

LETTER

Chemical Imprinting Technology Applied to Analytical Chemistry: Current Status and Future Outlook in Brazil

César Ricardo Teixeira Tarley^{1,2}  

¹Universidade Estadual de Londrina (UEL), Departamento de Química, Centro de Ciências Exatas, Rodovia Celso Garcia Cid, PR 445 km 380, Londrina, Paraná, CEP 86050-482, Brazil

²Instituto Nacional de Ciência e Tecnologia (INCTBio) de Bioanalítica, Universidade Estadual de Campinas (UNICAMP), Departamento de Química Analítica, Cidade Universitária Vaz s/n, Campinas, CEP 13083-970, São Paulo, Brazil

Chemical imprinting technologies based on molecularly imprinted polymers (MIPs) and ion imprinted polymers (IIPs) have been widely applied in different fields of analytical chemistry since their discoveries in 1972¹ and 1976², respectively. MIPs and IIPs are considered biomimetic materials with tailor-made synthetic receptors and are, essentially, obtained by co-polymerization of functional and cross-linking monomers in the presence of a target analyte (a molecule for MIPs and an ion for IIPs). The great advantages of these materials over biological recognition systems include their relatively low cost, quick preparation, and, most importantly, their stability in different media. To date, these biomimetic materials have experienced a rapid development with wide applications in electrochemical sensors, luminescence sensors, separation science, sample preparation, and more specific sensor applications such as surface plasmon resonance (SPR) and quartz crystal microbalance (QCM) sensors. In addition, they have been applied for analysis of samples of environmental, food, and forensic interests, as well as for disease diagnostics.³⁻⁸ Figure 1 depicts the increasing number of published papers per year over the past 20 years on the topic of MIPs and IIPs; as expected, most of these papers are devoted to the chemical imprinting of molecules.

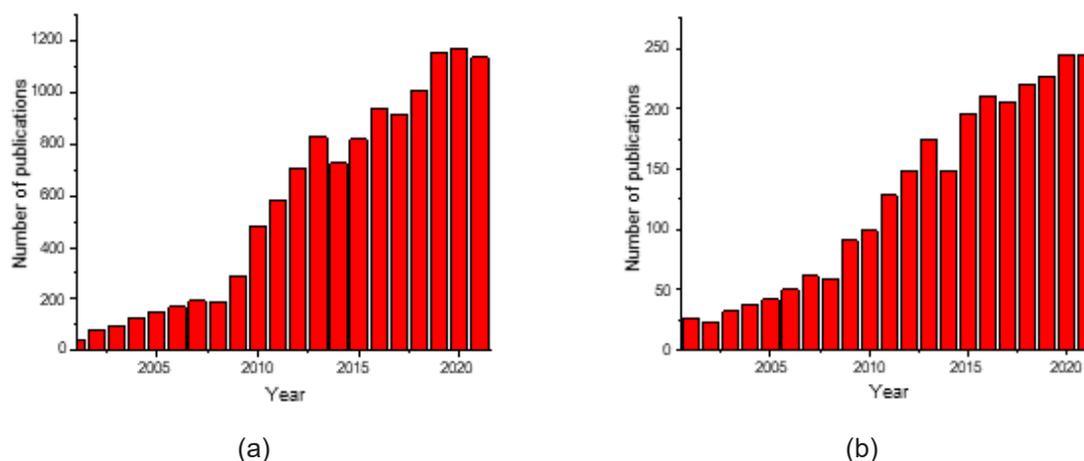


Figure 1. Number of papers published in Web of Science using the keywords (a) “molecularly imprinted polymer” and (b) “ion imprinted polymer”. Retrieved from Web of Science database (2022 March 07).

A literature survey also reveals that MIPs have been most used for sensor preparation (47%), separation techniques (36%), and sample preparation (17%). On the other hand, IIPs have been mostly prepared for separation techniques, including pre-concentration/extraction (62%), while sensor preparation is the second-most common application (38%). These outcomes were obtained using the Web of Science database platform on March 7th, 2022.

Due to tremendous advances in imprinting technology in the scientific literature, scientists and students now have a facile way to carry out rapid research on imprinted polymers on the free-to-use website MIPdatabase, supported by the Society for Molecular Imprinting, where Professor Mike Whitcombe (University of Leicester, UK) serves as webmaster.⁹ This website contains an up-to-date list of papers, books, chapters, patents, reviews, and conference proceedings in the field of imprinting technology.

Success in chemically imprinting polymers in terms of selectivity and stability depends on fully understanding the preparation technologies; therefore, multidisciplinary studies involving scientists with solid knowledge in analytical chemistry, characterization techniques and materials synthesis are indispensable.

Different approaches for MIP and IIP synthesis can be adopted. However, in general, when these materials are applied to separation science, including solid phase extraction-based methods and chromatography, radical polymerization and sol-gel processes have been the most used.¹⁰ Radical polymerization can be carried out in bulk, in which a monolithic morphology material is obtained. However, during the milling process irregular-shaped particles are obtained. To obtain regular-shaped particles, syntheses in heterogeneous media, such as suspensions or emulsions, or homogeneous media, such as precipitation, dispersion or the sol-gel process, have been performed.¹⁰ Aside from these, surface imprinting techniques based on imprinted polymers grafted on the surface of magnetic or carbon-based nanostructured particles (such as carbon nanotubes or graphene oxide) by using the living/controlled "grafting from" polymerization method or exploring free-radical polymerization (FRP) have also been reported.¹¹ These approaches have given rise to materials with high imprinted sites per volume due to the nanoscale imprinted polymer grafted on the surface of the substrate, thereby increasing the availability of selective binding sites and improving the adsorption kinetics. Another way to improve the adsorption capacity of chemically imprinted polymers is by obtaining a more porous material by using structure-directing agents, such as surfactants or non-ionic block copolymer surfactant templates, exploiting the dual-template docking oriented chemical imprinting strategy.¹² This strategy is well-established in obtaining inorganic polymers synthesized by means of the sol-gel method; however, efforts to understand the influence of structure-directing agents in organic imprinted polymers have only been reported more recently.^{13,14}

It is important to emphasize that the use of MIPs and IIPs in complicated matrices, including biological fluids and food samples, is limited due to the adsorption of macromolecules (proteins, carbohydrates, and others) on the surface of the polymers, which hinders the specific recognition of target molecules. For this reason, the synthesis of MIPs and IIPs with restricted access materials (RAM) has been proposed to overcome this drawback. These materials contain hydrophilic functional groups and/or proteins on the external surface with the exclusion properties of macromolecules.^{15,16}

Regarding the use of MIPs and IIPs in electrochemical sensor development, their integration onto the surface of the transducer electrode is of paramount importance for the successful performance of the device. Different synthesis/preparation approaches have been reviewed in the literature, such as electropolymerization; carbon/MIP or IIP paste-based electrodes; and nanocomposites based on graphene and carbon nanotubes, grafted on polymeric matrices using drop-casting for film formation.¹⁷ Additionally, there is a trend in the development of electrochemical MIP sensors using metallic nanoparticles (NPs) such as gold or silver for improving sensitivity, and quantum dots (QDs) or carbon dots (CDs) for optical sensing applications.¹⁸

One important issue that must be considered in the development of chemically imprinted polymers is the presence of selective binding sites. It is known that adsorption capacity and surface area do not have a direct relationship with the presence of selective binding sites, since these features can be influenced by

the porogenic solvent. Therefore, the selectivity should be determined from competitive rebinding studies using the chemically imprinted polymer and the non-imprinted polymer (NIP), followed by the determination of distribution (K_d), selectivity (k), and the relative selectivity (k') coefficients, as shown in Equations 1–4.¹⁹

$$K_d = \frac{(C_i - C_f) V}{C_f M} \quad (1)$$

where C_i and C_f are the initial and final concentration of target analyte (template) and concomitants, V is the solution volume, and M is the mass of MIP and NIP;

$$k_{MIP} = \frac{K_d(\text{template})}{K_d(\text{structurally similar concomitant})} \quad (2)$$

$$k_{NIP} = \frac{K_d(\text{template})}{K_d(\text{structurally similar concomitant})} \quad (3)$$

$$k' = \frac{k_{MIP}}{k_{NIP}} \quad (4)$$

When $k' > 1$, this indicates that successful imprinting has occurred.

The use of imprinting factor (IF) for assessing the selectivity of MIPs and IIPs has also been reported, and is defined by Equation 5. It should be noted that this selectivity parameter can only be used for competitive rebinding studies; however, some studies have wrongly reported the absence of structurally similar concomitants, mainly for sensor applications.^{20,21}

$$IF = \frac{Q_{(\text{equilibrium binding capacity}) \text{ of MIP}}}{Q_{(\text{equilibrium binding capacity}) \text{ of NIP}}} \quad (5)$$

One of the main bottlenecks of chemically imprinted polymers is their commercialization, which has been considered a slow process, most likely due to the possible occurrence of nonspecific binding sites in the material. This, in turn, depends upon the nature of the interaction between the template and binding sites of functional monomers. Despite this, companies have been founded by early proponents of the use of MIPs in separation science. These companies include MIP Technologies, founded in 1999 in Sweden with Sellergren and Mosbach as the principal researchers. Later, this company was acquired by Biotage AB, where SPE cartridges are currently commercially available. Semorex was founded in 2001 in the USA, POLYintell in 2004 in France, NanoMyp in 2011 in Spain, and MIP diagnostics in the UK in 2015; all of these are companies that make use of chemical imprinting technology. These companies offer MIP-based extraction materials, point-of-care devices, drug delivery systems, and MIP particles based on core-shell morphologies.¹¹

In Brazil, the first studies published on the topic of chemically imprinted polymers were supervised by Professor Lauro Tatsuo Kubota at UNICAMP in 2005.^{5,6} Presently, the number of scientists working with a focus on chemically imprinted polymers has increased and become widely distributed throughout Brazil. Most research involves the use of MIP-based materials for solid phase extraction on columns, magnetic dispersive solid phase extraction, chromatographic purposes, drug delivery systems and

sensor (electrochemical and optical) preparation. These studies have been carried out at several different universities, including UERJ, UFRJ, UFF, Unifal-MG, UNICAMP, USP, UEL, UFSJ, UNESP, UFBA, UESB, UNEB, UFOP, UFMG, UFVJM, UFAM, UnB, UFSE and UFScar.

Considering the number and the quality of published papers by Brazilian scientists, the research on chemical imprinted technology can be considered well-established and mature. However, as also observed worldwide, there are still challenges and opportunities including the large-scale production of particles for a wide range of analytes (ions, small and large molecules); synthesis of chemically imprinted polymers with restricted access and without losses of selectivity; and studies based on chemical speciation and integration of MIPs in microdevices based on microfluidics for rapid diseases diagnostics.

Acknowledgments

The author acknowledges the financial support and fellowships from “Conselho Nacional de Desenvolvimento Científico e Tecnológico” (CNPq) (Grant No 307505/2021-9 and 420097/2021-0) and “Instituto Nacional de Ciência e Tecnologia de Bioanalítica” (INCTBio) (FAPESP Grant No 2014/50867-3 and CNPq Grant No 465389/2014-7).

REFERENCES

- (1) Wulff, G.; Sarhan, A. On the use of enzyme–analogue–built polymers for racemic resolution. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 341–344.
- (2) Nishide, H.; Tsuchida, E. Selective adsorption of metal ions on poly(4–vinylpyridine) resins in which the ligand chain is immobilized by crosslinking. *Makromol. Chem.* **1976**, *177*, 2295–2310. <https://doi.org/10.1002/macp.1976.021770807>
- (3) Malik, M. I.; Shaikh, H.; Mustafa, G.; Bhangar, M. I. Recent Applications of Molecularly Imprinted Polymers in Analytical Chemistry. *Sep. Purif. Rev.* **2018**, *48*, 179–219. <https://doi.org/10.1080/15422119.2018.1457541>
- (4) Beluomini, M. A.; Silva, J. L.; De Sá, A. C.; Buffon, E.; Pereira, T. C.; Stradiotto, N. R. Electrochemical sensors based on molecularly imprinted polymer on nanostructured carbon materials: A review. *J. Electroanal. Chem.* **2019**, *840*, 343–366. <https://doi.org/10.1016/j.jelechem.2019.04.005>
- (5) Tarley, C. R. T.; Sotomayor, M. D. P.; Kubota, L. T. Polímeros biomiméticos em química analítica. Parte 1: preparo e aplicações de MIP (“Molecularly Imprinted Polymers”) em técnicas de extração e separação. *Quim. Nova* **2005**, *28*, 1076–1086. <https://doi.org/10.1590/S0100-40422005000600024>
- (6) Tarley, C. R. T.; Sotomayor, M. D. P.; Kubota, L. T. Polímeros biomiméticos em química analítica. Parte 2: aplicações de MIP (“Molecularly Imprinted Polymers”) no desenvolvimento de sensores químicos. *Quim. Nova*, **2005**, *28*, 1087–1101. <https://doi.org/10.1590/S0100-40422005000600025>
- (7) Marestoni, L. D.; Sotomayor, M. D. P. T.; Segatelli, M. G.; Sartori, L. R.; Tarley, C. R. T. Polímeros impressos com íons: fundamentos, estratégias de preparo e aplicações em química analítica. *Quim. Nova*, **2013**, *36*, 1194–1207. <https://doi.org/10.1590/S0100-40422013000800018>
- (8) Ansari, S. Combination of molecularly imprinted polymers and carbon nanomaterials as a versatile biosensing tool in sample analysis: Recent applications and challenges. *TrAC Trends in Anal. Chem.* **2017**, *93*, 134–151. <https://doi.org/10.1016/j.trac.2017.05.015>
- (9) <https://mipdatabase.com/index.php> [Accessed on March 3, 2022].
- (10) BelBruno, J. J. Molecularly Imprinted Polymers. *Chem. Rev.* **2019**, *119*, 94–119. <https://doi.org/10.1021/acs.chemrev.8b00171>
- (11) Dong, C.; Shi, H.; Han, Y.; Yang, Y.; Wang, R.; Men, J. Molecularly imprinted polymers by the surface imprinting technique. *Eur. Polym. J.* **2021**, *145*, 110231–110256. <https://doi.org/10.1016/j.eurpolymj.2020.110231>
- (12) Chen, Y.; Li, X.; Yin, D.; Li, D.; Bie, Z.; Liu, Z. Dual–template docking oriented molecular imprinting: a facile strategy for highly efficient imprinting within mesoporous materials. *Chem. Commun.* **2015**, *51*, 10929–10932. <https://doi.org/10.1039/C5CC03207E>

- (13) Germiniano, T. O.; Corazza, M. Z.; Segatelli, M. G.; Ribeiro, E. S.; Yabe, M. J. S.; Galunin, E.; Tarley, C. R. T. Synthesis of novel copper ion-selective material based on hierarchically imprinted cross-linked poly(acrylamide-co-ethylene glycol dimethacrylate). *React. Funct. Polym.* **2014**, *82*, 72–80. <https://doi.org/10.1016/j.reactfunctpolym.2014.05.012>
- (14) Silva, R. C. S.; Santos, M. N.; Pires, B. C.; Dinalli, L. A. F.; Suquila, F. A. C.; Tarley, C. R. T.; Borges, K. B. Assessment of surfactants on performance of molecularly imprinted polymer toward adsorption of pharmaceutical. *J. Environ. Chem. Eng.* **2019**, *7*, 103037–103051. <https://doi.org/10.1016/j.jece.2019.103037>
- (15) Cajamarca, F. A. S.; Tarley, C. R. T. Performance of restricted access copper-imprinted poly(allylthiourea) in an on-line preconcentration and sample clean-up FIA-FAAS system for copper determination in milk samples. *Talanta* **2019**, *202*, 460–468. <https://doi.org/10.1016/j.talanta.2019.05.023>
- (16) Zuo, H. G.; Yang, H.; Zhu, J. X.; Ding, Y. Preparation of a novel RAM-MIP for selective solid-phase extraction and gas chromatography determination of heptachlor, endosulfan and their metabolite residues in pork. *Anal. Methods* **2017**, *9*, 6009–6018. <https://doi.org/10.1039/C7AY01941F>
- (17) Gui, R.; Guo, H.; Jin, H. Preparation and applications of electrochemical chemosensors based on carbon-nanomaterial-modified molecularly imprinted polymers. *Nanoscale Adv.* **2019**, *1*, 3325–3363. <https://doi.org/10.1039/C9NA00455F>
- (18) Ahmad, O. S.; Bedwell, T. S.; Esen, C.; Garcia-cruz, A.; Piletsky, S. A. Molecularly Imprinted Polymers in Electrochemical and Optical Sensors. *Trends Biotechnol.* **2019**, *37*, 294–309. <https://doi.org/10.1016/j.tibtech.2018.08.009>
- (19) Ndunda, E. N. Molecularly imprinted polymers – A closer look at the control polymer used in determining the imprinting effect: A mini review. *J. Mol. Recognit.* **2020**, 2855–2866. <https://doi.org/10.1002/jmr.2855>
- (20) Pengkamta, T.; Mala, M.; Klakasikit, C.; Kanawuttikorn, P.; Boonkorn, P.; Chuaejedton, A.; Karuehanon, W. Synthesis and Evaluation of Molecularly Imprinted Polymer as a Selective Material for Vanillin. *Suan Sunandha Sci. Technol. J.* **2020**, *7*, 1–6. <https://doi.org/10.14456/ssstj.2020.2>
- (21) Ahmad, A. L.; Lah, N. F. C.; Chun, L. S. Hybrid Molecular Imprinted Polymer (MIP) Electrode for Pesticide Detection of Electrochemical Sensor. *J. Phys. Sci.* **2018**, *29*, 33–40. <https://doi.org/10.21315/jps2018.29.s1.5>



César Ricardo Teixeira Tarley is currently a Full Professor at the Universidade Estadual de Londrina (UEL), where he teaches undergraduate courses and supervises research projects. He has experience in chemistry, with an emphasis on the development of solid-phase preconcentration systems using chemically imprinted polymers, nanomaterials and mixed oxides, as well as cloud point and dispersive liquid-liquid microextraction coupled to chromatographic, electroanalytical, and spectroanalytical techniques. Tarley has published more than 230 papers, 16 book chapters, and 6 patents, and has supervised more than 40 doctoral dissertations and Master's theses. [CV](#)