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### Materials and devices for spatial multi-dimensional liquid chromatography

Passamonti, M.

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# **Chapter 6**

*Concluding remarks and future prospects*

## **Abstract**

In this chapter, ideas for future development are described.

Developments in the 3D-printing materials explored in the first chapter of this thesis are presented. The improved design of a two-dimensional microfluidic device is shown and described. Finally, alternative stationary phases are suggested. Specifically, hypercrosslinked and hybrid monoliths are explored. Another possible approach based on the 3D-printing of monolithic stationary phases and direct integration within the channels of complex microfluidic devices is described.

## 6.1 3D-printing materials: glass, PEEK, titanium

In this work, several materials were explored for 3D-printing microfluidic devices. The potential of glass as construction material is very high. Our efforts to 3D-print glass devices have been described in Chapter 1. The process proved time-consuming and often failed process. This shed doubt on this option with the current state of technology. In recent years, glass has been used for creating microfluidic devices using an etching process. This is a simpler process, and it has been proven successful, although complex three-dimensional structures may be harder to design and construct than with 3D-printing. Also, 3D-printing can often be performed in-house, allowing faster prototyping. In recent years, Kots *et al.*<sup>1</sup> founded a company (Glassomer), which offers resins to 3D-print glass pieces. They also offer 3D-printed pieces on demand. A commercial resin is often synonymous to higher repeatability.

Another challenging, but potentially attractive material is PEEK. Possibilities for 3D-printing of this material have developed enormously in the last years. Better 3D-printers and 3D-printing processes have been developed. Our own efforts to print in PEEK have been described Chapter 1. The pieces that we prepared tended to be quite brittle. Commercial 3D-printed PEEK pieces are thought to be less brittle. As of today, 3D-printed PEEK pieces are used for missions of the European Space Agency (ESA). Such high-quality pieces require very expensive 3D-printers, but pieces can be printed on demand for a reasonable price.

3D-printing in titanium was the most successful option we pursued. However, as highlighted in Chapter 2 and Chapter 5, there are some points that still require improvements. In the research described in Chapter 2, a higher printer resolution would have allowed the construction of thinner walls within the heating-cooling-jacket (HCJ) device. This would have resulted in a better heating exchange between the jackets and the channels. In our case, this would have allowed sharper transitions between monoliths and empty spaces. However, the higher density of the monolith in the transition zone is likely to remain a problem, as it is characteristic of every polymerization process for creating a monolith, even in narrower channels.

Another possible improvement relies on the size of the titanium particles melted by the laser in the 3D-printing process. Smaller particles will result in smoother surfaces. Packing particles in channels could then be more successful because fewer airgaps would be formed, and more-uniform packing beds are expected to result. According to Sandron *et al.*<sup>2</sup>, it is possible to reach high plate counts only when using silica particles with sizes similar to the surface roughness of the 3D-printed titanium device. In order to verify these potential improvements, micro-selective-laser-melting ( $\mu$ SLM)<sup>3</sup> may be employed as 3D-printing technology to create “actual” microfluidic devices (*i.e.*, devices with sub-mm channels).

## 6.2 Development of multi-dimensional microfluidic devices

In the research described in Chapter 5, several microfluidic devices for multi-dimensional separations were explored. Several approaches were studied to confine flows to specific channels during a multidimensional separation. The freeze-thaw-valve (FTV) approach seems to be the most-feasible and most-universal approach. The simple liquid transfer (SLIT) approach, even if it proved a valid option for the transfer of fractions from the 1D channel to the 2D domain, does not seem to be applicable to a third

dimension. Moreover, a device consisting of multiple pieces is more cumbersome and more prone to leakages. Finally, the approach to create zones with greatly different permeabilities seems feasible based on the results of computational-fluid-dynamics studies. Unfortunately, the approach was found to have some significant drawbacks in practice. Introducing stationary phases with permeabilities that differed by three orders of magnitude between the  $^1\text{D}$  and  $^2\text{D}$  channels is far from easy. Moreover, the repeatability of all processes to create stationary phases, either through packing particles or through the creation of monoliths by *in-situ* polymerization, has proven poor, especially in devices with rough internal surfaces.

Below, is a design of a microfluidic device to perform spatial 2D-LC separations, which we call Ultimate COSMIC.

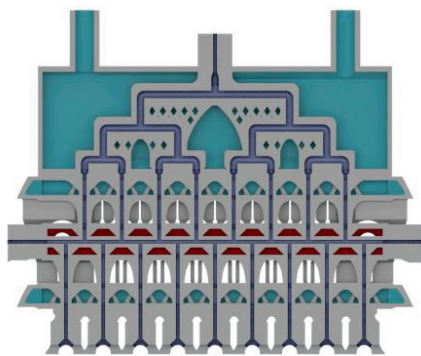


Figure 1. CAD design of the Ultimate COSMIC

This design is based on combining all the information gathered over the past four years. In the COSMIC-2D device, the  $^1\text{D}$  channel, the flow distributor (FD) and the  $^2\text{D}$  channels were geometrically closer compared to the ones in the COSMIC. Moreover, due to the 3D-printing process, several supporting structures had to be created. This proximity of the different parts and the supporting structure, and the smaller dimensions of the COSMIC-2D rendered the ratio between area and volume unfavourable for the formation of the frozen plugs needed to confine the flow. In this final design, we restored the correct ratio, also taking into account the supporting structures. Another important feature was added to this final design, *i.e.*, a jacket around the FD. Creating a stationary phase in the FD, for example through thermal polymerization, may help to confine the flow in the  $^1\text{D}$  channel, making the FTV approach more robust. Finally, the internal cone created for the inlets and outlets of our device was corrected to obtain a favourable angle of  $45^\circ$ . This new design of the connections was first introduced in SLIT pieces, and these proved less prone to leakage.

### 6.3 Materials for stationary phases

Nowadays, particles are the most-used stationary phase in LC. They are commercially available and show a wide range of selectivities and functionalities. While packing cylindrical housings has been widely investigated, the introduction of a homogenous bed of particles in complex microfluidic devices lacks experimental data. In the past four years, only two scientific articles explored possible ways to pack and

confine particles in the complex types of microfluidic devices that are of interest for the STAMP project. Roca *et al.* showed how to achieve a homogeneously packed cuboid bed, while Abdulhussain *et al.* relied on the presence of tapered outlets and the creation of monolithic frits to confine the particles. The latter could be photo-polymerized *in-situ*, thanks to the use of a transparent device. In order to use monolithic frits in opaque devices, the approach described in Chapter 2 and applied in Chapter 5 could form an alternative. However, these methods are quite complex not highly repeatable. Overall, more effort should be devoted to this topic, because particles remain the most efficient LC separation media. However, as of today, the *in-situ* creation of monoliths is a much simpler method to introduce stationary phases within confined regions of a microfluidic device. Monoliths have their limits, such as narrow pH range (silica monolith), limited surface area (polymer monoliths). Polymer monoliths are easiest to prepare, but they typically do not perform well in the separation of small molecules while their mechanical stability is modest. In the last 10 years, hypercrosslinked and hybrid monoliths have become more and more popular, because they address these limitations. Hypercrosslinked monoliths were introduced by Davankov *et al.*<sup>4</sup> They were prepared by first creating linear polymer chains, and subsequently cross-linking these through Friedel-Craft alkylation. Urban *et al.*<sup>5,6</sup> used hypercrosslinked monoliths to create LC columns with a surface area of 663 m<sup>2</sup>/g and a large fraction of stagnant pores, allowing separations of polystyrene standards under size-exclusion chromatography conditions. Such an approach may be used in a complex microfluidic device. First, the same polymer backbone structure can be prepared throughout the device. Subsequently, this structure could be chemically modified in the different regions (dimensions), to provide the orthogonality required.

Hybrid monoliths are another valid option. They consist of a silica backbone functionalized with organic moieties. Such monoliths combine the advantages of silica and polymer monolith, yielding a good mechanical strength, high surface area, easy preparation, and, importantly, a good chromatographic performance. They can be created using three different processes *viz.* the sol-gel approach, the “one-pot” approach, the free-radical polymerization. The sol-gel process proposed by Nischang *et al.*<sup>7</sup> uses polyhedral vinyl-silsesquioxane as the sole monomer to create materials with high surface areas and both macro- and mesopores.

In the “one-pot” approach a polycondensation of silane compounds is followed by the polymerization of the organic moieties in the presence of supramolecular template. By using this approach with two different organic monomers, Wu *et al.*<sup>8</sup> created a mixed-mode (hydrophilic and hydrophobic) monolith to separate peptides.

Free-radical polymerization is extensively used to create polymer monolith due to its simplicity. Following this method, Wieder *et al.*<sup>9</sup> created a monolith by using *p*-methylstyrene and bis(vinylbenzyl)dimethylsilane as monomers. This material exhibited high mechanical stability and high separation efficiency.

Finally, it is the author’s belief that incorporating different stationary phases in an already-built microfluidic device will always be challenging and is likely to involve a certain lack of repeatability. However, 3D-printing could enable the production of highly ordered stationary phase, as demonstrated by Fee *et al.*<sup>10</sup> In recent year, new materials have been developed to 3D-print stationary phases. Simon *et al.*<sup>11</sup> developed a material to 3D-print highly order monolithic columns containing anion exchange

functional group in one step. The possibility of 3D-printing multi-materials objects enables the creation of complex microfluidic devices integrating highly ordered stationary phase. The STAMP project could be fuelled by the future development of 3D-printing technology and achieve the full potential.

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