and the LC columns employed; this review will not include such information. The reader may also be interested in reviews of newly released works on comparable subjects [3-5]. There are two sections to this review. The first (and primary) section discusses methods for sample preparation that rely on online interactions, particularly those that use solid phase extraction (SPE) columns. Other names for SPE columns include enrichment columns, desalting columns, and trap columns. The phrase "trap columns" is probably the most frequently used when referring to nLC systems, and it is utilized in this article. We emphasize methods for the trap columns that provide high sensitivity, high selectivity, and great resilience (of course, these traits do not exclude each other). The second section discusses methods based on online comments. For greater speed and automation, various research groups have proposed an upfront on-line enzymatic digestion prior to chromatography, particularly for proteomics. There is a brief description of other developed frontal devices and approaches.

Materials and Methods

High sensitivity: use of trap columns for large sample volume introduction

Increased sensitivity with concentration-sensitive detectors, such as electrospray ionisation (ESI)-MS [6], is possible by employing nLC columns, and the sample size need is also decreased. However, the available sample size should be employed as much as feasible for the analysis to achieve the best sensitivity for analytes in a particular sample. Despite internal sample loop volumes as low as 4 nL being possible, such a tiny injection volume is neither desirable nor easily achievable with current technologies [7-10]. Even though they are small, biological samples are frequently prepared/stored in a somewhat greater volume (L-scale). As much of the available sample as feasible is desired for analysis because the concentration of the analyte(s) in such samples is frequently quite low. By utilising on-column focusing, or bringing the analytes to the analytical separation column in a low elution strength solvent, larger injection volumes (L-size) are made achievable. Nevertheless, injecting a big volume onto a nLC column at nL/min flow rates requires a lot of time; for example, it takes more than 15 minutes to inject a 5 l sample onto a 75 m ID column at a flow rate of 300 nL/min. Additionally, desalting prior to chromatography and MS is not possible with this method. Using a trap column in a column switching system to introduce samples takes less time. Salts and low retained compounds are discharged to waste utilising a reversed

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phase (RP) column switching technology, whereas retained analytes are concentrated on the trap column. The trap column frequently has bigger dimensions than the analytical column (both in terms of particle size and column ID), which enables the injection of larger volumes at higher flow rates (L/min) than those utilised in the nLC separation step. A low-volume switching valve is then used to move the analytes to the analytical column in either the front-flush mode or the back-flush mode (Figure 1). Since it often contributes less to band broadening, the back-flush variation is frequently used as a configuration. When the analyte is eluted from the trap column to the analytical column using a nLC pump, band broadening frequently happens in front-flush mode due to the analyte having to travel more through the stationary phase in the trap column at a non-ideal mobile phase flow rate. However, some instrument setups can only support a front-flush design without significant alterations. The trap column in a commercial chip system had dimensions of 75 mm by 9 mm and 75 mm by 43 mm, and both were filled with 5 mm porous graphite carbon (PGC) particles. PGC particles have a remarkable degree of adaptability, which includes the capacity to retain very polar molecules. The setup was utilised to investigate how the therapy with a potential new medication affected the glycosylation of leukaemia cells. Other investigations employing commercial chip-systems only provided the C18 trap column's volume (40 nL–500 nL), not its size. A trap column, which can be a packed column or a pillar array column, has also been used in conjunction with pillar array columns (PACs). Recently, the use of porous monoliths for on-line sample preparation was evaluated; nevertheless, comparatively few investigations have used monolithic trap columns for nLC. Brede employed an analytical column with a length of 100 mm and a 20 m ID custom-made RP organic polymer monolith trap column, whereas Berg. To improve the injection volume in a system containing a 10 m open tubular poly (styrene-co-divinylbenzene) analytical column, Ribeiro da Silva (Figure 2) employed a poly (styrene-co-octadecene-co-divinylbenzene) porous layer open tubular multi-lumen trap column. A layer of organic polymer covered each of the several channels that made up the multi-lumen capillary. The 12 cm long multi-lumen trap column provided for faster loading (of up to 10 L) and sufficient focussing of sulfonamides on the open tubular analytical column when compared to employing a monolith or particle packed trap column.

Discussion

High robustness: sample introduction with exchangeable single use trap columns

The lack of a reliable technology for nLC column systems, such as

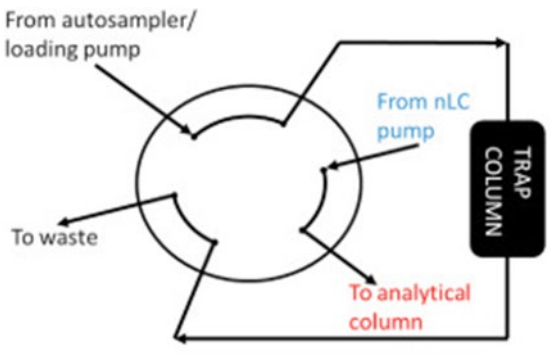

Figure 1: Front-flush and back-flush configurations of a switching valve. A loading pump and an autosampler load the sample, and B front-flush mode elution off the trap column completes the process. Samples are put into an autosampler and a loading pump in steps C and D, and then they are back-flushed off the trap column.

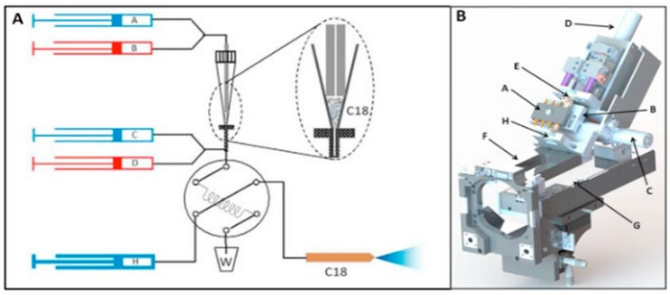

Figure 2: The Evosep system, A schematic representation of the system. The peptides are removed from the C18 Evotip by pumps A and B. Pumps C and D create the gradient, which the peptides and capillary loop collectively store (low pressure). The high-pressure (H) pump pushes the gradient and the peptides over the analytical column when the valve is opened.

clinical laboratories, has been one of the problems. In order to remedy this, Spencer et al. created an automated trapping exchanger with four custom trap columns. By applying linear compression to create zero-dead-column connections between the trapping column and the autosampler or analytical column, the robot enables autonomous exchange of trapping columns. In a high-throughput nLC-MS approach, the between-trap column retention duration was found to be sufficiently repeatable without the requirement for changing the selection windows. Cocaine was selectively extracted from biological samples using a monolithic molecular imprinted polymer (MIP) trap column (100 m 50 mm), which was connected online to a 75 m 150 mm C18 analytical column. A high concentration interfering chemical that was eluting near to the target analyte required to be removed with selectivity. The in-situ creation of the monolithic MIP made it possible to successfully extract cocaine from saliva and plasma. In other domains, a selective trap column has also been used to improve selectivity. In lipidomics, the Folch method is a well-liked off-line liquid-liquid extraction technique. showed that employing a short 100 m ID trap column serially packed with Nucleodur® hydrophilic interaction liquid chromatography (HILIC) and C4 particles in conjunction with a C18 RP analytical column, equivalent recoveries of phospholipids could be accomplished for urine samples. They also discovered that using an online approach for the extraction reduced undesired oxidation.

Concluding Remarks

For achieving sensitivity, adaptability, resolving power, robustness, speed, and automation, front-line devices are continually being developed. The emphasis on standard clinical applications and difficult samples is on the rise. These samples may contain single cells, a hot issue in proteomics right now. A degree of instrumental complexity as well as the fact that many concepts do not place a strong emphasis on method validation in the publications that describe the technology is obstacles to the applicability of upfront online devices. It can be beneficial to place more emphasis on this crucial area of analytical chemistry in order to illustrate new ideas to a larger pool of potential consumers.

Declaration of Competing Interest

The authors affirm that they have no known financial or interpersonal conflicts that would have appeared to have an impact on the research presented in this study.

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