



Design of monoliths through their mechanical properties



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ABSTRACT

Chromatographic monoliths have several interesting properties making them attractive supports for analytics but also for purification, especially of large biomolecules and bioassemblies. Although many of monolith features were thoroughly investigated, there is no data available to predict how monolith mechanical properties affect its chromatographic performance. In this work, we investigated the effect of porosity, pore size and chemical modification on methacrylate monolith compression modulus. While a linear correlation between pore size and compression modulus was found, the effect of porosity was highly exponential. Through these correlations it was concluded that chemical modification affects monolith porosity without changing the monolith skeleton integrity. Mathematical model to describe the change of monolith permeability as a function of monolith compression modulus was derived and successfully validated for monoliths of different geometries and pore sizes. It enables the prediction of pressure drop increase due to monolith compressibility for any monolith structural characteristics, such as geometry, porosity, pore size or mobile phase properties like viscosity or flow rate, based solely on the data of compression modulus and structural data of non-compressed monolith. Furthermore, it enables simple determination of monolith pore size at which monolith compressibility is the smallest and the most robust performance is expected. Data of monolith compression modulus in combination with developed mathematical model can therefore be used for the prediction of monolith permeability during its implementation but also to accelerate the design of novel chromatographic monoliths with desired hydrodynamic properties for particular application.

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1. Introduction

Chromatographic monoliths consist of a single piece of highly porous material. They can exhibit very different microscopic structure and chemical composition [1–4]. Common feature is however their void structure consisting of open pores forming a network of channels through which the mobile phase flows. It provides several unique features such as very high porosity, high binding capacity, low dispersion for very large molecules, low buffer consumption and flow unaffected chromatographic properties like resolution and dynamic binding capacity [5]. Monoliths were found to be especially advantageous for the analysis and purification of biologic macromolecules like proteins, plasmid DNA, RNA, virus like particles and viruses [6,7]. A plethora of applications is to some extent a consequence of a straightforward optimization of monolith structure in terms of pore size and porosity. For methacrylate

monoliths it is possible to prepare monoliths in a broad range of porosity and pore size simply by changing porogen composition or porogen to monomer ratio [8,9] and polymerization temperature [10–12], preserving in this way a skeleton chemical composition.

Since monoliths consist of a single piece of material, problems related to the column packing are absent while dispersion and permeability are determined by a monolith microstructure topology, pore size distribution and porosity [13–21]. While most of the materials chromatographic monoliths are made of are not totally rigid, the applied pressure should cause changes in their structure and consequently in performance. Because of that one can speculate that measuring monolith mechanical properties, like compression modulus, would be beneficial, since it would allow prediction of monolith structural deformation under applied stress and consequently changes in permeability during its usage. Based on this information, pressure drop on the monoliths of different microstructure, volume and geometry could be predicted, thus allowing accurate process design. Despite this, there are very few reports in literature connecting mechanical properties of chromatographic monoliths, or even chromatographic resins in general, with their structural features. In early 1980s Horak and co-workers [22] investigated mechanical properties of methacrylate beads. It was concluded that the modulus of penetration (similar

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to compression modulus) is inversely proportional to the bead average pore size and porosity. A decade later, Hradil with co-workers [23] reported on mechanical properties of methacrylate monoliths. They measured tensile modulus of monolithic sheets and discovered similar correlations as Horak et al. A decrease of tensile modulus with increasing porosity was attributed to lower cross section of samples due to the pores present. Muller and co-workers performed measurements of mechanical properties on authentic and diethylaminoethyl modified methacrylate beads [24], demonstrating that original beads exhibited higher penetration modulus giving similar information as compression modulus. Very recently Laher and coworkers investigated microscopic scale mechanical properties of polymeric chromatographic monoliths [25]. Applying atomic force microscopy they were able to investigate how stiffness decreases from inner regions of the globules toward outside as a consequence of different degree of crosslinking. This finding was confirmed also with methacrylate-based monolithic polymer bearing the ion-exchange functionality. Therefore, it would be interesting to investigate how heterogeneity found in the structure reflects on microscopic scale mechanical properties of chromatographic monoliths.

The aim of this work is to investigate how do methacrylate chromatographic monolith porosity, pore size distribution and chemical modification affect monolith volumetric compression modulus. These data were correlated to the monolith permeability under different chromatographic conditions and used for an estimation of pressure drop on preparative monolithic columns. Derived mathematical correlations enabled prediction of monolith compression with varying microscopic structure under different experimental conditions.

2. Material and methods

2.1. Material

Glycidyl methacrylate 97% (GMA), ethylene dimethacrylate (EDMA), glycerol, sodium citrate and diethylamine (DEA), were from Sigma–Aldrich (St. Louis, MO, USA), dodecanol (DoOH) and cyclohexanol (CyOH) were from Fluka (Buchs, Switzerland) and ethanol was from Kefto (Ljubljana, Slovenia).

All solutions were prepared with deionized water purified by Watek IWA 80 roi (Ledec nad Sázavon, Czech Republic) water purification system and analytically grade reagents. Buffer solutions were filtered through a 0.45 μm filter made of Sartolon polyamide (Sartorius, Goettingen, Germany).

Custom made CIM 8 ml tube monolithic columns and CIM 80 ml tube monolithic columns of different pore size used for permeability measurements (Section 2.2.5) were kindly provided by BIA Separations (Ljubljana, Slovenia). CIM 80 ml tube monolithic columns had outer diameter of 35 mm, inner diameter 3 mm and height of 85 mm, while CIM 8 ml tube monolithic columns had outer diameter of 15 mm, inner diameter 6.3 mm and height of 55 mm.

2.2. Methods

2.2.1. Preparation of monoliths having different porosity and pore size

Methacrylate monoliths were prepared from the monomer mixture consisting of GMA, EDMA and porogens CyOH and DoOH. Monoliths of different porosity were prepared by varying porogen content between 20% and 70% while monoliths with different pore size were prepared by fixing porogen content at 60% and varying temperature between 58 and 70°C according to Merhar and co-workers [8]. Once polymerization was completed monoliths were

washed extensively with ethanol to remove porogens and cut as described in Section 2.2.4.

2.2.2. Modification of monolith with diethylamine

The methacrylate monoliths previously washed with ethanol were immersed for 48 h in 50% solution of DEA and ethanol. The temperature was kept constant at 40°C. After completing the chemical modification, samples were washed with deionized water, which was changed once a day for one week.

2.2.3. Determination of monolith average pore size and porosity

Pore size distribution was measured by a Pascal 440 (Thermo-Quest Italia, Rodano, Italy) mercury porosimeter within a range of 15–10 000 nm. Approximately 0.1 g of dried monolith sample was measured.

Porosity was determined from the measurements of mass difference. Monolith samples were thoroughly washed with water, weighed and their dimensions were measured. After that, they were thoroughly washed with 1.2 M solution of sodium citrate, pH 8.0 having density of 1.260 g/ml and finally weighed and measured again. The volume of the monolith was found to be constant. Porosity was calculated according to Eq. (1):

$$\varphi = \frac{V_{\text{pore}}}{V_n} = \frac{\Delta m / \Delta \rho}{V_n} = \frac{(m_{\text{salt}} - m_{\text{water}})}{(\rho_{\text{salt}} - \rho_{\text{water}}) \cdot V_n} \quad (1)$$

where Δm is mass difference, $\Delta \rho$ is density difference, m_{salt} is a mass of monolith having pores filled with sodium citrate solution, m_{water} is a mass of monolith having pores filled with water, ρ_{salt} is sodium citrate solution density, ρ_{water} is water density, V_{pore} is monolith pore volume, V_n is total monolith volume.

2.2.4. Determination of volumetric compression modulus

Compression properties of monoliths were measured at a constant room temperature using Instron 3345 device (Norwood, USA). Cylindrical shaped monoliths had a diameter and height of 12 mm and their dimension were precisely measured to determine the monolith initial volume. To determine volumetric compression modulus monoliths were compressed at a constant velocity of 1.0 mm/min. At the axial strain of around 15% their new dimensions and the applied pressure were measured. The volumetric compression modulus is defined according to Eq. (2), as a difference between the initial and the compressed volume of the sample for a certain pressure difference [26]:

$$K = V_n \frac{\Delta P}{\Delta V} \quad (2)$$

where K is volumetric compression modulus and $\Delta P / \Delta V$ is volume change under the applied pressure and V_n is volume of a non-compressed monolith.

2.2.5. Determination of monolith permeability

Experiments were carried out with an HPLC system (Knauer, Berlin, Germany) built of two K-500 pumps and an UV-VIS K-2500 detector. The mobile phase was pumped through the monolithic column at a linearly increasing flow rate and differential pressure on the monolith column was recorded by differential manometer (Mid-West Instruments, Sterling Heights, MI, USA).

According to the Darcy law the relation between pressure drop and the monolith is defined as:

$$\frac{d(\Delta P)}{dL} = \frac{v\eta}{B} \quad (3)$$

where ΔP is pressure drop on the monolith, η is viscosity, v is mobile phase linear velocity, L is monolith length and B is monolith permeability.

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