Crosslinking Density in Imprinting Polymerization

Subjects: Polymer Science

Contributor: Anja Mueller

The crosslinking density of a material determines its physical properties, such as the porosity of the material. In imprinting polymerizations, the porosity determines access to internal binding sites and thus the capacity of the imprinted material. This entry is about effect of the commonly used crosslinking density in imprinting polymerization for a variety of applications.

molecularly imprinted polymer | MIP | crosslinking density | specific binding

1. Introduction

Imprinting polymerization is an exciting technique: By just adding one additional step to the synthesis of a common polymer, a material can be made specific to a chemical. Basically, that chemical, the template, is added to the synthesis solution. The monomers will surround the template automatically and form the strongest bonds possible, since thermodynamically that happens to be the lowest energy state and thus is preferred. The monomers will then be polymerized and crosslinked, and with that the three dimensional structure with the strongest bonds to the template will be conserved. The additional step is to remove the template. This results in a pocket ideal for rebinding the template [1].

How useful specific binding is can be seen in biochemistry. A cell contains a large number of compounds and intermediates, but despite that, enzymes choose one specific compound to react without any side products, simply by providing a very specific binding site. In organic chemistry that is only possible in very few cases with complicated, many-step syntheses resulting in low yields. Another example are antibodies that recognize one specific compound on the surface of pathogenic bacteria to then destroy those bacteria and thus prevent a possible deadly infection. Imprinting polymerization promises specific binding to allow for analogous applications in technology.

Early proof-of-concept for the specific binding with imprinting polymerization came from Mosbach's group [2][3]. One of the earliest applications that implemented molecularly imprinted polymers (MIPs) was the separation of chiral compounds using chiral solid phases in column chromatography [4][5]. At this point, MIPs are used in many different applications. Broadly, they can be grouped into two categories: Detection and sensing for a variety of compounds, from contaminants to proteins in cells [6][7][8][9][10][11][12][13][14][15][16][17][18] and extraction and purification of compounds from environmental and biological samples [19][20][21][22][23][24][25].

The crosslinking density of a material determines its physical properties, such as the porosity of the material. In imprinting polymerizations, the porosity determines access to internal binding sites and thus the capacity of the imprinted material. The aim of this work is to analyze the effect of the commonly used crosslinking density in imprinting polymerization for a variety of applications. This will be accomplished by selecting current examples of imprinting polymerization and correlating the details of their syntheses with MIP capacity and polymer science data. This will not be a comprehensive review of imprinting polymerization. In fact, only a small number of studies of the vast imprinting polymerization literature will be used.

2. Common Syntheses for Imprinting Polymerizations

Imprinting polymerization generally uses a similar synthesis: A “functional monomer” is selected that is effective in binding the template, the “structural monomer”, which is the crosslinker, is chosen to match the polarity needed for the reaction and possibly also to bind to the template. A solution with the template and monomers is given time to bind to each other, then the initiator is added to the mixture and the polymer is formed. After isolating the polymer, the template is removed [1]. This results in specific binding sites that allow for the specific binding that differentiates imprinted polymers from non-imprinted resins [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26].

Most commonly, imprinting polymerization is based on non-covalent forces, but covalent and semi-covalent imprinting has also been reported [27]. There are variations in where the imprinting occurs (bulk imprinting or surface imprinting [28]), as well as what materials are used (polymeric materials, inorganic materials [29] or hybrid materials [30][31]). In this work, the focus is on either bulk or surface imprinting in polymeric materials.

Looking at bulk imprinting of polymeric materials in more detail, the ratio between the template, functional monomer, and crosslinker is important [32]. The amount of functional monomer is directly related to the amount of template since there has to be sufficient functional monomer to interact with all of the template molecules. The crosslinker then fixes the three-dimensional structure that binds the template most effectively. An effective ratio between template:functional monomer:crosslinker has been identified as 1:4:20 [32]. This has been used in the following syntheses as the starting point for optimization of the system and the application in question [33].

Surface imprinting was developed due to two common problems that were found with bulk imprinting, the difficulty to remove all templates after MIP synthesis, and the difficulty to access internal binding sites [34]. In surface imprinting, the MIP is commonly prepared as a coating onto a hard particle. The starting ratio of template:functional monomer:crosslinker is also 1:4:20 [34].

3. The Effect of Porogen and Crosslinking on Imprinted Materials

In this work, specifically the ratio between the functional monomer and crosslinker is highlighted since that determines the physical properties of the resulting MIP. That ratio also determines the number of accessible

binding sites. **Table 1** lists the ratio and the total capacity for a variety of examples in recent literature. A large majority is based on the 1:5 ratio described in the preceding section.

Table 1. Functional monomer ratio and total capacity for MIPs for a variety of applications cited in selected recent literature.

Monomer:Crosslinker Molar Ratio	Template Crosslinker	Maximum Capacity (mg/g)	Comments	Reference
1:2.7	UO_2^{2+} EGDMA [2]	125	Bulk imprinting BET A[2] 670 m^2/g, pore vol. 1.439 mL/g, avg. pore Ø 2.2 nm [1] Adsorption dependent on pH, initial conc., regeneration	[35]
1:5	Cu(II) Pentaerythrol triacrylate [3]	2.16	Bulk imprinting BET A[2] 6.7 m^2/g, pore vol. 0.0088 mL/g, avg. pore Ø 5.2 nm [1]	[36]
1:4.5	Extracellular matrix peptides Pentaerythrol triacrylate [3]	49.55	Bulk imprinting Most templates trapped	[37]
1:3, 1:5	Serotonin reuptake inhibitors EGDMA [2]	27.3	Bulk imprinting BET A[2] 193.8 m^2/g, pore vol. 0.37 mL/g, pore Ø 7.7 nm [1]	[38]
1:3, 1:4, 1:5	Sarafloxacin EGDMA [2]	58.6	Bulk imprinting Several functional monomers More crosslinking, less capacity	[39]
1:4 to 1:20	Sialic acid EGDMA [2]	24.7	Bulk imprinting Specialized acrylates 1:4 highest capacity	[40]
1:2.5	Sulfonylurea pesticides Divinylbenzene	1.6	Bulk imprinting BET A[2]: 409.7 m^2/g [1]	[41]
1:4	2-(3,4-dimethoxyphenyl)ethylamine Trimethylopropane trimethacrylate [3]	24.5	Bulk imprinting Optimized crosslinker and porogen	[42]

Monomer:Crosslinker Molar Ratio	Template Crosslinker	Maximum Capacity (mg/g)	Comments	Reference
1:0.38	Atrazine EGDMA [2]	3.45	Bulk Imprinting Investigating porogen BET A^2 237.5 m^2/g, pore vol. 0.0268 mL/g, pore Ø 0.57 nm [1]	[43]
1:5	4-Hydroxy-3-nitrophenylacetic acid EGDMA [2]	0.106	Bulk Imprinting Porogen, pore structure, and sorption investigation	[44]
1:5	Chloramphenicol EGDMA [2]	64.3	Surface imprinting, hollow rods 1–3 µm long, Ø 50–180 nm [1]	[45]
1:4.5	Peptide EDMA [4]	76.9	Surface imprinting, hollow	[46]
1:1.2	Cytidine EGDMA [2]	33.39	Surface imprinting, magnetic MIP BET A^2: 980 m^2/g [1]	[47]
1:2.5, 1:5	$Cd(NO_3)_2$ $EGDMA^2$	32	Membrane Less crosslinking, more adsorption Less imprinting molecule, less adsorption	[48]
1:1	Acteoside $EGDMA^2$	62.83	Surface imprinting, membrane	[49]
1:1.3	$Cd(NO_3)_2$ Ethylene diamine	250.7	Surface imprinting Surface crosslinking only BET: A^2 192.2 m^2/g, pore vol. 0.052 cm^3/g, pore Ø 113 nm [1]	[50]
1: 0.68	Sulfa-methoxasole EGDMA [2]	20.0	Surface imprinting, magnetic MIP Computational study	[51]
1:0.44	Sulfonamides EDMA [4]	0.559	Surface imprinting, magnetic MIP Hybrid with silicon	[52]

Monomer:Crosslinker Molar Ratio	Template Crosslinker	Maximum Capacity (mg/g)	Comments	Reference
1:4	Pseudohepericin EDMA [4]	450	Hollow particle Prepared by emulsion polymerization Inner Ø ca. 30 µm [1]	[53]
1:5	Estrogens EGDMA [2]	12.1	Hollow particle Ca. 250 nm inside Ø [1]	[54]
1:5	Celecoxib EGDMA [2]	43.29	Hollow particle	[55]
1:0.2	Cr(VI) Trimethylopropane trimethacrylate [3]	66.6	Bulk imprinting BET: A^2 4.78 m^2/g, pore vol. 0.00554 cm^3/g, pore Ø 2.35 nm [1]	[56]
1:0.0079	(S)-Naproxen EGDMA [2]	127	Surface imprinting, magnetic MIP Enantioselectivity 4:1	[57]
1:2.5	Quinine Trimethylopropane trimethacrylate [3]	15.38	Start with colloidal silica crystal microsphere Coat MIP on porous crystal, then remove crystal BET: A^2 216 m^2/g, pore vol. 0.66 cm^3/g, avg pore Ø 12.2 nm	[58]
1:1.05	Artimisin 3-Aminopropyltriethoxysilane	45.89	Start with polydopamine as the core Coat imprinted Si around by the sol-gel method Phase inversion, then cast as membrane	[59]
1:0.005	Cd(II) EGDMA [2]	950	Bulk Imprinting Increased porosity by bubbling N through the reaction	[60]

[1] A^2: Surface area; Ø: Diameter. [2] Ethylene glycol dimethacrylate. [3] Trifunctional crosslinker. [4] Ethylene dimethacrylate.

It is common to use porogens to increase the surface area and with that the capacity of the imprinted polymers [42–44,61–65]. Most porogens are solvents or solvent mixtures. The solubility of the template, monomer(s), and

crosslinker is one of the major factors determining the surface area [44,63,65]. Using a solvent or co-solvent that is a non-solvent can lead to phase separation. If the phase separation leads to precipitation of the complex or the polymer, that generally leads to reduced surface area [42,44,63]. If the non-solvent creates an emulsion, that can lead to cracks or pores, which often increase the surface area [42]. An effective way to increase the surface area is to use a solid porogen, usually a salt particle that can later be dissolved and washed out [61,62]. Insoluble polymers have been reported as porogens, as well [61].

When more crosslinkers than monomers are used, each repeating unit of a polymer chain is connected to its neighbors as well as to a repeating unit of a different polymer chain. That allows for minimal free volume between each polymer chain, likely with a lot of interspersed crystalline regions. That means that only imprinting sites on the surface are accessible for binding, and trapped templates will not be able to be removed.

This demonstrates another problem that internal imprinted sites have in an MIP: For a template to be able to reach the site, there has to be a continuous channel to that site, as well as a flow of solvent with the template to be able to move into the site and rebind. Especially with water as the solvent, the amount of water around a solute molecule has to be large for an aqueous solution to be free-flowing [61]. Water has shown to be very viscous due to its extensive hydrogen bonding, and around hydrophilic compounds water can be strongly bound or even crystalline [61].

Which brings up another point: The kinetics of reaching binding sites that are on the surface vs. inside a particle. Templates that bind to surface sites can bind quickly, since the binding sites are readily accessible. Templates that bind to internal sites have to move through a viscous solvent in likely bent channels to reach the binding sites. Therefore, the kinetics of binding to internal sites will always be slower than the kinetics of binding to surface sites. And yet, most studies using bulk imprinting report linear binding kinetics.

The combined evidence from polymer science suggests that when more crosslinkers than functional monomers are used, the inside of the particle is extremely dense and the internal binding sites will not be accessible. Essentially, bulk polymerization and surface polymerization will result in the same outcome, as the data in **Table 1** also suggested. In fact, one has to go to very low crosslinking densities (0.5 to 5% of crosslinker) to create materials with accessible internal binding sites.

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