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Journal of Pharmaceutical Analysis

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Review Paper

Advancements in the preparation of high-performance liquid chromatographic organic polymer monoliths for the separation of small-molecule drugs

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ARTICLE INFO

Article history:
Received 27 January 2017
Received in revised form
26 January 2018
Accepted 1 February 2018

Keywords:
High-performance liquid chromatography
Polymer monolith
Preparation methods
Small molecules

ABSTRACT

The various advantages of organic polymer monoliths, including relatively simple preparation processes, abundant monomer availability, and a wide application range of pH, have attracted the attention of chromatographers. Organic polymer monoliths prepared by traditional methods only have macropores and mesopores, and micropores of less than 50 nm are not commonly available. These typical monoliths are suitable for the separation of biological macromolecules such as proteins and nucleic acids, but their ability to separate small molecular compounds is poor. In recent years, researchers have successfully modified polymer monoliths to achieve uniform compact pore structures. In particular, microporous materials with pores of 50 nm or less that can provide a large enough surface area are the key to the separation of small molecules. In this review, preparation methods of polymer monoliths for high-performance liquid chromatography, including ultra-high cross-linking technology, post-surface modification, and the addition of nanomaterials, are discussed. Modified monolithic columns have been used successfully to separate small molecules with obvious improvements in column efficiency.

Contents

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http://dx.doi.org/10.1016/j.jpha.2018.02.001

Please cite this article as: X. Ding, et al., Advancements in the preparation of high-performance liquid chromatographic organic polymer monoliths for the separation of small-molecule drugs, J. Pharm. Anal. (2018), http://dx.doi.org/10.1016/j.jpha.2018.02.001

1. Introduction

As a new fourth generation of chromatographic separation media, monolithic columns with good permeability and high mass transfer speed play an increasingly important role in analytical investigations in the fields of environmental science, pharmaceutical analysis, food and chemistry [1,2]. Depending on the type of substrate, monoliths can be divided into three categories: organic polymer monoliths, inorganic monoliths (mainly silica monoliths) and hybrid monoliths [3–5]. Inorganic silica monoliths use the alkoxysilane as the main material, with columns prepared by direct sintering or the use of a sol-gel. The preparation of organic polymer monolithic columns usually involves light- or heat-induced polymerization using crosslinking agents, porogens and initiators [6,7] as raw materials. Compared with inorganic silica monoliths, the preparation process for polymeric monoliths is relatively simple, with an abundant choice of monomer species, a wide pH range (2–12) and easy surface modification [8]. Therefore, polymeric monoliths have wide range of applications, and are extensively used for the separation and enrichment of complex samples. The overall structure of micropores is an important factor that determines the separation performance of organic polymer monoliths. Therefore, a suitable pore structure is essential to obtain good resolution. Although organic polymer monoliths prepared by traditional methods have many advantages, there have few mesopores and almost no micropores, and thus their ability to separate small molecules is poor [9,10]. According to the International Union of Pure and Applied Chemistry (IUPAC), micropores have pore sizes of $\leq$ 2 nm, mesopores have pore sizes of 2–50 nm, and macropores have pore sizes of $>$ 50 nm. Thus, in recent years, studies on high-performance liquid chromatographic monoliths have concentrated on polymeric materials, which are suitable for separating small molecules. To improve the performance of organic polymer monoliths for separating small molecules, researchers have mainly examined optimization of the preparation conditions and surface modifications with metal-organic frameworks or nanomaterials [11,12].

2. Factors affecting the polymerization reaction of monolithic column

The structure of a polymer monolithic column must provide a large surface area, similar to those achieved using silica monoliths. Although macropores are necessary to achieve monolithic columns with good permeability, they have little effect on the overall surface area of a polymer monolithic column [13]. Therefore, the current literature has focused mostly on finding preparation processes that both retain the advantages of high velocity and increase the overall surface area of the column. From the viewpoint of chemical polymerization, several factors can influence the surface area and permeability of the column, including the selection of monomer and crosslinker; the proportion of monomer, crosslinker, and porogen; and the polymerization temperature and reaction time [14].

2.1. Selection of monomer and crosslinker

The selection of monomer and crosslinker not only affects the formation of the pore structure in the polymer monolith, but also determines the chemical composition of the polymer monolith, which is the main factor affecting the performance of the monolith. Note that the density and rigidity of the prepared column depend, to a large extent, on the nature and the initial concentration of the monomer [15]. Therefore, to obtain high column efficiency and strong mechanical stability, the selection of the monomer is a very important step.

Table 1
Properties of different monomer types.

Monomer type	Monomer properties	Advantages	Disadvantages
Acrylamides	Strong hydrophilicity	For gel electrophoresis	Poor stability
Styrenes	High hydrophobicity	High hardness, stable properties	Difficult modification
Acrylates	With epoxy active functional groups	Easy to modify	Unstable properties

At present, because various monomers have been used to prepare different monoliths for the separation of different small molecules, investigations into the influence of monomer type on the structure of the monolith are ongoing.

Based on the type of monomer, organic polymer-based monolithic columns can be divided into three categories: styrenes [16], acrylates [17], and acrylamides [18]. Different monomers have different advantages and disadvantages, as summarized in Table 1.

In 2014, Bai [19] prepared a monolithic column with a uniform framework, good permeability, and high column efficiency. The monolith was applied as a high-performance liquid chromatography (HPLC) stationary phase to separate alkaline, acidic and neutral small molecules. The results showed that alkaline,acidic small molecular compounds were separated quickly and efficiently on the monolithic column (Fig. 1). The good performance of the column was related to the uniform pore structure, originating from the use of trimethylolpropane triacrylate (TMPTA), which contains three terminal double bonds (Fig. 2).

Liu et al. [20] used a 1-dodecene polymeric monolith to separate benzotriazole, benzene, biphenyl, anthracene, and other small molecules successfully. The combination of 1-dodecene, which is highly hydrophobic, with an acrylate results in a monolith with the desired pore structure. They also optimized the preparation conditions and found that the amount of crosslinking agent directly affected the column pressure. Excessive amounts of crosslinking agent caused a high column pressure, which decreased the permeability of the column. On the contrary, when the amount of crosslinking agent is too low, the monolith structure will be loose. They also found that too much porogen led to low mechanical strength, as well as a loose monolith structure.

It has been reported that higher crosslinker concentrations can provide higher mechanical stability and a higher surface area [21]. Liu et al. [22] has suggested that significant advantages are realized when a single-monomer/crosslinker is used, including straightforward optimization of the polymerization solution, improved column-to-column reproducibility, better mechanical stability, and higher surface area owing to a highly crosslinked network effect of monomer content on the overall column efficiency, porosity, and surface area was investigated. It was found that the surface area, porosity, and column efficiency increased when the

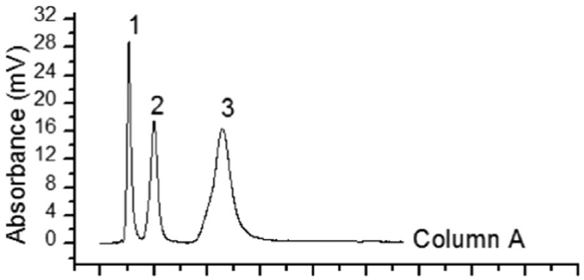

Fig. 1. Chromatogram showing the separation of small molecules on the poly(TMPTA-co-EDMA) column. Conditions: mobile phase: methanol:water (75:25, v/v); flow rate: 1.0 m L/min. Analytes: (1) 1*H*-benzotriazole, (2)*p*-xylene, (3) biphenyl [19].

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