Chapter

Monoliths Media: Stationary Phases and Nanoparticles

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Abstract

Monoliths media are gaining interest as excellent substitutes to conventional particle-packed columns. Monolithic columns show higher permeability and lower flow resistance than conventional liquid chromatography columns, providing high-throughput performance, resolution and separation in short run times. Monolithic columns with smaller inner diameter and specific selectivity to peptides or enantiomers have been played important role in hyphenated system. Monolithic stationary phases possess great efficiency, resolution, selectivity and sensitivity in the separation of complex biological samples, such as the complex mixtures of peptides for proteome analysis. The separation of complicated biological samples using columns is being revolutionized by new technologies for creating monolithic stationary phases. These techniques using porous monoliths offer several advantages, including miniaturization and on-line coupling with analytical instruments. Moreover, monoliths are the best support media for imprinting template-specific sites, resulting in the so-called molecularly-imprinted monoliths, which have an extremely high selectivity. In this chapter, the origin of the concept, the differences between their characteristics and those of traditional packings, their advantages and drawbacks, theory of separations, the methods for the monoliths preparation of different forms, nanoparticle monoliths and metal-organic framework are discussed. Two application areas of monolithic metal-organic framework and nanoparticle monoliths are provided.

Keywords: monoliths media, advantages of monoliths, hybrid monoliths, nanoparticle monoliths, monolithic metal–organic framework

1. Introduction

Liquid chromatography is a separation technique that uses a fluid phase through a porous bed. In order for the sample components to quickly equilibrate between the fluid and solid phases and spend a sizable portion of their entire residence durations in both, the fluid and bed materials must be selected carefully. The core of chromatography is a porous bed because the percolation of the mobile through the stationary phase is a crucial aspect of the chromatographic procedure. Solute molecule exchanges between the mobile phase stream and the stationary phase should occur quickly and often. Fast mass transfer kinetics, diffusion, close spacing within the bed, and a sizable surface area of contact between the stationary and mobile phases are all desirable

characteristics for the column bed. High column efficiency is required if adsorption serves as the retention mechanism [1].

However, the bed's hydraulic resistance to the stream of the mobile phase should be kept at a reasonable level. The maximum length of the column that can be used with a specific pumping system will be impacted by a high hydraulic resistance. Fine particles should enhance separations in the early stages [2]. Unfortunately, there is not much that can be done to improve a packed bed's permeability. This permeability is determined by the packing density of the particles, which is best determined by the external porosity of the bed, and by their average size. With rising porosity, the permeability rises quickly in almost perfect proportion to its fifth power [3].

Now, imagine a porous bed that is the converse of a packed column bed. All the parts of the packed column bed result in a slower mobile phase flow velocity. The trend, so far, has been to prepare columns that have a high volume of through pores, hence a low hydraulic resistance leading to increase velocity. This makes it possible to prepare columns that have a high efficiency, because they can be long and yet can be operated with an acceptable head pressure, and are relatively fast, because they are operated at high flow velocity. In actual practice, a decrease in the column inlet pressure is far less attractive than a decrease in the elution time of the last eluted sample component or an increase in the column efficiency [4].

The popular English dictionary defines the monolith as a geological or technological feature such as a mountain or possibly a boulder, consisting of a single massive stone or rock [5]. Erosion usually exposes these formations, which are most often made of very hard and solid metamorphic rock. However, large pieces of rocks excavated from quarries, such as obelisks, are called artificial monoliths (**Figure 1**).

Figure 1.
Photograph of the porous monolith erected at the entrance of the Summer Palace Park, Beijing, China (Reprinted from Ref. [6]).

2. Monoliths

2.1 Definition

Monolith, in its broadest sense, refers to a column made out of a single substantial stone block. The name comes from the Greek words monos, which means "single," and lithos, which means "stone." It resembles a continuous single rod of porous material in chromatographic terms [7].

2.2 Advantages of monoliths

Due to the homogeneous distribution of macropores and mesopores across the network, which enables the separation of numerous analytes, monoliths are distinguished by a high permeability. While mesopores offer a significant surface area for separation and the permeability for solvent flow, macropores allow 100% of the mobile phase to pass through the column. In addition, packing like in a particle-packed column is not essential because the monolith can be created in place using poly-mediation. Due to the issue of the monolith shrinking in capillaries with greater i. d., this polymerization technique is only permitted in capillaries (typically less than 200 m in internal diameter i.d.). The distinctive characteristics of monolith, which have drawn the attention of numerous researchers and have been demonstrated to be an effective instrument in column technology [8], are high porosity and low back pressure. Pioneer efforts by Hjerten *et al.* [9] and Svec and Frechet [10] on developing polymer monolith and later by Minakuchi *et al.* [11] and Ishizuka *et al*. [12] developed silicon monolith have revolutionized the field of column technology.

Initially restricted to academic research, monolith is now acknowledged as a legitimate member of stationary phases. Other than permeability, monolithic columns are similar to conventional columns in terms of phase ratio and enantioselectivity [13]. The preparation and modification of monolithic columns to the correct porosity and pore diameter to meet various purposes are also simpler [14]. Through co-polymerization, specific selectors, such as chiral selectors, can be integrated into the monoliths and preserved there. In comparison to a particle column, the elution time can be cut by a factor of 5 to 10 [15]. All of these processes do not require any specialized knowledge, which makes interlaboratory investigations simple and comparable [13].

2.3 General characteristics of monoliths

Monolithic columns are made of a single piece of porous material that is hermetically sealed against the tube wall. As a result, the mobile phase stream is unable to bypass any appreciable portion of the bed and must instead percolate through it. A bimodal pore size distribution of the porous material is frequently used to describe it. This distribution's huge size mode corresponds to through pores or macropores. These pores are connecting into the channels that carry the majority, if not nearly all, of the mobile phase. In order to maintain the correct flow rate, the mobile phase must be pushed into the column at a head pressure determined by the average size of these channels, which also determines the column's permeability. Concerning the connection of the channels generated by these *via* pores, their constriction, and column permeability. The mesopore structure of the proton's polarons and all of these variables work together to determine the kinetics of mass transfer and column efficiency.

Practically no small size mode can be seen in the pore size distribution of the majority of polymeric materials [16–18].

Mesopores are represented by the small size mode of the pore size distribution of inorganic monoliths, such as silica. Between the channels that the through pores have created, there are lumps of porous material that contain these mesopores. For lack of a better term, these lumps are referred to as "porons." The lumps of porous material between the larger holes of particles with a bimodal internal porosity were first given this term [6]. The total porosity of the bed and its mechanical stability (the bed must withstand the pressure drop applied to cause the mobile phase to percolate through it) as well as the internal porosity and the precise surface area of contact between the two phases of the chromatographic system are correlated with one another. The latter regulates the solutes' retention factors and phase ratio. Therefore, the internal porosity of the column must strike a balance between the demands for small porons, a significant portion of the column's volume occupied by these porons, and a relatively large average size of the through pores [6]. More than two forms of pore size distribution may exist in monolithic materials. Because of their high adsorption energy and delayed mass transfer kinetics, micropores in any adsorbent have consistently had a negative impact on chromatographic performance. In polymer matrices and with silica-based adsorbents, microspores are uncommon [19], although they are prevalent in carbon-based adsorbents [20]. Another option is the mode associated with pores that have an average size that falls somewhere between the diameters of mesopores and through pores. This would be related to a certain class of monoliths with geometrical properties resembling those of the particles with bimodal porosity that were promoted for perfusion chromatography [21].

2.3.1 The through pores

Numerous research teams, including those of Nakanishi [22–24], Tanaka *et al*. [25], and later Cabrera [26, 27] and Leinweber [28], have explored the porous architectures of silica monoliths in depth. Phase separation is a byproduct of the acid-catalyzed hydrolysis and gelation of an alkoxysilane solution (such as tetramethoxysilane) in the presence of sodium polystyrene sulfonate, as demonstrated by Nakanishi and Soga [29]. Then, these researchers were able to create a solid mass of porous silica with a bimodal porosity by switching polyacrylic acid (PAA) with polystyrene sulfonate [22, 23]. Later, HPAA was effectively used to replace polyethylene oxide (PEO) [30]. Chromolith silica rod, a commercial item from Merck KGaA (Darmstadt, Germany), is depicted in **Figure 2** as having a porous structure [27]. By varying the solvent composition, the concentration of porogen, and the temperature, it is possible to modify the gel shape. The average size of the through holes grows with increasing porogen concentration (for example, HPAA). At low porogen concentrations, the big pores are not linked, whereas at high concentrations, distinct particles form [22]. Mercury intrusion porosimetry was used to estimate the average size of the through pores, which was found to be close to 1.7 m, and the external porosity or porosity of the through pores, which was calculated at 0.65 m [31].

2.3.2 The porons

The through pore network and the entire column of porons are filled with a continuous porous solid called porons. The monolith made using the method described by Nakanishi *et al*. [22, 24, 29] and bound to octadecyl dimethyl silyl groups

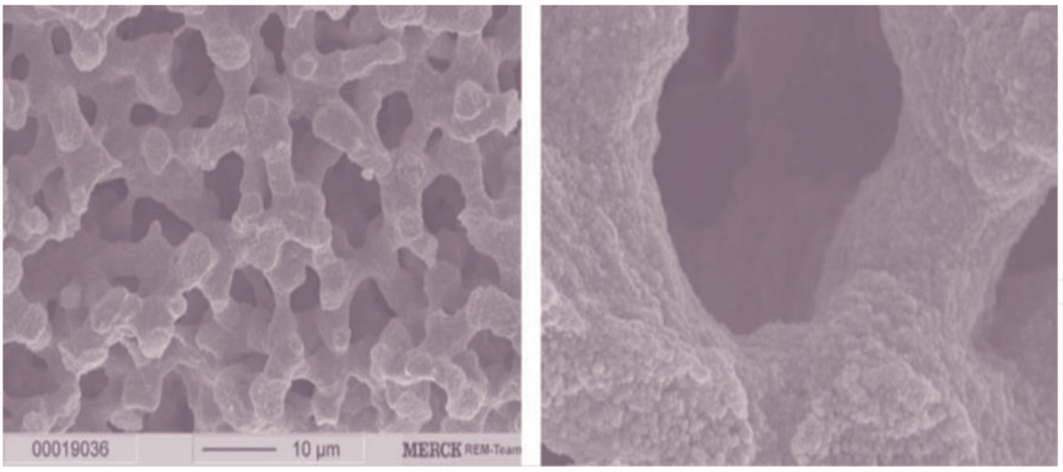

Figure 2.
Image of the porous structure of a typical monolithic silica column (left) and enlarged view of the entrance to a macropore or through pore (right) (Reprinted from Ref. [27]).

was shown by Nakanishi *et al*. [24] to be a porous solid with bimodal porosity. It was discovered that the porons had an average size of roughly 1 m. For neat silica, the mesopores or internal porosity are about 0.20 m [32].

3. Theory of separation

The most important characteristics of any chromatographic column are its permeability, which is determined by the average size of its through pores and external porosity, its efficiency, which is determined by the average sizes of its through pores and porons, the structure of the mesopore network, and the mobile phase velocity, and its capacity for retention (that is related to the specific surface area of the adsorbent, to the internal porosity and the pore size distribution). The monolithic beds prepared for liquid chromatography and the relationships between the characteristics of monolith beds and the permeability and efficiency of the prepared columns. Finally, the characterization of the monolithic columns and the conventional packed columns is used to compare these columns [33].

4. Separation mechanism

Hydrophilic interaction is hypothesized to be the main mechanism of hydrophilic interaction liquid chromatography (HILIC) separation for neutral polar molecules. The impact of the organic solvent concentration (mostly, acetonitrile, ACN) on the retention of small compounds (such as toluene, thiourea, and acrylamide) has frequently been studied in order to assess the HILIC capabilities of new stationary phases. The retention of polar molecules increases with increasing organic solvent content in HILIC stationary phases, which often exhibit typical HILIC behavior at high organic solvent content before returning to an apparently reversed phase (RP). When the stationary phases contain some hydrophobic characteristics and the organic solvent, content is below a threshold composition. In order to determine the polarity of HILIC stationary phases, one can use the critical composition of the mobile phase,

which corresponds to the change from the HILIC to the RP mode [34]. The critical composition typically transitions to a lower concentration of ACN in the mobile phase with more polar stationary phases, permitting the use of mobile phases with higher water content in the HILIC mode. Porous zwitterionic monolithic columns exhibited very high selectivities for polar analytes, particularly tiny peptides, it was claimed [35–38]. Electrostatic repulsion-hydrophilic interaction chromatography was a new phrase proposed by Alpert [39] (ERLIC). Unique selectivity for charged polar analytes is provided by the interaction between hydrophilic contact and electrostatic repulsion. Numerous HILIC monolithic columns have shown similar ERLIC behavior. Ibrahim *et al*. [40] examined the impact of mobile phase salt concentration on the retention of two amino acids on coated silica monolith. Improving the quantity of methyl phosphonate decreases the electrostatic attraction between the cationic analyte and the cationic latexes, increasing the retention of the basic amino acid histidine. For the acidic amino acid, aspartic acid, however, raising the quantity of methyl phosphonate shields the electrostatic attraction, lowering its retention. The monolithic columns built with acrylamide also included an intriguing mixed-mode separation mechanism. A number of polar aromatic compounds were often used to analyze these relatively polar stationary phases [41]. The retention factors of the better-retained compounds were drastically reduced by a rise in mobile phase polarity, as would be expected for HILIC. However, some elution orders also changed, indicating that other mechanisms besides simple hydrophobic changes may be at play. This suggests that the elution order was not merely the inverted form of the reversed-phase separation [42]. It was reported that polar and charged analytes were retained by a mixed mode of mechanisms, including hydrophilic interaction, electrostatic interaction, H-bridging interaction, interaction, and possible aromatic adsorption [43, 44].

Similar to HPLC, the mechanism of mass transfer involves hydrophobic adsorption on the sorbent's surface and partition into bound alkyl chains. When transferring analytes to the adsorption process, physical parameters (such as surface area, average pore diameter, and pore volume of the adsorbents) are also taken into account. In general, the surface area of the adsorbent has a direct relationship with its adsorption capacity. The molecules adsorbed in the diffusion process have a relationship with the pore size. The saturation capacity of monolithic and packed silica columns was compared *via* frontal analysis for four distinct compounds, and the results showed that the monolithic columns had a 30–40% greater capacity while the binding constants were almost identical for both [45].

This shows that even while the chemistry of both surfaces is extremely similar, resulting in the same elution order for many analytes, the monolithic column's efficacy or accessible surface area is greater than that of the packed column. However, a conventional column of the same size has a far better load capacity since monolithic columns have a much lower density. In other words, within a certain velocity range, the shape of the breakthrough behavior of monoliths (BTCs) does not change. This indicates a very fast mass transfer and allows the speculation that the mass transfer is not dominated by the chromatographic velocity [45].

BTC shape is determined by equilibrium isotherm, mass transfer resistances, and axial dispersion [45].

Because the flow pattern can be represented as an axial dispersion plug flow, the differential fluid phase mass balance is:

$$-D_L\,\delta^2\,c/\delta z^2 + u\,(\delta c/\delta z + \delta c/\delta t) + (1 - \acute{\varepsilon}/\acute{\varepsilon})\,\delta q/\delta t = 0 \qquad (1)$$

with D_L the axial dispersion coefficient, q the sorbate concentration averaged over the particle, c the fluid phase concentration, z the column length, u the interstitial fluid velocity, t the time, and $\acute{\varepsilon}$ the voidage of the adsorbent bed.

The mass balance for an adsorbent particle yields the adsorption rate expression, which may be written as.

$$\delta q/\delta t = f\,(q, c) \tag{2}$$

The global mobile phase power model, apparent solid phase power model, or two-film model were all used to solve this equation. The mobility phase apparent total driving force model can be used to explain the mass balance of the adsorbed particle.

$$\delta q/\delta t = 6/d_p\ K_c\ (c–c^*) \tag{3}$$

or the apparent overall solid-phase driving force model.

$$\delta q/\delta t = 6/d_p\ K_q\ (q^*–q) \tag{4}$$

where c* is a fictitious concentration in the mobile phase that is in equilibrium with q, and q* is a fictitious concentration in the solid phase that is in equilibrium with c. The apparent total mass-transfer coefficients are Kc and Kq, respectively, while the surface-to-volume ratio for spherical particles is 6/dp. (c - c*) and (q* - q) are the apparent total driving forces, respectively. The overall apparent driving forces are, respectively, (c - c*) and (q* - q) [45].

The linear driving forces in the two-film theory are (c - c0) and (q0 - q), where subscript 0 designates a concentration at the two films' interface at which c0 and q0 are by definition in equilibrium, that is.

$$\delta q/\delta t = 6/d_p\ K_f\ (c–c_0) = 6/d_p\ K_s\ \left(q_0–q\right) \tag{5}$$

where k_f is a velocity-dependent external mass-transfer coefficient and k_s is the solid-phase mass-transfer coefficient. $1/k_f$ and $1/k_s$ are termed the external and solid-phase resistances.

Analytical formulas for the BTC can be established for various limiting forms of the isotherm, such as linear or rectangular, and axial dispersion is ignored.

BTCs can be predicted appropriately assuming that the equilibrium isotherm is rectangular when the actual equilibrium constant is greater than five [45].

At constant pattern, the mobile and solid-phase concentrations are related by Eq. (6).

$$q/q_F = c/c_F \tag{6}$$

where qF is the appropriate equilibrium concentration and cF is the feed concentration. The flow equations are transformed into ordinary differential equations under circumstances of the constant pattern. The constant pattern relation, Eq. (6), is changed to y = x because it is convenient to add the dimensionless concentrations x = c / cF and y = q / qF. The flow can be represented as a function of x by inserting Eq. (6) into Eqs. (3) and (4) and calculating c* and q*.

$$dq/dt = q_F\ dx/dt = 6/d_p\ K_c\ c_F\ \beta x(1–x)/1 + \beta(1–x) \tag{7}$$

and

$$dq/dt = q_F\, dx/dt = 6/d_p\, K_q\, q_F\, \beta x(1–x)/1 + \beta x \quad (8)$$

where $\beta = bc_F$.

Inserting the Langmuir expression and the constant pattern relation in the two-film model, Eq. (5), yields.

$$\delta(x–x_0) = (1 + \beta)x_0/1 + \beta x_0 – x \quad (9)$$

where δ is the scaled mass-transfer resistance ratio.

$$\delta = k_f\, c_F/k_s\, q_F \quad (10)$$

The interfacial mobile phase concentration without dimension x0 is obtained by solving Eq. (9), which in this instance may be done analytically [45]. The flux in the two-film model is expressed as a function of x by solving Eq. (9) for x0 and inserting it in Eq. (5). The solution is.

$$dq/dt = q_F\, dx/dt = 6/d_p\, k_f\, c_f\, (x–x_0) \quad (11)$$

Despite having identical properties (i.e., particle sizes of less than 2 m), monolithic silica adsorbs the analyte with the narrow band on the column because its back pressure is significantly lower than that of the particle sorbent [46]. In contrast, the analyte adsorbed is quickly eluted by a little volume of elution solvent since the analyte is concentrated in the column. In order to provide adequate sample capacity and extraction efficiency, the standard solid-phase extraction cartridge often needs an elution volume that is two or three times the volume of the sorbent bed. Monolithic silica, on the other hand, only requires 100 L of eluent to elute the analyte adsorbed [46].

5. Types of monoliths

Based on the type of materials used in their preparation, monoliths are broadly categorized. Numerous monolith kinds may exist depending on this, although they are often divided into organic and inorganic-based monoliths. The chemistry of these two forms of monoliths serves as the basis for all other monolith types, whether through specific alterations or the use of many monomers. Organic monomers, like acrylamide [47, 48] and methacrylates [49, 50], are used for organic monoliths [51, 52], whereas inorganic monomers, like alkoxides of silicon [53, 54] are used for inorganic monoliths. The two categories differ in their chemistry of preparation, in which polymerization is applied for the organic monolith and hydrolytic polycondensation for the inorganic monolith.

5.1 Organic polymer monoliths

The idea of a monolith is thought to have originated from organic monoliths, which are composed of organic polymers. Developments in column technology have drawn a lot of interest since Hjerten *et al*. [9] introduced the first polymer monolith. His innovative work transformed the field of chromatographies by giving separating media new meaning and opening up new possibilities. They are a promising tool for separation in HPLC and capillary electrochromatography (CEC) modes due to the

ease of fabrication, high permeability, porosity, and their ability to function in a wide pH range. They can be made using a variety of techniques, like radical polymerization (thermal or photoinduced) [55, 56], polycondensation reaction [57], and ring-opening metathesis polymerization [58, 59] depending on the type of stationary phase. Since the invention of the organic monolith, plenty of work has been carried out and it has been extensively reviewed. A mixture of monomers, a porogenic solvent, and an initiator are added to the chromatographic column or capillary to create polymer-based monoliths there. The final step is to treat the entire column or capillary to heat- or UV-initiated polymerization [60]. The initiator, which starts the polymerization of monomers, is converted into radicals. The leftover monomers and solvating solvents are distributed to the nuclei (precipitates) that the developing polymers create. The nuclei get bigger as the polymerization process goes on, which leads to clusters coalescing to produce a homogeneous integrated structure [61]. The monolith, which are uniform gels or stiff rods, is made up of interconnected clusters of globules [62]. The manufacture of organic polymer-based monolith typically involves the use of tubing with 8 mm i.d. capillaries for HPLC and 20–500 m i.d. capillaries for micro LC and CEC. Teledyne Isco, Inc. offers polymer monolithic columns for sale (IscoSwift®) [61]. Methacrylates, acrylamides, and styrene are frequently utilized as the monomers in organic monoliths [20]. Methacrylates monoliths have been thoroughly studied by Svec and his colleagues [55, 63]. Polystyrene was used to create a monolith by Wang et al. Several scientists then replicated their method to create the monolithic columns in a capillary style. The monolithic poly (polyphenyl acrylate-co-1,4-phenylene diacrylate) capillary columns were created by Bisjak *et al*. [64], and they investigated the impact of different polymerization parameters on the effectiveness of the separation. The monolith was created by thermally inducing the co-polymerization of phenyl acrylate and 1,4-phenylenediacrylate in the presence of azoisobutyronitrile, a radical initiator. The degree to which these parameters varied, including the choice and composition of the porogen, the temperature at which they polymerized, the amount of cross-linking monomer used, and the amount of initiator, affected how well the monolith separated. A reverse-phase HPLC system was used to test the produced monolith for the separation of proteins and oligonucleotides. In reverse-phase and ion-exchange chromatography, polymer-based monolithic columns are efficient for the high-speed separation of proteins, polypeptides, oligonucleotides, synthetic polymers, and some small molecules, but they exhibit relatively low efficiency for small solutes [51]. They can tolerate extreme changes in pH from 1 to 14 for reversing phase columns. Limitations include their relatively low mechanical stability and compared to conventional polymer beads, organic polymer monoliths provide higher efficiency and less swelling problems. The presence of micropores enhances analyte spreading which causes band broadening and finally leads to large mass transfer kinetics for small molecules [65].

5.2 Polar and nonpolar organic monoliths

Since they are known to have, among other things, the capacity to withstand a wide range of operational conditions and to offer solutions for a variety of separation problems, organic polymer monolithic stationary phases have attracted the attention of the separation science community in the past two decades. In order to adequately describe the numerous parameters involved in the manufacture of polar and nonpolar organic monoliths made of two distinct components, the author of this advanced review paper has attempted to do so. The first section discusses nonpolar organic

monoliths, and the second section discusses polar organic monoliths and variations on them. The methacrylate/acrylate-based monoliths, styrene-divinylbenzene (DVB)-based monoliths, and hyper cross-linked monoliths are the three subgroups of the nonpolar organic monolith component. However, the section on polar organic monoliths, which primarily deals with monoliths derived from methacrylates, divides the monoliths into different categories based on the surface-charged groups they contain (for example, neutral, anionic, cationic, and zwitterionic monoliths) as well as how they were functionalized after polymerization [66].

5.2.1 Nonpolar organic monoliths

There are three commonly used nonpolar organic monolithic stationary phases, namely, acryl amide-based, acrylate/methacrylate-based, and styrene-based monoliths. The latter two are the most suited monoliths for reversed-phase chromatography (RPC) and RP-CEC applications.

5.2.1.1 Acrylate/methacrylate copolymer-based monoliths

Generally, the acrylate/methacrylate-based monoliths are more polar than their styrene DVB monolith counterparts. The formation of different kinds of monoliths is mainly by the choice of the functional monomers and cross-linking monomers. The structures of the functional and cross-linking monomers used for nonpolar and polar organic monoliths are shown in **Figure 3**.

5.2.1.2 Nature of functional monomers

The effect of the alkyl chain length and shape of the functional monomer on the structural features of the monolith has been reported. Rathnasekara *et al*. [67] used different alkyl methacrylate monomers with butyl, cyclohexyl,2-ethyl hexyl, lauryl, and stearyl functional groups in the polymerization mixture with ethylene glycol dimethacrylate (EDMA) as the cross-linker. In every instance, 1,4-butanediol (BDO) and 1-propanol were selected as the porogens. Test solutes included conventional proteins and alkylbenzenes, and typical metrics such as column permeability, methylene content, and phenyl selectivity were evaluated. The butyl methacrylate (BMA) monolith had a high level of permeability, whereas the lauryl methacrylate (LMA) monolith had a low level of permeability. Stearyl methacrylate (SMA)-based monolith had the best methylene selectivity, whereas BMA-based monolith displayed the highest phenyl selectivity. By using gradient elution in HPLC, lauryl and cyclohexyl methacrylate offered slightly improved separations for the tested standard proteins. Puangpila *et al*. [68] in CEC also looked at the impact of the functional monomers' alkyl chain length on solute retention. The method was first discussed by Okanda and El Rassi [69] and by Karenga and El Rassi [70]. The authors reported neutral monoliths (empty of fixed charges) to entirely prevent electrostatic interactions formed between charged solutes and the otherwise surface-attached charged moieties.

Using the identical cross-linking monomer pentaerythritol triacrylate, two distinct series of monolithic columns with surface-bound C8, C12, and C16 chains were created (PETA). While a series of monoliths (series B) was prepared by keeping the same composition of functional monomers and cross-linker, it produced chromatographic retention that increased as expected in the order of increasing the n-alkyl chain length. The monoliths (series A) were produced by adjusting the composition of functional

2-Acrylamido-2-methyl-1-propanesulfonic acid (AMPS)
N-Acryloxy succinimide (NAS)
N-Acryloyltris(hydroxymethyl) aminomethane (NAHAM)
N,N-Dimethyl-N-methacryloxyethyl-N -(3-sulfopropyl)ammonium betaine (MEDSA/SPE)
Alkanediol dimethacrylate n=4-12
N-(3-Aminopropyl) methacrylamide hydrochloride (NAPMH)
Dioxyethylene dimethacrylate (DiEDMA)
Divinyl benzene (DVB)
α,α'-Dichloro-p-xylene
4,4'-Bis(chloromethyl)-1,1'-biphenyl
1,2-Bis(p-vinylphenyl)ethane (BVPE)
2-Ethylhexyl methacrylate
Ethylene glycol dimethacrylate (EDMA)
Formaldehyde dimethyl acetal
Bisphenol A dimethacrylate (BIDMA)
Bisphenol A ethoxylate diacrylate
Glyceryl methacrylate (GMM)
Glycidyl methacrylate (GMA)
1,6-Hexanediol dimethacrylate (HDDMA)
Bisphenol A glycerolate dimethacrylate (BisGMA/BIGDMA)
1,3-Butanediol dimethacrylate
1,6-Hexanediol ethoxylate diacrylate (HEDA)
2-Hydroxyethylmethacrylate (HEMA)
Butyl methacrylate (BMA)
1,4-Cyclohexanediol dimethacrylate
Cyclohexyl methacrylate
Hexamethylene dimethacrylate (HEDMA)
Lauryl methacrylate (LMA)
Methacrylic acid (MAA)
N,N-Dimethyl-N-(3-methacryl-amidopropyl)-N-(3-sulfopropyl) ammonium betaine (SPP)
N,N-Dimethyl-N-acryloyloxyethyl-N-(3-sulfopropyl)ammonium betaine (SPDA)

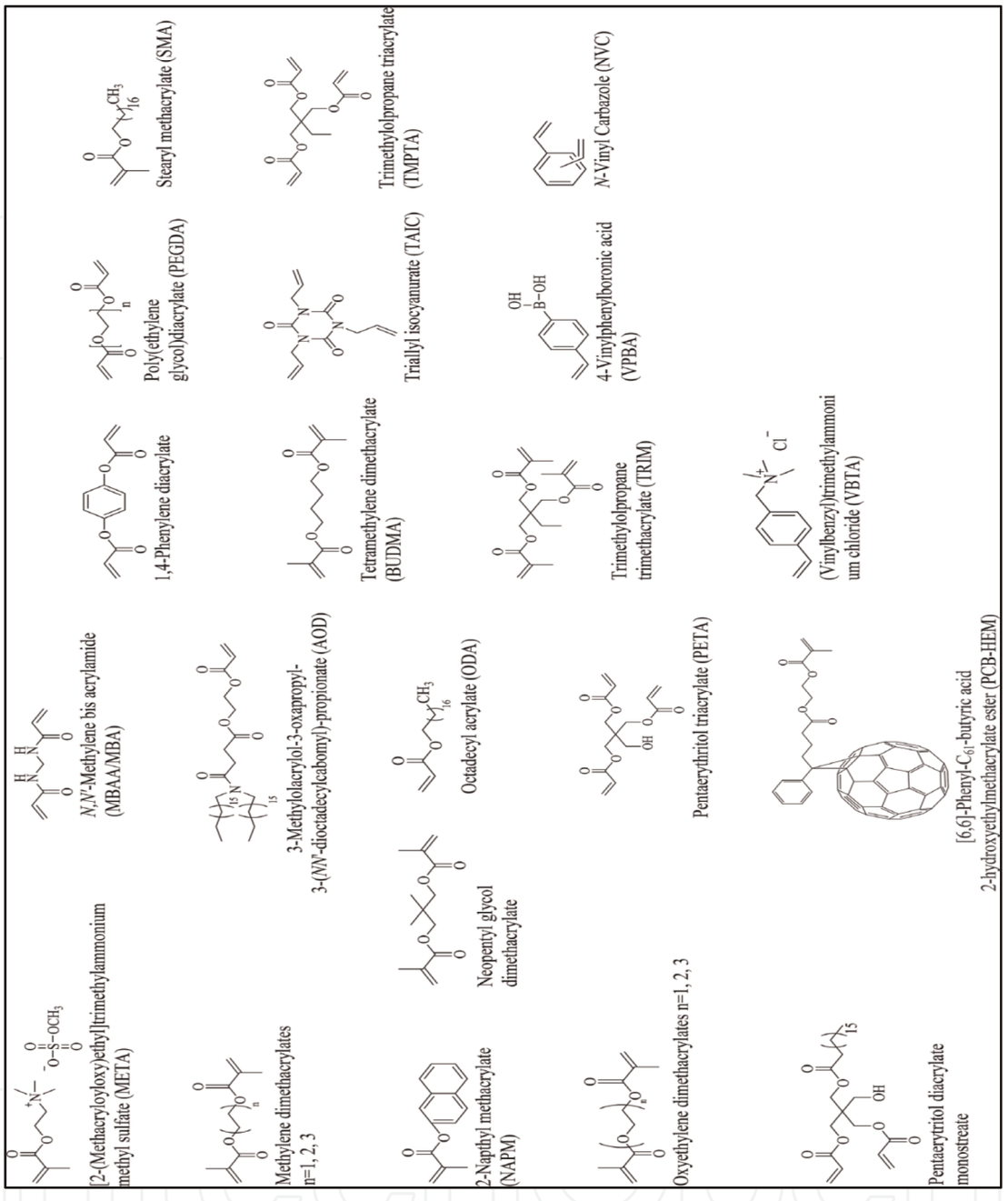

Figure 3.
Structure of functional monomers and crosslinked used in the preparation of nonpolar and polar monoliths, the monomers and cross-linked arranged alphabetically (Reprinted from Ref. [67]).

monomers and cross-linker to obtain comparable solute retention regardless of the alkyl chain length. The solvent was a ternary mixture of cyclohexanol, ethylene glycol, and water. The A series' C16 monolith produced the maximum separation performance for tiny solutes, however, the A column series was insufficient for separating proteins. The best separation efficiency for proteins was provided by the C8 monolith of the B series. The C16-monolith of the A series appears to offer the best separation for tryptic peptide mapping. An energetically "harder" C16 surface favored better separation of the smaller-size peptide solutes, whereas an energetically "softer" C8 surface permitted faster sorption kinetics and hence increased efficiency for big protein molecules. Briefly stated, proteins and peptides as well as neutral, polar, and

charged solutes were effectively separated, and the outcomes were consistent with earlier research on neutral monoliths by Karenga and El Rassi [71].

Mixed ligand monolithic (MLM) columns were created for CEC as a revolutionary method of achieving unique selectivity [72]. The creation of these columns involved the copolymerization of various mixtures of the functional monomers octadecyl acrylate (ODA) and 2-naphthyl methacrylate (NAPM) in the presence of the cross-linker trimethylolpropane trimethacrylate (TRIM) and a ternary porogenic solvent made of cyclohexanol, ethylene glycol, and water. In the CEC of neutral, polar, and charged solutes, the combined retentive characteristic of the ODA ligand, which is merely hydrophobic, and that of the NAPM ligand, which is both hydrophobic and an interaction provider, was utilized. As anticipated, the MLM's makeup impacted how large the EOF was. In comparison to the NAPM monomer, the ODA ligand generally showed a higher affinity for the mobile phase ions. This is because the NAPM is a monomer based on methacrylate, whereas the ODA is based on acrylate. **Figure 4** illustrates the discovery that columns formed by either ODA or NAPM alone did not match the unique selectivity for a given set of solutes produced by columns with a specific mix of both ligands.

By co-polymerizing, the functional monomer 3-methylacrylol-3-oxapropyl-3-(N, N-dioctadecylcarbomyl)-propionate (AOD) with the cross-linker EDMA, Duan et al. [73] presented a unique monolithic column with double C-18 chains for RPC. The monolithic column for HPLC was created using fused-silica capillary columns (100 m id). A poly (SMA-co-EDMA) C-18 monolith was also created for the comparison investigations in accordance with the author's earlier work [74]. We employed a binary porogenic combination of BDO and 2-methyl-1-propanol. The back pressure

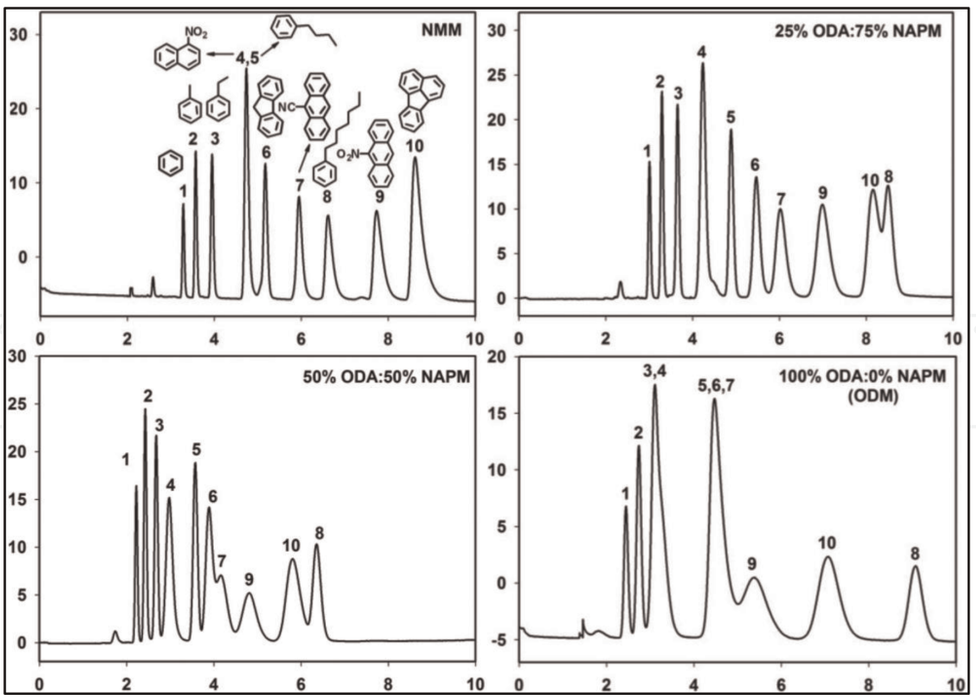

Figure 4.
Electrochromatograms showing the separation of five alkylbenzenes and five PAHs on monolithic columns with different mole fractions ODA/NAPM. Capillary column, 20 cm effective length, 27 cm total length × 100 μm id; mobile phase, 70% ACN, 1 mM sodium phosphate monobasic, pH 7.0, running voltage 20 kV; electrokinetic injection for 3 s at 10 kV. Solutes: 1, benzene; 2, toluene, 3,ethylbenzene; 4, 1-nitronaphthalene; 5, butylbenzene; 6, fluorene;7, 9-anthracenecarbonitrile; 8, heptylbenzene; 9, 9-nitroanthracene; and10, fluoranthene. EOF tracer, thiourea (Reprinted from Ref. [72]).

increased from 0.6 to 13.0 MPa at a flow rate of 500 nL/min as the monomer percentage changed from 50 to 70% w/w. Additionally, it was found that the back pressure increased from 0.6 to 13.0 MPa when the proportion of 2-methyl-1-propanol grew from 75 to 95% w/w. The results obtained were supported by the SEM images. The theoretical plate height of the poly (AOD-co-EDMA) monolith, which was 19.2 mm, was higher than that of the poly (SMA-co-EDMA) monolith, which was 32.1 mm at the same linear velocity of 0.85 mm/s. The permeabilities of this column with ACN, MeOH, and water were good. When strongly acidic and basic buffer were run over a sustained 30-hour period to test chemical stability, no noticeable deterioration was seen. The investigations into the batch-to-batch reproducibility studies and run-to-run repeatability research produced excellent results. In order to assess the effectiveness of the column and the behavior of the RP retention, respectively, Van Deemter plots and methylene selectivity tests were also performed. Using alkylphenols as test solutes, it was found that the methylene selectivity was 1.68, which was comparable to the 1.70obtained using the poly (SMAco-EDMA) monolithic column. Tocopherols (TOH) were utilized to test this column, and as can be shown in **Figure 5**, a complete separation of the, and TOH isomers was achieved in less than 30 minutes.

5.2.2 Polar organic monoliths

Despite offering a variety of chromatographic solutions for the separation, purification, and fractionation of a wide range of solutes, normal-phase chromatography (NPC), which employs polar stationary phases with nonpolar organic mobile phases, has its own limitations in the separation of highly polar analytes. Due to issues with hydrophilic materials dissolving in non-aqueous mobile phases, NPC of hydrophilic samples is challenging [75]. NPC has low repeatability for hydrophilic chemicals and poor mass spectrometry (MS) detection ionization efficiency [76]. Additionally, the

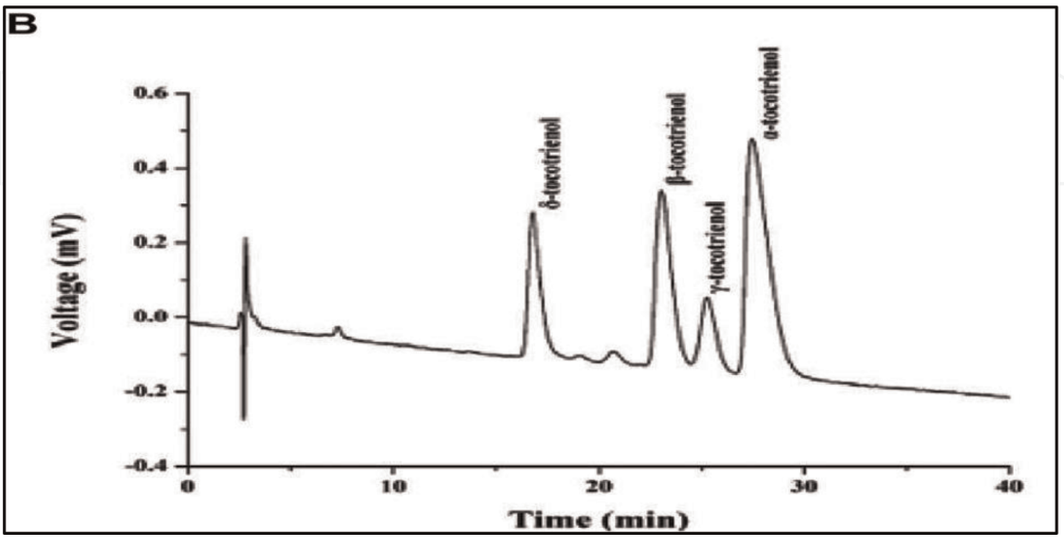

Figure 5.
A nano-LC separation of tocopherol homologs on the poly (AOD-co-EDMA) monolithic column. Conditions: Column dimensions 180 mm × 100 μm id; mobile phase: MeOH/H2O (93.5/6.5, v/v); detection, 292 nm; flow rate: 500 nL/min; injection volume: 20 nL (Reprinted from Ref. [73]).

majority of hydrophilic samples are poorly maintained on RP columns, eluting close to the column's dead time or displaying little to no resolution.

A chromatographic technique hydrophilic interaction liquid ion chromatography "HILIC" provides an alternative approach to effectively separate small polar compounds on polar stationary phases. In HILIC, polar analytes can be separated more effectively by combining a polar (hydrophilic) stationary phase with an organic-rich hydro-organic mobile phase. The inclusion of organic-rich mobile phase in HILIC offers some additional benefits that will increase the utilization of this method. These benefits include HILIC's appropriateness for direct coupling with MS detection and low column back pressure, which facilitates quick analyte separation with shorter analysis times [77]. The retention of polar solutes in HILIC and hydrophilic interaction CEC is strongly influenced by the makeup of the mobile phase (HI-CEC). HILIC/HI-CEC is typically operated with a low aqueous, highly organic mobile phase. The monolithic surface develops a water-rich layer under these HILIC circumstances. The adsorbed water layer on the surface of the stationary phase, the hydro-organic mobile phase, and the polar solutes in between are partitioned to create the separation. While HILIC frequently offers an efficient separation for polar analytes, a straightforward retention mechanism is not achievable for most molecules because hydrogen bonding, dipole–dipole, ion-dipole, and ion-ion interactions are also involved in addition to a partition mechanism [77].

During the past two decades, porous organic polymer monolithic columns have been widely employed as HILIC stationary phases due to their particular benefits, which include (i) high permeability, which reduces backpressure, (ii) low resistance to mass transfer, (iii) easy fabrication and surface functionalization, (iv) stability under severe pH values, and (v) a variety of functional monomers [78]. A variety of organic polymer monoliths with amino [79, 80], amide [81], hydroxyl [81], sulfoalkylbetaine [82], boronic acid [83], anilines and benzoic acids [84], and some other functionalities have been reported for use in HILIC/HI-CEC separations. **Table 1** summarizes the polar monoliths (neutral-cationic-anionic-zwitterionic monolith) and

Category	**Name of monolith [poly (functional monoer-co-corss-linker)]**	**Porogens used**	**Column id/ material**	**Polymerization condition**	**Format/separated analyte**
Neutral	Poly(GMM-co-PETA) (hydroxyl monolith)	Cyclohexanol, dodecanol, and water	100 μm id/fused silica	Thermal-initiation polymerization 60°C for 15 h with AIBN	HI-CEC/phenols, phenolic derivatives, nucleobases, and nucleosides
Neutral	Poly (NAHAM-co-PETA)	PEG in DMSO	100 μm id/fused silica	Thermal-initiation polymerization 60°C for 12 h with AIBN	CLC/ nucleosides, benzoic acid, anilines, nucleosides in urine
Cationic	Poly (NAPMH-co-EDMA) AP-monolith	Cyclohexanol, dodecanol, and methanol	100 μm id/fused silica	Thermal-initiation polymerization 50°C for 24 h with AIBN	HI-CEC/phenols, substituted phenols, and amides

Category	Name of monolith [poly (functional monoer-co-corss-linker)]	Porogens used	Column id/ material	Polymerization condition	Format/separated analyte
Cationic	Poly (VBTA-co-BisGMA)	Dodecanol, and methanol	100 μm id/fused silica	Thermal-initiation polymerization 60°C for 10 h with AIBN	HI-pCEC/benzoic acid derivative, phenols, nucleosides, and nucleobases
Cationic	Poly (META-co-PETA)	Cyclohexanol and ethylene glycol	100 μm id/fused silica	Thermal-initiation polymerization 60°C for 20 h with AIBN	pCEC/carboxylic phytohormones
Anionic	Poly(MAA-co-EDMA)	PEG and DMSO or dodecanol and toluene	100 μm id/fused silica	Thermal-initiation polymerization 60°C for 12 h with AIBN	cHILIC/anilines, benzoic acid derivatives, nucleosides, and tryptic digest of BSA
Anionic	Poly(AMPS-co-PETA)	Methanol ethyl ether and water	100 μm id/fused silica	Thermal-initiation polymerization 60°C for 20 h with AIBN	HI-CEC/neutral polar amides, phenol, and charge peptides
Anionic	Poly(GMA-co-VPBA-co-EDMA)	DEG and BDO	100 μm id/fused silica	Thermal-initiation polymerization 60 °C for 24 h with AIBN	CLC/alkaloids and protein
Anionic	Poly (HEMA-C0-MBAA)	DMSO, DMF, and water with Na_2HPO_4	100 μm id/fused silica	Thermal-initiation polymerization 60 °C for 24 h with AIBN	HI-CEC/nucleosides and some narcotic
Zwitterionic	Poly(SPP-CO-EDMA)	Methanol	100 μm id/fused silica	Thermal-initiation polymerization 70 °C for various time with AIBN	HILIC/benzoic acid derivatives, phenols, separation of ascorbic acid from dehydroascorbic acid
Zwitterionic	Poly(SPDA-co-MBA)/ poly(SPDA-co-EDMA)	Methanol and water	100 μm id/fused silica	Thermal-initiation polymerization 60 °C for 12 h AIBN	HILIC/ phenols, benzoic acid derivatives, peptides. Separation of alianation and urea in cosmetic products
Zwitterionic	Poly(SPE-co-PEGOA)	Isopropanol and decanol	75 μm id/fused silica	3 min under UV radiation with 2,2 dimethoxy-2-phenylacetophenone	HILIC/ amides benzoic acid derivatives and phenols
Zwitterionic	Poly(SPE-co-BVPE)	Methanol and toluene	200 μm id/fused silica	Thermal-initiation polymerization	HILIC gradient separation

Table 1.
Summary of polar monolith (neutral-cationic-anionic-zwitterionic monolith) and their applications for the separation of analytes.

their applications for the separation of analytes. Applications using polar organic monolith are shown in **Figures 6** and 7.

5.3 Monolithic metal: organic framework

5.3.1 A sol: Gel monolithic metal: Organic framework

The creation of a porous monolithic metal–organic framework (MOF) with a 259 cm^3 (STP) capacity following effective packing and densification. This is the greatest value for conforming shape porous solids documented to date, and it represents a more than 50% improvement above any experimental value previously reported. A significant advancement has been made in the use of mechanically robust conformed and densified MOFs for high volumetric energy storage and other industrial applications when nanoindentation tests on the monolithic MOF revealed robust mechanical properties, with hardness at least 130% greater than that previously measured in its conventional MOF counterparts [85].

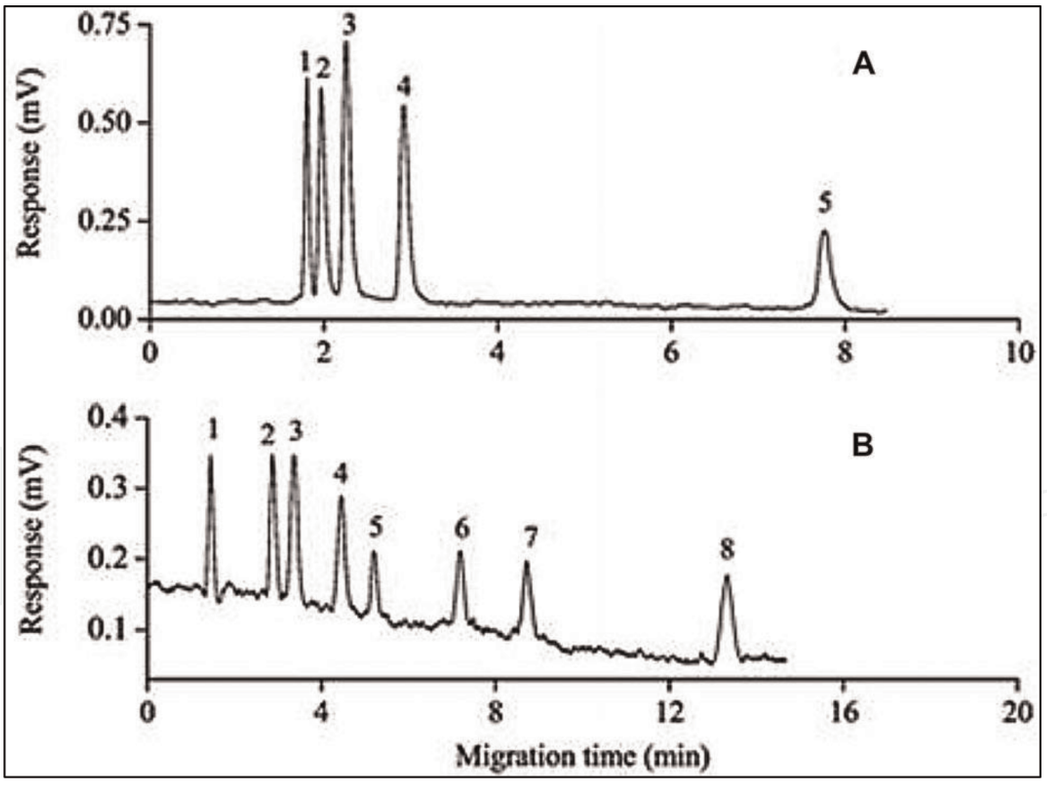

Figure 6.
Electrochromatographic profiling of phenols (A) and nucleic acid bases and nucleosides (B) on poly(META-co-PETA monolith. The profile (A) was recorded in the mobile phase 5 mM ammonium formate, pH 3.0, at 95% v/v ACN; pump flow: 0.02 mL/min; backpressure 250 psi; applied voltage: +10 kV. Solutes: (1) phenol; (2) catechol; (3) hydroquinone; (4) resorcinol; (5) pyrogallol. The profile (B) was recorded in the mobile phase 5 mM ammonium formate, pH 5.0, at 90% v/v ACN; the other conditions were the same as for (A). Solutes: (1) uracil; (2) adenine; (3) adenosine; (4) cytosine; (5) uridine; (6)guanine; (7) cytidine; (8) guanosine (Reprinted from Ref. [79]).

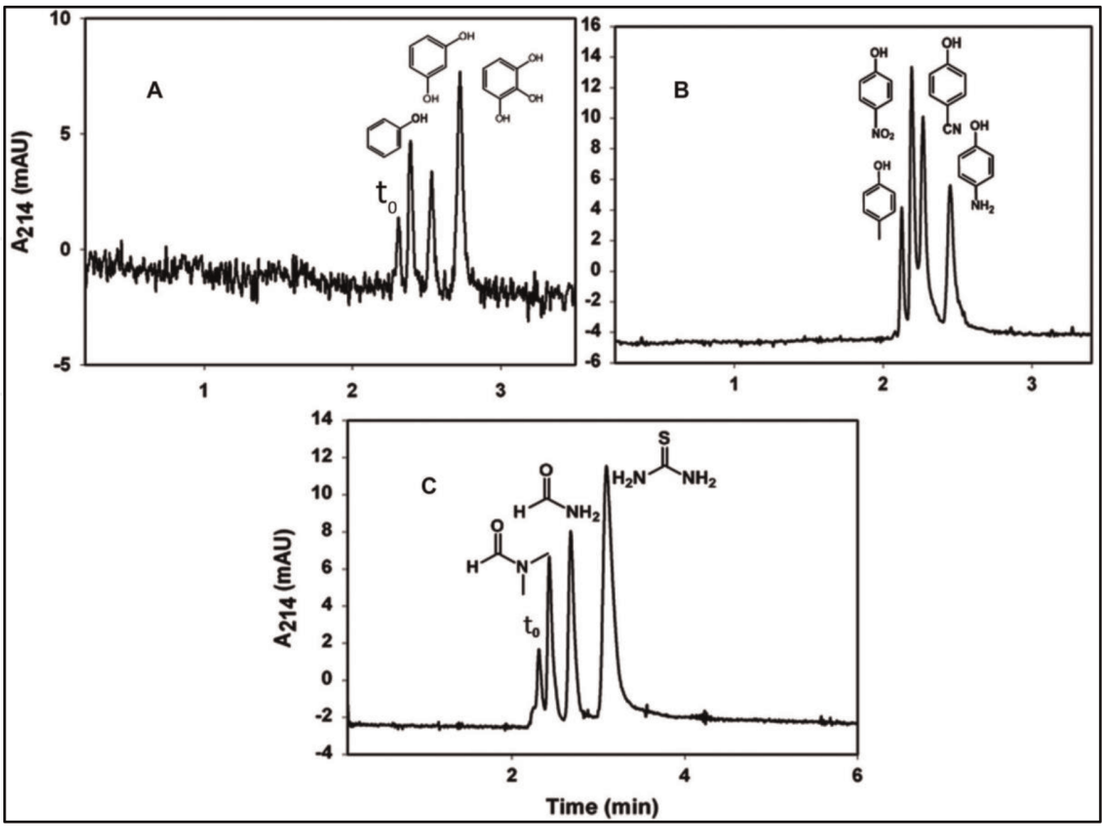

Figure 7.
Separation of three phenols (A), four phenol derivatives (B), and three other compounds (C) obtained on the neutral hydroxymonolith. Condition: Hydro-organic mobile phase, 5 mM NH4Ac (pH 8.0) at 95% ACN (v/v), running voltage 20 kV, column temperature 20°C, sample injection, pressure at 5 bar for 10 s. solutes in C are DMF, formamide, and thiourea (left to right) (Reprinted from Ref. [81]).

5.3.2 Metal–organic frameworks in biomedicine

5.3.2.1 Influence of the composition

For biomedical applications, porous materials must have a composition that is conducive to living things. There are not many toxicity studies that involve MOFs or coordination polymers at this time. Most of the information is limited to the assessment of the individual toxicity of the metals and linkers. Of course, only metals with a tolerable level of toxicity should be taken into account here. The choice to exclude a certain composition from biomedical use could be based on a number of factors, including the application, the trade-off between risk and benefit, and the kinetics of degradation, biodistribution, accumulation in tissues and organs, and excretion from the body. All metals and linkers could therefore be employed in these applications, although at varying doses based on the aforementioned requirements. According to their oral lethal dosage 50 (LD50), the most suitable metals at first look are Ca, Mg, Zn, Fe, Ti, or Zr, whose toxicity ranges from a few g/kg to more than 1 g/kg (calcium). The most popular one is the use of exogenous linkers, either made synthetically or naturally from substances that do not interfere with bodily cycles. Relevant exogenous MOFs for bio-applications include those made from iron (III) polycarboxylates, such as MIL-100(Fe) [86], zinc adeninate-4,40 biphenyldicarboxylate BioMOF-1 [87, 88], and magnesium coordination polymers, such as the magnesium 2,5-dihydroxoterephthalate CPO-27(Mg) (CPO for Coordination Polymer from Oslo) [89] (**Figure 8**).

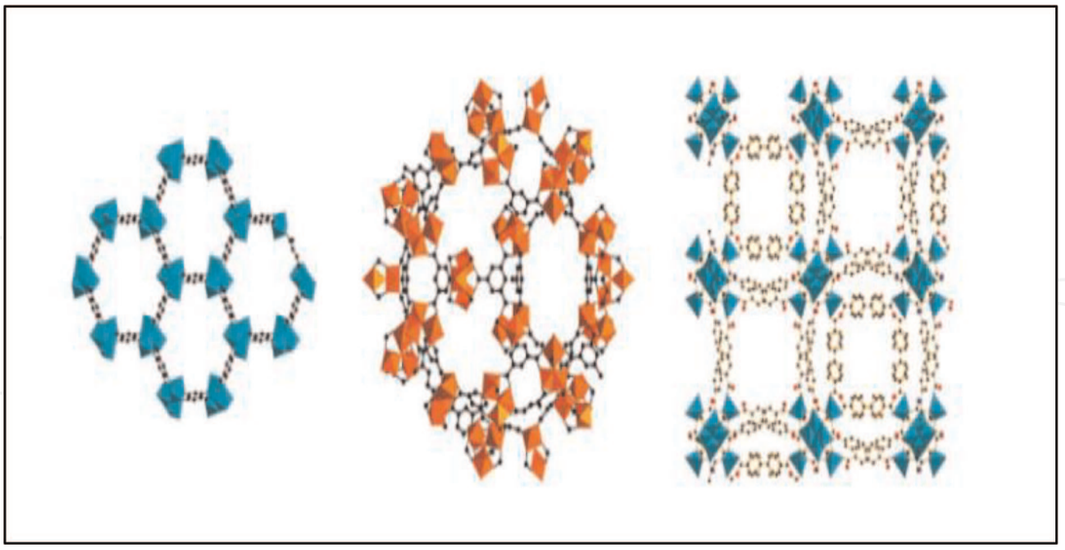

Figure 8.
View of the structures of a few topical MOFs, here CPO-27(Mg, Zn) (left), MIL-100 (Fe) (center), and Bio-MOF-11 (right), based on exogenous linkers for bioapplications. Metal polyhedra and carbon atoms are in blue (Zn, Mg) or orange (Fe), and black, respectively (Reprinted from Ref. [88]).

These solids have large pores (4–29) and surfaces between 1200 and 2200 m^2. Biomolecules (NO, CO, H_2S, medicines, etc.) may coordinate strongly at these accessible Lewis acid sites to better control the release [90–92]. The structures of a few MOFs based on endogenous linkers such as Bi citrate [93], Mg formate [94], Cu aspartate [95], Zn-dipeptide [96], Fe gallate [97], Fe Fumarate [98] and Fe muconate [99] are shown in **Figure 9**.

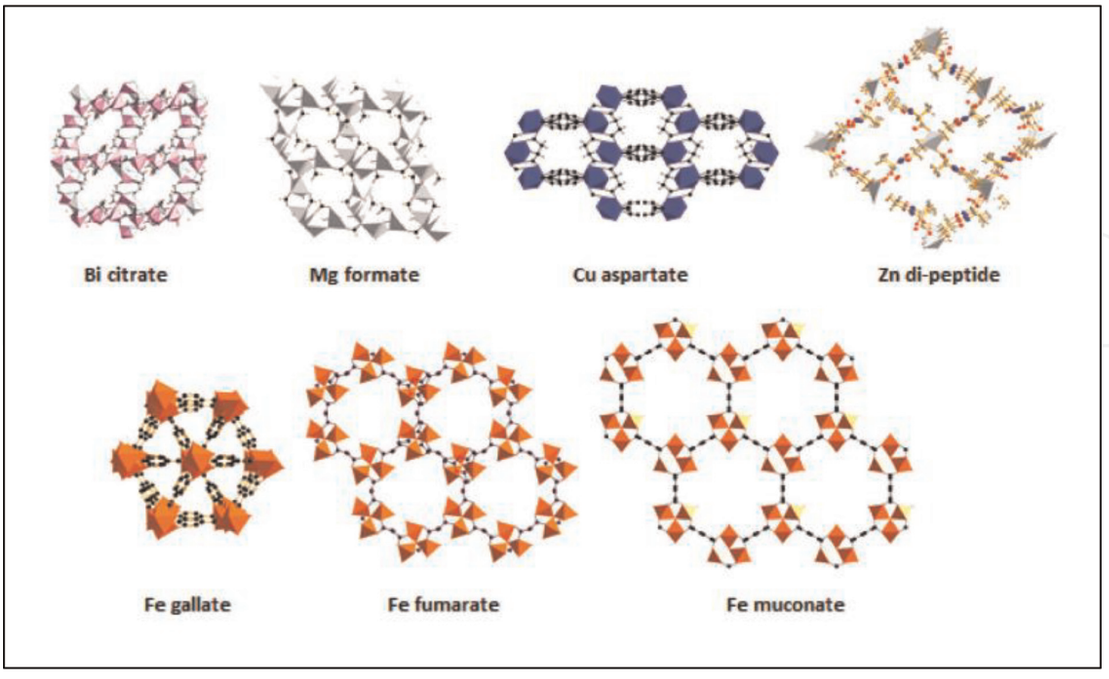

Figure 9.
View of the structures of a few MOFs based on endogenous linkers such as; Bi citrate [93], Mg formate [94], Cu aspartate [95], Zn-dipeptide [96], Fe gallate [97], Fe fumarate [98], and Fe muconate [99]. Metal polyhedral are in pink, gray, gray, blue, or orange (for Bi, Mg, Zn, Cu, and Fe, respectively) and carbon atoms in black, respectively.

Exogenous linkers should be eliminated from the body following the *in vivo* delivery of the MOFs in order to prevent potentially harmful side effects. As a result of their high polarity and ease of removal under physiological conditions, typical polycarboxylic or imidazolate linkers are not initially thought to be very toxic, with rat oral doses of 1.13, 5.5, and 8.4 g/kg for terephthalic, trimesic, 2,6-napthalenedicarboxylic acid, and 1-methylimidazole, respectively.

The use of functionalized linkers to adjust MOFs' absorption, distribution, metabolism, and excretion is yet another potential application for exogenous linker-based MOFs (ADME). Additionally, the presence of functional groups inside the framework can alter the host-guest interactions for the adsorption and distribution of therapeutic molecules, enabling a better control of the release. While a number of porous MOFs based on modified linkers that contain polar or apolar functional groups such as amino, nitro, chloro, bromo, carboxylate, methyl, and perfluoro are known, the most prevalent functionalized systems involve porous metal terephthalates based on iron or zinc [100]. One could also cite a series of organically modified porous Zn imidazolate solids [101]. In the case of functions, flexible MOFs will not only modify the host and guest interactions, but will also drastically affect the flexibility of the MOF during the adsorption or delivery of the biomolecule [102, 103] (**Figure 10**).

5.3.2.2 Nanoparticle monoliths

For some administration routes, where highly exact sizes are needed, particle size is a limiting constraint. For instance, the parenteral method necessitates stable

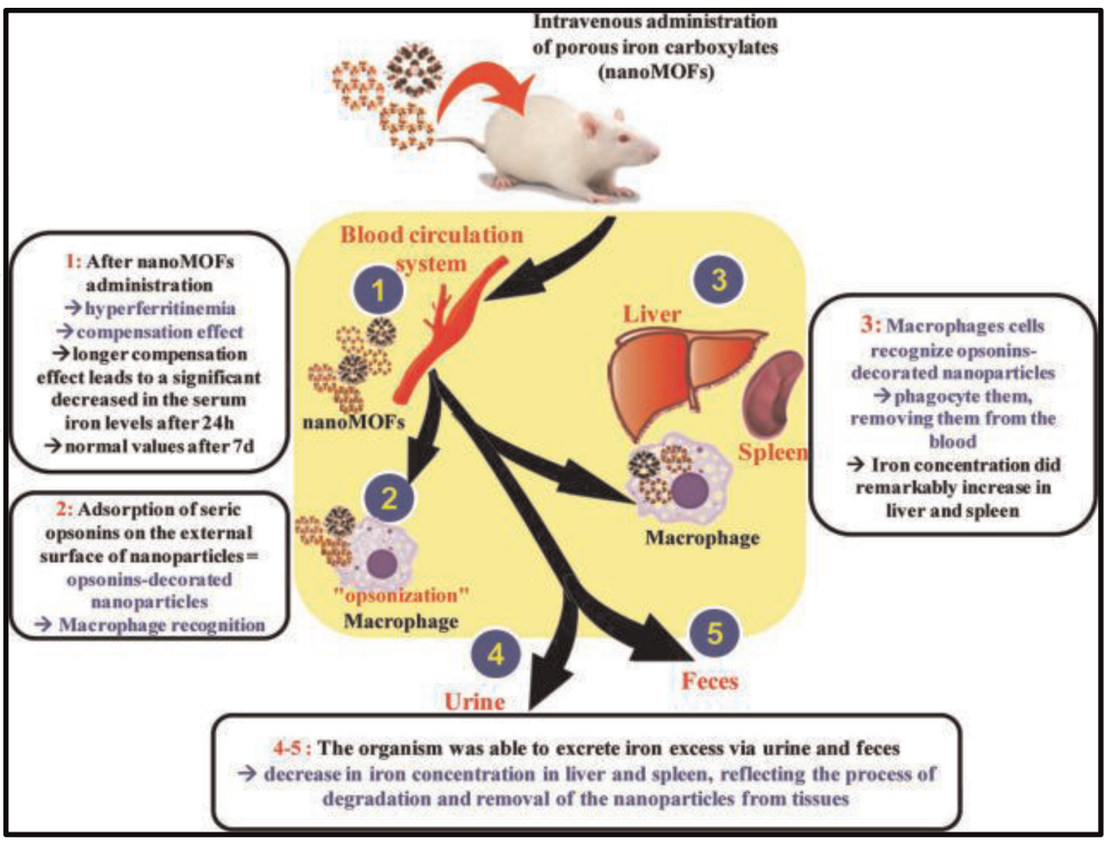

Figure 10.
Scheme of biodistribution of iron nanoMOFs according with the iron concentration (Reprinted from Ref. [88]).

solutions or suspensions of nanoparticles smaller than 200 nm in order for them to freely flow through the tiniest capillaries. Therefore, the creation of homogenous, monodispersed, and stable nanoparticles is a significant issue that has been addressed thus far using the following techniques:

5.3.2.3 The conventional hydro/solvothermal route

The conventional hydro/solvothermal method depends on a number of parameters, including reaction duration, temperature, stoichiometry, dilution pH, additives, etc. Topical examples include the porous zinc terephthalate MOF-5 (100–200 nm) [104] or the flexible porous Iron (III) dicarboxylates MIL-88A (150 nm) [105], MIL-88B-4CH3 (40 nm) [105], obtained by reducing reaction time or temperature, either employing low temperature or atmospheric pressure conditions. Alcohols can also be used to create nanoparticles of the zinc imidazolate ZIF-8 (40 nm) or the porous iron muconate MIL-89 (30 nm) [106] at low temperatures. Although particle sizes less than 100 nm are frequently achieved, the lack of homogenous and efficient heating typically results in a significant drop in yield and a high degree of polydispersity because the nucleation and growth stages are not under control [107]. Acidobasic or inhibitory additives (acetic acid, hydroxybenzoic acid, and pyridine) [106] are frequently used to adjust the reaction kinetics or slow the nucleation development process. Pyridine has been suggested as an inhibitor in the solvothermal production of porous indium terephthalate particles by Cho *et al*. [108]. Acetate ions were utilized by Horcajada *et al*. [106] to create tiny nanoparticles of the malleable, porous iron muconate MIL-89 as growth inhibitors (30 nm). Similar results were obtained by Tsuruoka et al. [109] with porous Cu2-(naphthalene dicarboxylate) 2(1,4-diazabicyclo (2,2,2) octane nanorods. A polyvinylpyrrolidone (PVP) polymer was used by Kerbellec *et al*. [110] to produce extremely tiny nanoparticles of a luminous terbium terephthalate (about 4–5 nm) at ambient pressure and room temperature. This approach was additionally used for various lanthanide (Tb, La, Tm, or Y) terephthalate MOF luminous micro- and nanoparticles [111].

5.3.2.4 Reverse-phase microemulsions

Reverse-phase microemulsions are based on a metal source, an organic linker, and micelles of cationic cetyltrimethylammonium bromide surfactant (CTAB) in a nonporous Ln [112–114] or Mn [115] based polycarboxylates MOFs with interesting imaging properties. This technique allows a control of particle size by tuning the dimensions of the micelles. Isooctane/1-hexanol/water mixture led to nonmetric nonporous Ln [112–114] or Mn [115] based polycarboxylates MOFs with interesting imaging properties technique allows a control of particle size by tuning the dimensions of the micelles.

5.3.2.5 Sonochemical synthesis

Micro and nanoscale MOFs have recently been synthesized using the quick, simple, and ecologically friendly sonochemical synthesis technique. Acoustic cavitation is caused by ultrasonic irradiation and results in the bursting of bubbles, localized hot patches, a significant temperature/pressure differential, and quick molecular movement. This encourages the development of high-energy microreactors, which causes MOFs to crystallize quickly [116, 117]. While other porous crystalline structures have

been successfully created at the nanometric scale under ultrasonic circumstances, the microporous flexible iron(III) terephthalate MIL-5376 and a stiff copper trimesate have been crystallized at the microscopic scale [118, 119]. The Seo research group has detailed the ultrasonic synthesis of porous copper trimesateHKUST-1 in DMF (10–200 nm) and zinc trimesate in ethanol (50–100 nm) at room temperature and ambient pressure using selective organoamine sensing [120]. The flexible porous iron fumarate MIL-88A's particle size can be varied between 100 and 740 nm, with the lowest particle sizes being obtained by using inhibitors, extremely high dilutions (0.01–0.008 M), or low temperatures (°C). As a result, only low yields (5 wt%) are produced [107].

5.3.2.6 Microwave-assisted hydro/solvothermal synthesis

For the creation of MOF nanoparticles, microwave-assisted hydro/solvothermal synthesis is an effective, homogeneous, and quick technique. The high thermal efficiency of polar solvents results in local superheated regions and high dielectric absorptivity, which favors a rapid and homogeneous nucleation process over crystal formation [121]. This technique was used to produce the zinc terephthalates IRMOF-1, 2, and 3 (100 nm) [122] and the mesoporous chromium terephthalateMIL-101 (∼22 nm) [123, 124]. Sefcjk and McCormick [125] have extensively studied the flexible microporous iron terephthalate MIL-53 (350–1000 nm), the mesoporous iron trimesate MIL-100 (200 nm), the iron aminoterephthalate MIL-101NH2 (120 nm) and the iron fumarate MIL-88A (∼20 nm), as shown in **Figure 8**.

5.4 Silica monoliths

Sol–gel synthesis, which enables extraordinary control over the composition and shape of the generated monolith, is typically used to create silicon alkoxide-based monoliths. This method is flexible and may be used to create a variety of monoliths. Starting with Si(OR)4, the reaction creates a siloxane (Si-O-Si) network in the polymer. Phase separation, condensation, and hydrolysis compete with one another to create a porous monolith [125]. There were several steps involved in creating the silicon alkoxide-based monolith. Alkoxy groups are replaced by hydroxyl groups in the first step of the process, which also results in the synthesis of silanol groups (SiOH) and alcohol. These extremely reactive silanol groups condense with additional alkoxy silanes or with one another in the next steps, creating a siloxane bond. Following these preparatory phases, a soil's precursors hydrolyze under acidic or basic conditions, forming a gel with a three-dimensional network following a series of condensation steps. To create the monolithic matrix, this gel ages and passes through phase separation under a certain set of circumstances [125]. Tetramethoxysilane (TMOS) and tetraethoxysilane (TEOS) are typically the two precursors that are employed the most in the preparation. By regulating the rate of condensation and hydrolysis, the reactivity of the precursors can regulate the distribution of subunits throughout the network. Several species are produced as a result of the reaction, and they all proceed through hydrolytic polycondensation at different speeds than the precursor. When compared to other precursors, TMOS undergoes rapid hydrolysis, making it one of the most reactive [126]. When compared to TEOS, it was found that TMOS produces pores that are more consistent, thinner, and have a higher surface area. Various strategies have been developed to address the issues of cracking and shrinkage. Despite various concessions in their performance or stationary phase

qualities, they proved to be useful. The initial method that distinguished the development was the creation of particle-loaded monoliths in a capillary format with the goal of creating a column without cracks. This method of preparation was first presented by Dulay *et al*. [127] with the idea of embedding particles inside the holes or cavities made inside the produced matrix. Using sol–gel technique, monoliths were created by embedding ODS particles (3–5 m) in tetraethoxysilane (TEOS). A 40 cm long, 75 m capillary was filled with the solution, and the resulting monolith was employed in CEC. A combination of aromatic and non-aromatic chemicals was used to assess the column's performance. Due to the ODS particles' deep embedding and non-homogeneous packing, which shields the particles from the analyst, different efficiency is attributed to these factors. Bakry *et al*. [128] adapted the above technique and enclosed silica particles within the polymeric backbone to address these issues (polystyrene divinylbenzene). In their process, silica particles were first packed into prepared silica capillary using the slurry packing method, and then an immobilizing fluid made up of styrene, divinyl benzene, azobisisobutyronitrile (AIBN), and decanol was added. After polymerization, the created monolith underwent a test to determine whether polyphenols, peptides, and proteins could be separated. Sometimes it is simpler to synthesize monoliths made in capillaries than bigger diameter columns because they can form a covalent bond with the inner capillary wall, which gives the monolithic bed more stability.

5.5 Hybrid monoliths

The sol–gel method, which entails a succession of hydrolysis and polycondensation stages to generate a three-dimensional network structure, is also used to prepare organic–inorganic hybrid monolithic materials [129]. Except for the co-polymerization of a second precursor, which is in charge of adding an organic moiety to the silica backbone to prepare a desirable stationary phase, the preparation techniques are the same as in the single alkoxide production. The addition of one or more modified precursors, such as 3-mercaptopropyltrimethoxysilane (MPTS) [130], sets it apart from pure organic and inorganic-based monoliths. The organic moiety is uniformly distributed throughout the matrix and connected to the expanding silicon network *via* a non-hydrolyzable Si-C bond, which improves the performance and efficiency of the monolith to the desired chromatography. Allyl, octadecyl, phenyl, and amino groups were adsorbed onto the matrix, eliminating the need for the time-consuming and laborious post-matrix modification issue [131–133].

As a replacement for the current stationary phases, a hybrid monolith made utilizing a sol–gel process and hybrid materials have been proposed. This hybrid monolith has shown promise because it offers more benefits than a traditional silica monolith. In order to increase column efficiency, stability, and selectivity, sol–gel hybrid materials are specifically created to have desired qualities and eliminate the ones that are undesired. Additionally, hybrid monoliths can be created directly by combining organic and inorganic monomers for the desired interaction, negating the need for the functionalization of stationary phases, which is more typical with the conventional method, which involves creating the monolith first and then functionalizing it. Therefore, Hayes and Malik [134] created the monoliths using the solution without using particles and without the necessity for frits in their hunt for a substitute to combine the preparation and functionalization of silica monolith in a single step. They provided a straightforward method for creating functionalized porous monoliths that are chemically adhered to the silica capillary's inner walls. The sol–gel precursor,

N-octadecyldimethyl [3-(trimethoxysilyl) propyl] ammonium chloride, was employed to create porous monoliths helpful for CEC studies with chemically bound ODS ligands. Later, employing methyltrimethoxy silane (MTMS) alone as a precursor, Laschober *et al*. [135] developed a capillary monolith based on the sol–gel process, which has the advantage of having increased hydrolytic stability of the Si-C bond. Additionally, they looked at how different parameters affected the monolith's morphology, which was shown by the size of its pores, skeleton, and surface. The prepared monolith is usable throughout a wider pH range. Due to their decreased compatibility with polar solvents, the monoliths produced by MTMS showed a higher tendency for spinoidal decomposition than tetraalkoxysilanes. Furthermore, unlike the case with tetraalkoxysilanes, synthesis does not call for the functionalization of the capillary walls or a hydrophilic polymer like polyethylene glycol. At pH 1, the reaction is conducted to create monoliths with bicontinuous morphologies. When compared to tetralkoxysilane, the surface area is less, which may be due to the involvement of only three of silicon's four valences in forming bonds with other organo-silica tetrahedrons. The monolith's chromatographic performance was evaluated using each component separately, and separation was predicted based on the components' various retention times. Dunn and Zink [136] recently evaluated the characteristics and uses of molecules trapped in a silica matrix made using the sol–gel method. In order to explore the impacts of changes in many factors, such as solvent composition, polarity, viscosity, pH, and speeds of chemical reaction, entrapped molecules acting as a spectroscopic probe offer insight into sol–gel chemistry. As probes, a variety of organic compounds have been used to track the chemical changes in sol–gels.

6. Preparation of hydrophilic monolithic columns

6.1 Silica-based monolithic columns

The Nakanishi and Soga team invented silica-based monolithic columns in the early 1990s [137]. The majority of these silica-based monoliths that have been described were created using methods that are comparable and involve the hydrolysis of one or more silanes, primarily tetramethoxysilane, in an acidic solution while the presence of an appropriate porogen. A sufficient mesopore is formed when the gel is aged and macerated in a basic solution. The gel is then dried and heated before having its surface modified with the appropriate ligands. One particular benefit of the silica-based monolithic column is that its macropores and mesopores can be tailored separately to achieve the best performance for specific analytical objectives. This is in addition to the two main generic advantages of all monolithic columns, namely, the high permeability and the low resistance to mass transfer. According to Jiang *et al*. [138], the majority of articles on silica monolithic columns dealt with applications based on commercial columns. He hypothesized that this was due to the fact that several stages (such as drying and cladding of the rods) are challenging to overcome in academic laboratories and that Merck, the producer, has carefully crafted patents designed to close any gaps [139]. The Chromolith Performance monolith, one of Merck's commercially available silica monolithic columns, has the potential for HILIC applications because it features a polar silica surface. However, based on these Chromolith Performance materials, just one such HILIC application has been documented. This column was employed by Pack and Risley [140] for the detection and quantification of lithium, sodium, and potassium in the HILIC separation mode.

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Additionally, certain monolithic capillary columns made entirely of silica have been created in academic labs and used for HILIC. The first silica-based monolithic capillary columns were created at the end of the 1990s [137] using the sol–gel method described by Nakanishi and Soga. However, the drying and calcination processes involved in its preparation take time. Additionally, Puy *et al*. [141], a 2 h water washing phase, which may remove 70% of the polyethylene glycol, was used in place of the 24 h calcination step (PEG). The monolith's stability, morphology, or chromatographic qualities are unaffected by the residual PEG. Later, they discovered that monolithic capillaries made of pure silica and employed in HILIC mode or normal phase mode did not require the hydrothermal treatment step at 120°C. The hydrothermal treatment was suppressed, which increased the retention factors but did not affect CEC or nano-LC efficiency [142]. The monolithic silica matrix synthesized from a sol–gel process was chemically modified by 3-aminopropyltrimethoxysilane, 3-(2-aminoethylamino) propyltrimethoxysilane [138], or diethylenetriaminopropyltrimethoxy silane [143] in order to produce a column for hydrophilic interaction applications. The surface modifications were simply carried out by a solution of

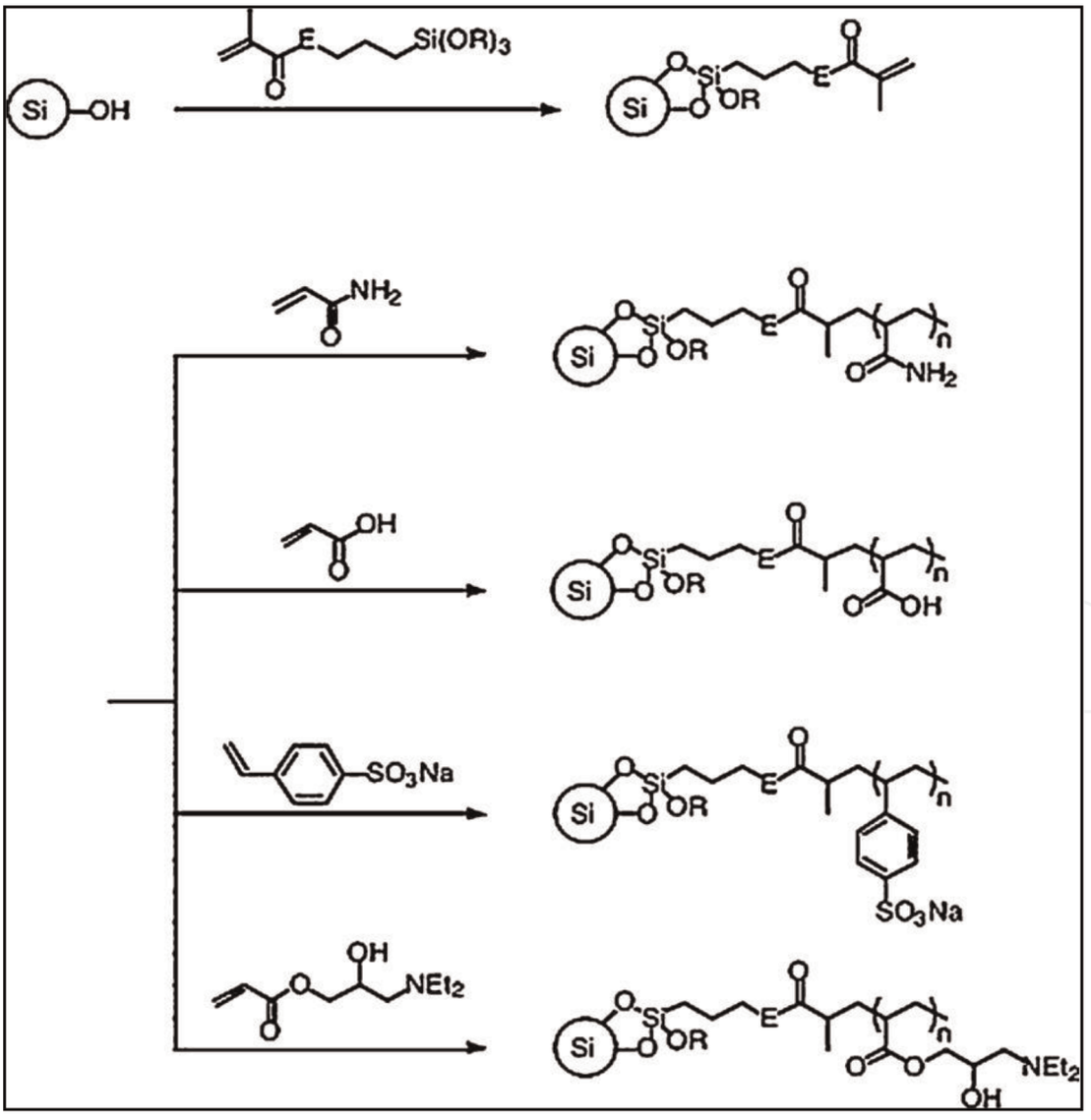

Figure 11.
Synthetic scheme of the polymer-coated monolithic silica columns (Reprinted from Ref. [144]).

pumping the silane in anhydrous toluene through the bare silica monolithic capillary column for 1 h which was thermostated at 75°C or 110°C for various times. These amino silica monolithic stationary phases exhibited HILIC behavior toward neutral solutes. However, no comparative research between these columns and bare silica monoliths has been reported. Moreover, Ikegami *et al.* [144] summarized a polymer coating procedure in their review article as shown in **Figure 11**.

6.1.1 Functionalization of silica-based monoliths

The study on the modification or functionalization of silica-based monolithic columns has been developed to satisfy the varied needs for the separation of complex substances in LC and CEC based on the silica-based monolithic columns created utilizing the aforementioned procedures. **Figure 12** illustrates how monolithic columns can entirely independently manage the chemical and porous properties by post-modification. Additionally, post-modification allows for the avoidance of the need to prepare a monolithic column's porous characteristics from scratch each time a change in chemical functionality is sought. For the functionalization of porous silica-based monoliths, a number of approaches have been identified. The far simpler method to change the silica-based monolithic columns, as shown in **Figure 13** [127], was to use various silane chemicals.

7. Selected monoliths media applications

Applications developed for monoliths media have been tremendous, and it would be impossible to review them all in this chapter book. We have, however, categorize studies of monoliths media with metal–organic framework and nanoparticle monoliths in chromatography separations. Some representative examples published over the last decade are summarized below to provide the reader with an appreciation of the possible breadth of applications.

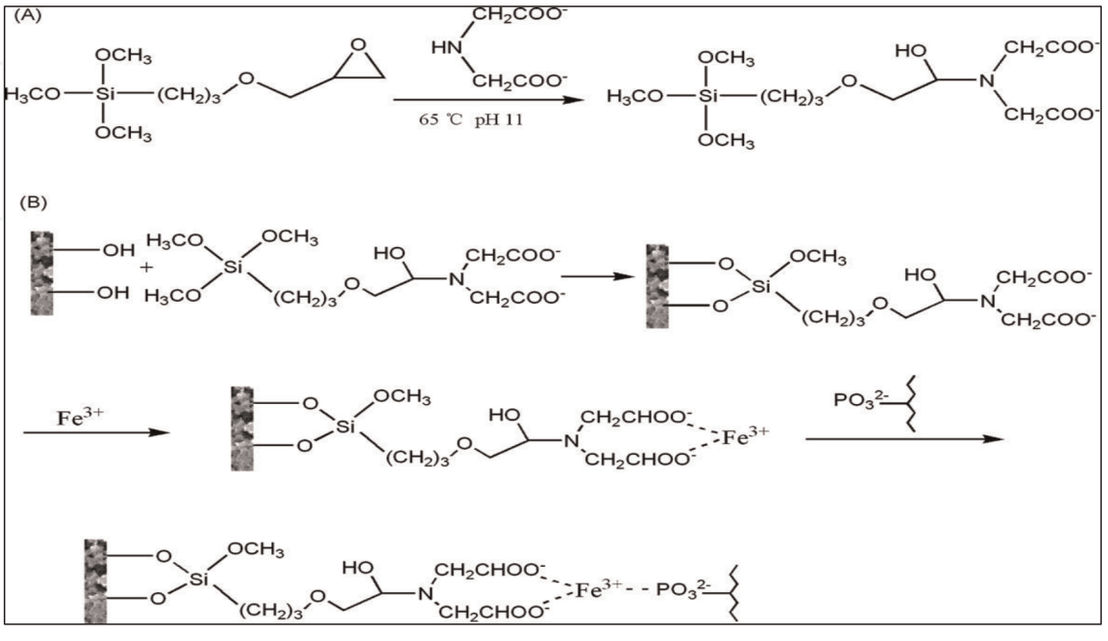

Figure 12.
Post-modification of silica monolith (Reprinted from Ref. [144]).

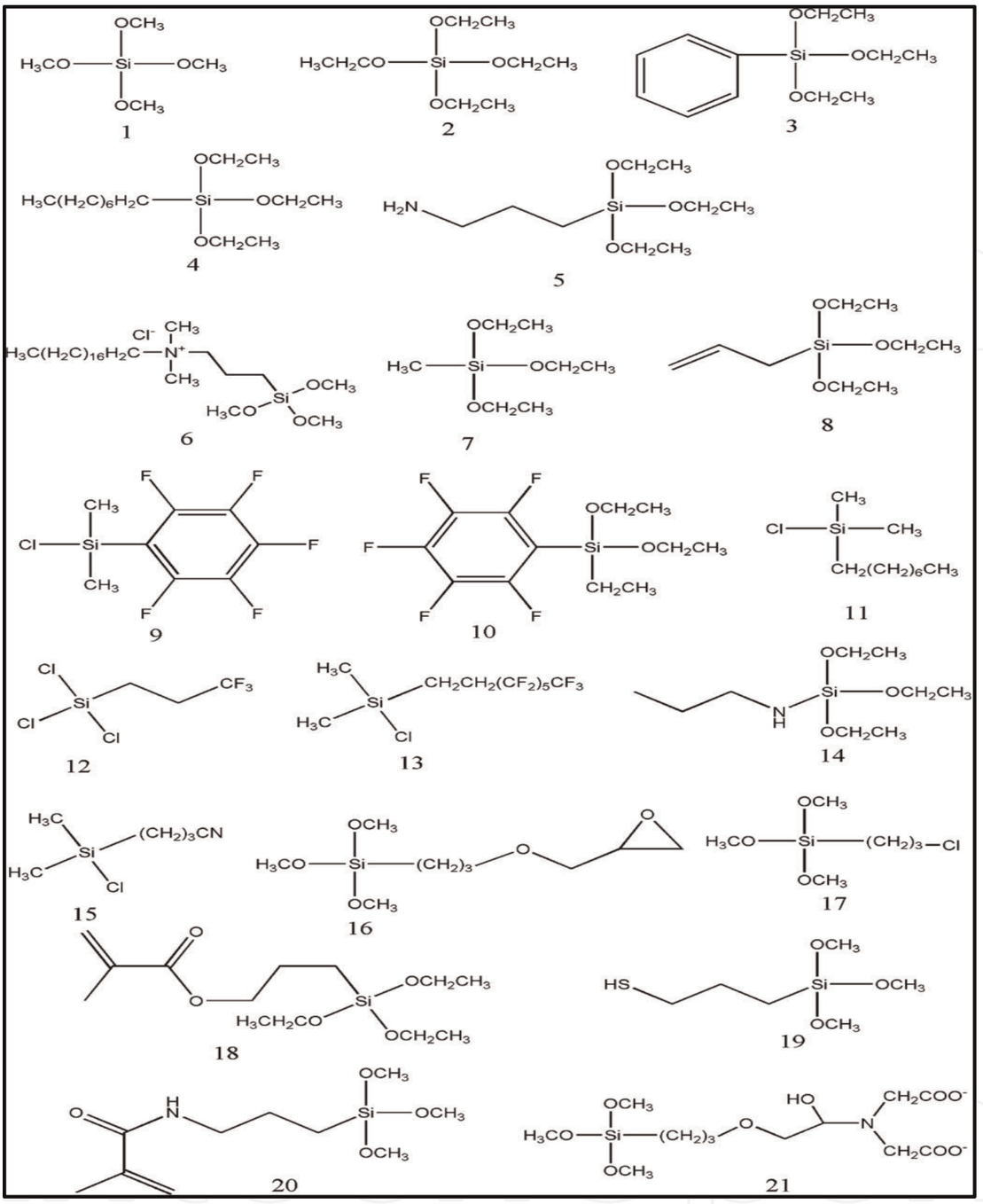

Figure 13.
List of silane reagents for silica-based monolithic stationary phases (Reprinted from Ref. [127]).

7.1 Applications of MOFs in LC

The use of MOFs for the LC separation of compounds, such as various aromatic molecules [145–147], medications [148], dyes [149, 150], pollutants [151], and peptides [152], has attracted a lot of interest. In fact, the early MOF-based HPLC separation of xylene isomers and ethylbenzene employed MIL-47 as the stationary phase. It was then employed to extract styrene and ethylbenzene [153]. Other MOFs that have been proposed as HPLC stationary phases include ZIF-8 [154], MIL-53 [155, 156], MIL-101 [157], MIL-47 [158], and MIL-53 [155, 156]. Direct packing of MOF particles,

on the other hand, led to low separation efficiency, undesired peak morphologies, and large column backpressures due to their irregular forms, sub-micrometer size, and wide size ranges. It can be challenging to regulate the pore size of silica deposition substrates and the synthesis of MOFs [159]. One method utilized to separate xylene isomers, dichlorobenzene, and chlorotoluene isomers, as well as ethylbenzene and styrene, was a MIL-101(Cr) packed column (5 cm 4.6 mm i.d.) [157]. For ethylbenzene, the packed column's efficiency was just 20,000 plates per meter, which is not particularly noteworthy. In comparison to the meta- and para-isomers, the affinities for o-dichlorobenzene and o-chlorotoluene were greater. These early MOF publications frequently omitted the fact that alternative, frequently commercial, LC columns had been able to separate these compounds more effectively for years.

The deposition of MOF thin films onto core-shell silica particles was regulated using a layer-by-layer deposition technique [160]. In this work, MOFs such MIL-101 (Fe) NH2 (Fe3(O)(BDC NH2)3(OH)(H2O)2, BDC = benzene-1,4-dicarboxylic acid, and UiO-67 (Zr6O4(OH)4(BPDC)6, BPDC = 4,4′ -biphenyldicarboxylate) were employed. Mixed-mode liquid chromatography was used to manufacture and analyze metal–organic framework-assisted hydrogel-bonded silica composite microspheres (Zn-BTC MOF, DNs-hydrogel@SiO2) [161]. A more tolerable efficiency for this kind of chromatographic column is 90,300 plates per meter (sucrose). Alkylbenzenes, organic acids, carbohydrates, a few antibiotics, polycyclic aromatic hydrocarbons, insecticides, and anions could all be isolated from nucleosides and their bases (**Figure 14**). All of them have, of course, been readily separable on a variety of commercial stationary phases for many years. A chiral sorbent made of a Zn + 2-based MOF with L-lactic acid ligands was utilized to extract a variety of sulfoxide enantiomers [162]. Additionally, it was utilized in chiral alkyl aryl sulfoxides' traditional LC separation. In open tubular capillary electrochromatography, a different D-(+)-camphoric acid + Zn + 2-based MOF was utilized to separate the enantiomers of flavanone and praziquantel [163]. Additionally, several achiral compounds were isolated. Magnetic particles were utilized in conjunction with another chiral MOF to

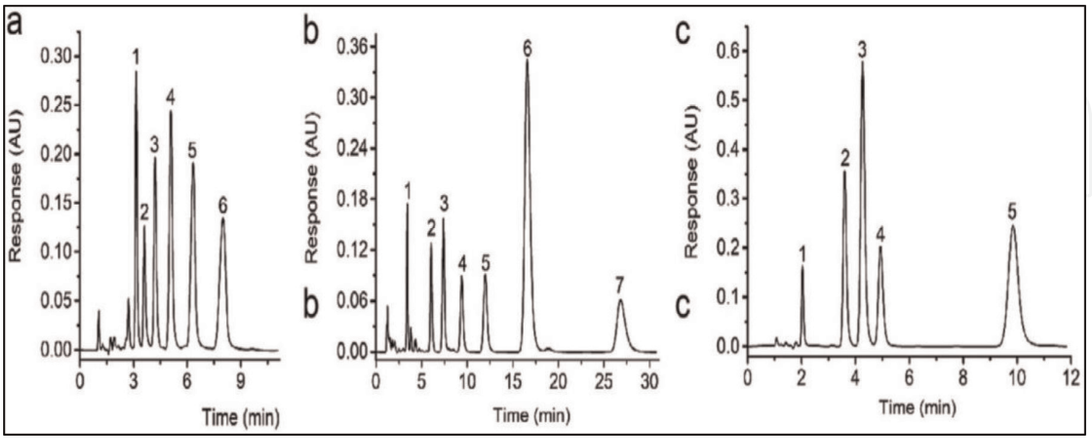

Figure 14.
Chromatograms for the separation of (a) alkylbenzenes, (b) polycyclic aromatic hydrocarbons, and (c) pesticides on DNs-hydrogel@SiO_2 column. Analytes: (a) 1. Benzene, 2. Methylbenzene, 3. Ethylbenzene, 4. Propylbenzene. 5, butylbenzene. 6, Pentylbenzene; (b) 1. Benzene, 2. Naphthalene, 3.2-methylnaphthalene, 4, fluorene, 5. Phenanthrene, 6. Fluoranthene, 7. Benzoanthracene; (c) 1. Flufenoxuron, 2. Meturon, 3. Chlortoluron, 4. Diuron, 5. Diflubenzuron. Mobile phase: (a) ACN/H_2O (40/60, v/v); (b) ACN/H_2O (38/62, v/v) and (c) ACN/H_2O (35/65, v/v). UV detection at 254 nm. Column temperature: 25°C. flow rate: 1.0 mLmin-1 (Reprinted from Ref. [161]).

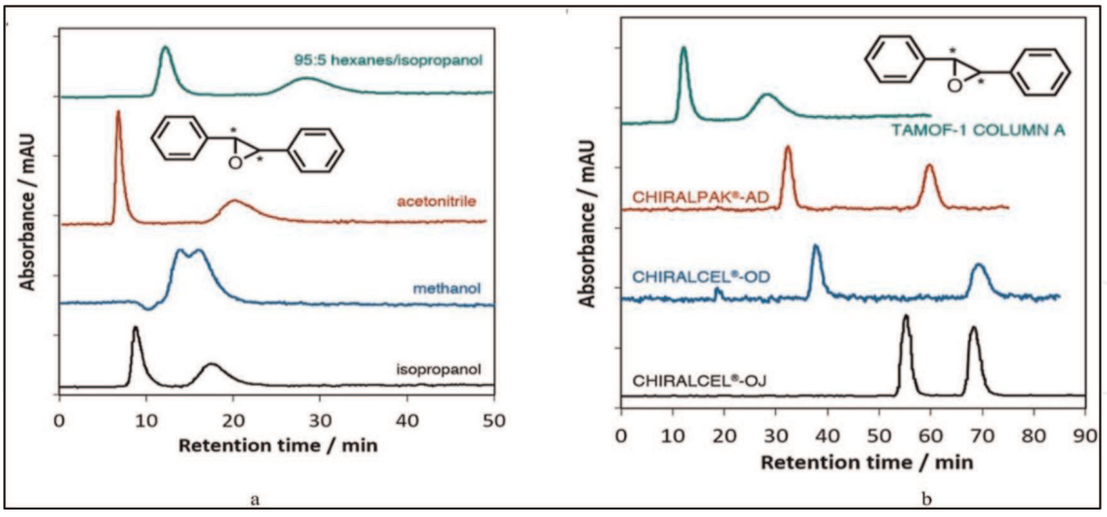

Figure 15.
Representative chromatograms for the separation of trans*-2,3-diphenyloxirane enantiomers with HPLC column packed with TAMOF-1: (a) separation with different mobile phases using column A: Isopropanol, methanol, acetonitrile, and 95:5 hexanes/isopropanol (v/v). (b) Comparison with commercial columns CHIRALPAK®-AD, CHIRALCEL®-OD and CHIRALCEL®-OJ in 95:5 hexanes/isopropanol (v/v) (Reprinted from Ref. [165]).*

enantioselectively enrich an enantiomeric pharmacological intermediate from the solution [164].

It has been claimed that the porous and durable homochiral (MOF) TAMOF-1, which was made from copper (II) and a natural L-histidine linker, can separate a few racemic combinations, including several medications [165]. There have been claims that it performs better than some commercial HPLC chiral columns, but the outcomes do not appear to back up even this extremely superficial comparison (**Figure 15**). For the enantioseparation of 18 racemates, including alcohols, phenols, amines, ketones, and organic acids, a similar homochiral D-his-ZIF-8@SiO2 composite was tested [166]. The separations were carried out using n-hexane/isopropanol as the solvent in the standard phase mode. For reversed phase separations in capillary electrochromatography, a monolithic column made of 1-allyl-methylimidazolium chloride (AlMeIm + Cl-) copolymerized with ZIF-8 was utilized [167]. This method produced monolithic columns that were used to separate neutral chemicals, anilines, and phenols. The performance of the column efficiency was improved by the synergistic interaction between the ionic liquid and ZIF-8. The maximum column efficiency was found in toluene, which measured 2.07×10^5 theoretical plates m^{-1}.

7.2 Applications of nanoparticle-based monoliths

7.2.1 Gold nanoparticles

Due to their simple and inexpensive synthesis, huge surface area, molecular recognition properties, and compatibility with living things, gold nanoparticles (GNPs) are among the nanomaterials that have been the subject of the most research. GNPs have been used in a variety of contexts and are receiving more interest in the monolithic sphere. A new silica monolithic stationary phase functionalized with octadecanethiol GNPs for CEC was created by Ye *et al*. [168]. In response to neutral solutes, the resulting GNP-modified silica monolith displayed normal reversed-phase

electrochromatographic activity. Due to the great affinity of gold for these moieties, GNPs can be covalently linked to surfaces containing amino, thiol, or cyano functionalities [169]. A-glucosidase was then easily and stably immobilized onto GNPs due to the strong affinity between gold and enzyme amino groups, which was achieved by the same group [170] by covalently attaching GNPs to the surface of a polymer monolith *via* the creation of an Au-S bond. Additionally, silica monoliths coated with bovine serum albumin-gold nanoparticles (BSA-GNPs) conjugate were reported to be employed as chiral stationary phases for the CEC enantioseparation of various phenylthiocarbamyl amino acids [171]. Lv and colleagues [172] created a novel method for creating porous polymer monoliths with improved GNP coverage of pore surfaces. This method considerably improved the immobilization of GNPs, and it was discovered that the density of pore surface covering was significantly influenced by the size of the GNPs. As a "universal" intermediate ligand, the surface of the attached gold was subsequently functionalized with 1-octanethiol and 1-octadecanethiol to produce the desired monoliths for the separation of proteins in reversed-phase mode. In **Figure 16**, three proteins are separated in a gradient of acetonitrile (ACN), with the order of elution determined by the hydrophobicity of the proteins. Monoliths modified with 15, 20, and 30 nm NPs provided the best separations because these sizes produced the densest covering of the pore surface with GNPs. The combination of GNPs attached by layered architecture to hypercrosslinked polymer-based monoliths and functionalized with hydrophilic properties was initially described by the same group [173]. With its use in the separation of tiny polar analytes, such as nucleosides and peptides, under hydrophilic interaction chromatographic conditions, this effective monolithic stationary phase was proven.

7.2.2 Silver nanoparticles

The advantages of silver nanoparticles (AgNPs) over other nanostructured metal particles, such as their advantageous electrical conductivities [174], antibacterial activities [175], and optical properties [176], are well established. Monolithic columns with embedded AgNPs were created and tested in order to combine the unique properties of AgNPs with monoliths [177]. Investigated how the presence of AgNPs affected the polymer matrix's morphological and chromatographic characteristics. AgNPs have a very strong affinity for the anions of heavy halogenides like astatide and iodide. In order to remove these constituents from solutions, AgNPs may, therefore, be a great candidate [178]. The creation of a macroporous monolithic column with anchored AgNPs for the removal of extra radioiodine from a radiolabeled pharmaceutical was demonstrated by Sedlacek et al. [179].

7.2.3 SiO_2/TiO_2 nanoparticles

As a result of their better chemical affinities and amphoteric characteristics, metal oxides have been introduced into monolithic structures with increasing effort. Although TiO_2 has received the greatest attention and is the most often utilized metal oxide, few research studies have successfully created monolithic capillary columns made entirely of pure TiO_2 [180, 181]. Without a doubt, creating monoliths based on TiO_2 presents a number of difficulties. Additionally, according to several related reports, SiO_2/TiO_2 composite materials outperform pure TiO_2 materials in the enrichment of phosphorylated targets [182–184]. Wang *et al.* [185] developed a facile sol–gel method for preparing a novel SiO_2/TiO_2 in-capillary composite monolith under mild

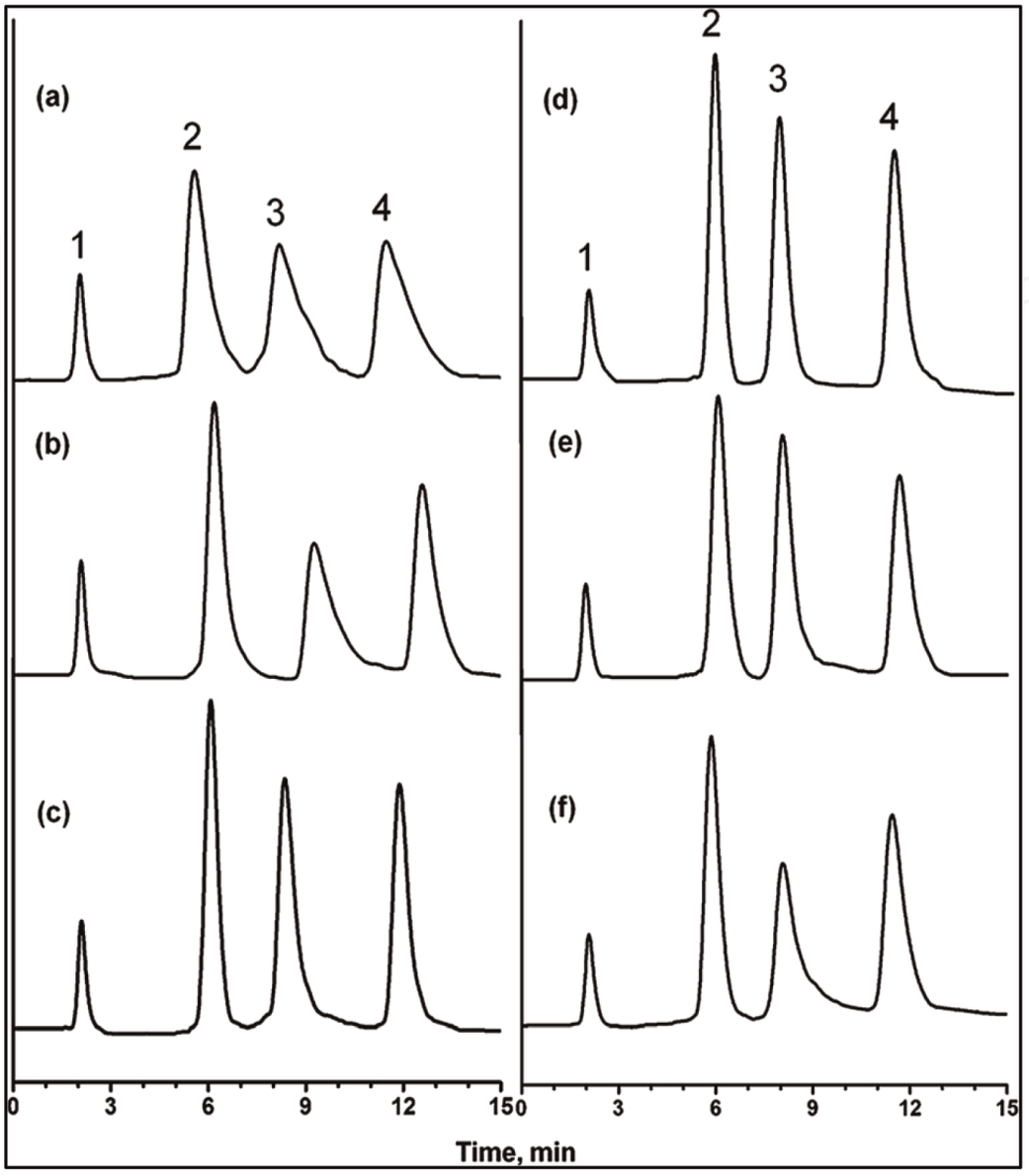

Figure 16.
Reversed-phase separation of proteins using monolithic columns containing GNPs modified with 1-octanethiol. Conditions: Columns: (a) 5 nm GNP, 100 mm × 100 mm I.D.; (b) 10 nm GNP, 110 mm _ 100 mm I.D.; (c) 15 nm GNP, 110 mm × 100 mm I.D.; (d) 20 nm GNP, 108 mm × 100 mm I.D.; (e) 30 nm GNP, 80 mm × 100 mm I.D.; and (f) 40 nm GNP, 89 mm × 100 mm I.D.; mobile phase: A 0.1% aqueous trifluoroacetic acid, B 0.1% trifluoroacetic acid in ACN, gradient from 20 to 70% B in A in 20 min, flow rate: 1.0 ml min^{-1}, injection volume: 10 nl, detection wavelength: 210 nm. Peaks: (1) impurity from ribonuclease A, (2) ribonuclease A, (3) cytochrome C, and (4) myoglobin (Reprinted from Ref. [172]).

conditions, which was successfully applied to specifically capture phosphopeptides as a metal–oxide affinity chromatography material.

7.2.4 Zirconia nanoparticles

Zirconia is a desirable and appropriate substitute for silica as the support, primarily due to its exceptional and one-of-a-kind chemical, mechanical, and thermal stabilities [186–188]. The benefits of zirconia NPs include the fact that they are stable at temperatures up to 200°C and exhibit no discernible evidence of disintegration over a wide pH range. Zirconia-based stationary phases can avoid certain notable limitations

of silica-based stationary phases, such as restricted use in a constrained pH range and temperature range. Zirconia's distinct surface chemistry, meanwhile, expands the range of chromatographic separation applications [189]. A porous zirconia monolith (ZM) modified with cellulose 3,5-dimethylphenylcarbamate (CDMPC) was created by Kumar and Park [190] and employed as a chiral stationary phase for the CEC separation of a group of fundamental chiral chemicals.

Subsequently, they reported other zirconia-based chiral stationary phases for the CEC separation of β-blockers [191], chiral acids and bases [192], basic compounds [193], and other chiral analytes [194].

7.2.5 Silica nanoparticles

Liu *et al.* [195] developed a novel cage-like silica NP-functionalized silica hybrid monolith based on the "one-pot" method using thiolene click chemistry. The resulting hybrid monolithic column was characterized and evaluated, and the results showed that it possessed homogeneous macroporous morphology, high permeability, and a strong EOF throughout a wide pH range from 2.7 to 11.2. On the constructed monolith, anilines and phenols were effectively separated by CEC, and 2-aminophenol demonstrated the best theoretical efficiency of 470,000 N m^{-1}. Reversed-phase and cation-exchange interactions served as the basic foundation for the retention mechanisms. In order to create organic-silica hybrid monoliths, this work illustrated a novel technique for directly integrating modified nanoparticle monomers.

8. Challenges and future trends

There is still a need for additional work to design distinct inventive NP-based monoliths for various particular applications. The majority of pertinent studies in this sector are, however, still in their infancy, and study in this area has only lately begun, thus there are still many restrictions and difficulties. The issue with characterization is the first worry. It will take further work to fully characterize the substrate, including its chemistry, functional surface, and stability. Because most separation mechanisms are still not fully known, a further obstacle lies in the extensive research in theoretical studies. Furthermore, there is still significant work to be done to ensure their reliable and repeatable production in actual applications, as opposed to only for standard separations. Studies on NPs are still ongoing, with a focus on how they can be used in monolithic matrices for chromatographic separations. These studies aim to control the selectivity of the separations as well as the overall performance of the chromatography by designing and synthesizing highly selective interaction sites on the surfaces of NPs and functionalizing monolithic matrices with a wider variety of NPs bearing different functional groups. In-depth research should also be done on the creation of new functionalization techniques that enable the encapsulation of a greater number of NPs in the polymerization mixture. Additionally, it is important to note that research on innovative organic–inorganic hybrid monolithic columns containing NPs is still in its infancy. Instead, the majority of recent investigations have mostly focused on porous polymer monolithic stationary phase as the matrix for functionalization with NPs. Further research into these NP-modified hybrid materials is therefore necessary in order to uncover novel solutions to some long-standing issues and provide fresh ideas for expanding the extensive application of NPs in chromatography.

Significant advancements have also been made in the functional applications, controlled synthesis, and structural design of MOFs. However, their lackluster stability and exorbitant price restrict their usefulness. MOFs with porous or nonporous silicas can be combined to improve stability and characteristics, and the resulting composites can be used for a variety of applications. Another obstacle is the lack of commercially accessible MOF-based materials for dynamic LC separations, but given how quickly this subject is developing and how many studies have been done in this area, this may not be too far off from becoming a reality. Industry demands that stationary phases be stable in the presence of both water and organic solvents. Additionally, a greater study is required on MOF properties and the variables affecting them. Future research should concentrate on improving existing models that are applicable to MOF synthesis circumstances and creating computer tools that will help researchers improve the conditions and take other elements into account.

9. Concluding remarks

Due to the distinctive qualities of the porous monolithic method, such as simple production, superior permeability, and quick mass transfer, monolithic matrices have attracted increasing interest in the field of liquid chromatographic separation. Monolithic stationary phases have been extensively used in hyphenated systems coupled with mass spectrometers, miniaturized devices, and quick and high-efficiency one- and multi-dimensional separation systems. The separation of complex biological materials using columns is being revolutionized by new monolithic stationary phase preparation technologies. Direct synthesis is a convenient and versatile route to prepare the monolithic columns for microscale separation. Whereas obtaining desired monoliths with chromatographic properties is not easy to succeed because of the complexity of direct synthesis. Compared to the direct synthesis, the post-modification or post-functionalization of monoliths certainly represents a complementary and flexible technique for the preparation of monolithic stationary allows complete independent control of the porous properties.

For the separation of complicated biological samples, such as complex mixtures of peptides for proteome analysis and/or enantiomers, monolithic columns with longer lengths, smaller inner diameters, and specialized selectivity to peptides or enantiomers will play a crucial role in hyphenated systems. A new field of study in the field of chromatographic separation science has been made possible by the invention of monolithic stationary phases, which is now playing a considerably more significant role in a wide range of application areas. In comparison to other carriers like inorganic porous solids (mesoporous silica) or organic polymers, MOFs or coordination polymers have many advantages for the adsorption and release of biomolecules because of their tunable composition, structure, pore size, and volume, easy functionalization, flexible network, and/or accessible metal sites. By selecting the right metal, linker, and structure, one can alter the biodegradable properties of these materials, causing a degradation in body fluid that can last anywhere from a few minutes to many weeks. Even if actual porosity "BioMOFs" are still hard to come by, endogenous linker-based MOFs are one of them and are of particular interest. Making a bioactive MOF with the drug as the linker and releasing the drug through the degradation of the MOF is an alternative method of releasing large amounts of drugs. You can also use a bioactive metal (Ag, Zn, Ca, Mn, Gd, Fe, etc.) as the inorganic cation to add extra properties like antibacterial activity or imaging properties.

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Declaration of competing interest

The authors declare no conflict of interest.

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