

Selective Sorbents for Solid-Phase Extraction Based on Molecularly Imprinted Polymers

**Kees Ensing,
Christine Berggren, and
Ronald E. Majors**

Highly selective sorbents for solid-phase extraction (SPE) are desirable tools for the development of selective and sensitive methods for trace analysis. Molecular imprinting is an emerging technique that can yield analyte- or group-selective polymeric sorbents. Guest authors Ensing and Berggren and column editor Majors discuss the basic principles of molecular imprinting and compare the technique with conventional sorbent and immunoaffinity-based SPE. They use real-life examples to illustrate the potential of molecularly imprinted polymer-based SPE.

Ronald E. Majors
Sample Prep Perspectives Editor

Solid-phase extraction (SPE) is a technique for extracting and purifying analytes in solution. When concentrations of the target analytes decrease, the number of matrix components that potentially can interfere with quantitation or identification will increase and create higher demands on the selectivity and sensitivity of an applied analytical method. Many analytical methods comprise a sample-pretreatment step followed by either separation and detection steps that can discriminate to a variable degree between the analyte and the matrix components or quantitation in a competitive binding assay (1,2).

The general idea is that all elements of a method should contribute to its required sensitivity and selectivity. In many cases, however, bioanalytical sample pretreatment is regarded as a step to get rid of water, salts, and bulk amounts of proteins present in the samples. In trace analysis, many other compounds, some of which may have very similar structures to the analytes of interest, also are present in addition to these interferences. These compounds also can interfere with analyses. Highly selective phases that can discriminate and isolate the target analyte from the multitude of other compounds remaining in the sample are desirable.

So far, the most selective phases used for SPE are based on immunoaffinity. These immunoaffinity columns strongly contribute to the selectivity of trace analytical methods, especially for identifying pollutants and drug residues (3). It is not without reason that immunoaffinity columns are used less widely for many different compounds because a selective antibody must be developed for each analyte. Developing a specific antibody is a long and arduous process that can take as long as 12

months. Furthermore, because of the costs of producing immunoaffinity columns, long-term use of those columns is necessary. Operational conditions that cause denaturation or mobilization of the antibodies bound to the column should not be used (4–6).

An alternative technology, using molecularly imprinted polymers, currently is being extensively evaluated by academic and industrial research groups (7). In this “Sample Prep Perspectives” column, we will provide relevant background information about the basic principles of molecular imprinting, the advantages and drawbacks of molecularly imprinted polymer use in method development and routine applications, and some examples that illustrate the potential of molecularly imprinted polymers for highly selective SPE.

Molecular Imprinting

Molecularly imprinted polymers are highly stable polymers that possess recognition sites within the polymer matrix that are adapted to the three-dimensional (3-D) shape and functionalities of an analyte of interest (8,9). These molecularly imprinted polymers can be produced in a covalent or a noncovalent manner. In covalent imprinting, the print molecule — the so-called template — is chemically coupled with one of the building blocks of the polymer, and, after the polymerization, the resulting bond must be cleaved to obtain free selective binding sites. The most common approach is noncovalent imprinting, which relies upon self-assembly between the template and carefully selected functional monomers. After polymerization in the presence of a cross-linking monomer, the resulting highly reticulated polymer will contain a binding site equipped with functional groups in a defined 3-D arrangement.

Figure 1 depicts this entire synthesis process schematically.

The selective interactions between the template and the monomers are based upon hydrogen bonds and ionic and hydrophobic interactions. In general, the most selective binding occurs in organic solvents in which hydrogen bonding will strongly contribute to interactions with the analyte, although some templates also are well-recognized in aqueous media (10,11). For that reason, most polymers are produced in organic solvents such as toluene, methylene chloride, and acetonitrile. Polymerization can yield either a monolith (12) that must be ground and sieved into the desired particle size range or monodisperse particles (13). The latter approach is seldom used for producing molecularly imprinted polymers because it generally is less applicable. It is good to emphasize that both the morphology and the number of functional groups of the template and analyte play important roles in selective recognition (14,15).

An increasing number of interacting functional groups in a molecule will increase the selectivity, whereas the morphology is important for site accessibility and the mass transfer properties of the sorbent. With the present systems, the upper limit in the molecular weight of the template-analyte is approximately 1000. On one hand, these molecules must be able to diffuse into and out of the polymer; on the other hand, an increased number of interactions will slow dissociation from the

binding sites. Molecularly imprinted polymers can recognize one or a group of analytes depending upon the template choice.

Ferrer and co-workers (16) showed a good example of group-selective extraction for triazines. They extracted six chlorotriazines — deisopropylatrazine, deethylatrazine, simazine, atrazine, propazine, and terbuthylazine — on a terbuthylazine-imprinted polymer. They loaded a 50–100 mL groundwater sample, spiked with 1 µg/L of the chlorotriazines, onto a molecularly imprinted polymer column. They washed the column with 2 mL of methylene chloride and eluted the chlorotriazines with 8 mL of methanol. Their recoveries were higher than 80% for all the chlorotriazines except for propazine, for which it was 53%. Figure 2 is a chromatogram depicting the extracted triazines and the cleanup efficiency.

Removing the template molecule from the polymer is necessary not only to make the binding sites available for binding of the analyte but also to limit possible interference of the template with the analyte's quantitation. Some small amount of template molecule always remains in the polymer despite the best attempts to extract it. Residual template presence in the molecularly imprinted polymer and subsequent leaching (bleeding) in practical usage is considered to be a drawback of the present state of molecularly imprinted polymer technology by some. However, it is unrealistic to expect that molecularly imprinted polymers can be developed that show no

leaching because that could rule out the analyte's use as template molecule for the imprinting process in trace analytical methods. Neglecting this prerequisite actually has slowed down the implementation of the technology. The practical consequence of this occurrence is that a suitable structural analog of the analyte should be available for molecularly imprinted polymer synthesis (17).

Molecularly imprinted polymers are very stable and can withstand heating to temperatures higher than 120 °C and treatment with organic solvents, strong acids, and bases with only small losses in selectivity (18,19). In a controlled environment, molecularly imprinted polymers can be produced in a reproducible fashion. In our experience, the batch-to-batch variation of parameters such as avidity, binding-site density, and selectivity are small and can be considered negligible.

History of Molecularly Imprinted Polymers

The idea of molecular specificity that could be tailored in sorbents has been around for a long time. In 1931, Polyakov (20) demonstrated that molecular specificity could be imprinted into silica gel by pretreating silicic acid with organic adsorbates before polycondensation. Later, Dickey (21,22) performed more extensive investigations. Dickey precipitated silicic acid in the presence of alkyl orange dyes and found that after drying the hydrogel and removing as much of the excess imprinting agent as possible, the resulting xerogel had a greatly increased adsorption capacity for the particular dye present during gelation. In addition, the natural selectivity of silica gel for one dye in a series of azo dyes could be reversed by this pretreatment procedure.

Modern molecular imprinting has its roots in Europe with the extensive investigations of Wulff and co-workers (23,24) and Ramström and colleagues (25). Sellergren (26) and a host of others have brought molecular imprinting to the forefront of selective chromatographic sorbents with potential applications in widely different fields such as selective sorbents in SPE for trace analysis, sorbents for scavenging purposes, and polymeric selectors for preparative chiral separations.

Practical Use of Molecularly Imprinted Polymers

Molecularly imprinted polymers can be packed in disposable cartridges for off-line SPE or in columns for on-line SPE. Experi-

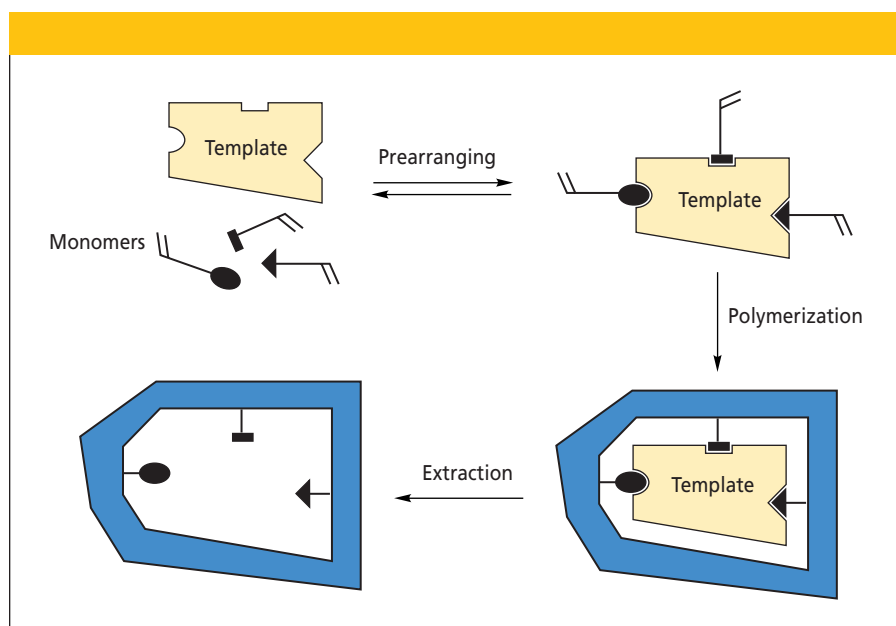


Figure 1: Schematic of the molecular imprinting principle, in which the template is the structural analog of the target analyte.

mental parameters such as particle-size distribution, packing uniformity, and flow characteristics affect recovery and reproducibility in the same manner as they do with conventional SPE materials (1).

The operational use of SPE consumables containing molecularly imprinted polymers is very similar to the use of other SPE sorbents for preconditioning, sample loading, washing, and elution. Using the molecularly imprinted polymer with the same range of solvents used in SPE, the polymer will behave like an ordinary reversed-phase or ion-exchange material. To obtain built-in selectivity, it is essential during the extraction process to use conditions that

generate the selective interactions. As mentioned above, these selective interactions generally occur in organic solvents that were used in the polymerization process. Real-life samples may contain substantial amounts of water that will impair the selective binding of the analyte of interest (27).

Analysts can use two approaches to obtain the required selectivity, and these are outlined in the accompanying sidebar, "Nonselective and Selective Adsorption of Molecularly Imprinted Polymers for SPE." If the analyte can be trapped on the molecularly imprinted polymer by ionic or hydrophobic interactions, users can load

an aqueous sample directly and retain it by using nonselective interactions. If the trapping is performed in water, the washing step with organic solvent will remove nonselectively bound matrix components, and the analyte of interest that is retained on the molecularly imprinted polymer will switch from nonselective to selective binding. Washing solvents can be methylene chloride or acetonitrile, the latter solvent with or without small amounts of basic or acidic modifiers. In an alternative approach, users can transfer the analyte into an organic solvent first, thereby providing selective binding when loaded onto the molecularly imprinted polymer.

Eluting the analyte from the columns can be achieved with a solvent or mixtures that break or disrupt the strong and multiple interactions of the analyte with the polymer. This solvent can be methanol that contains a larger amount of a modifier, such as acetic acid or triethylamine, or mixtures of water with either methanol or acetonitrile. The elution volumes can be less than 1 mL, but researchers have reported using volumes of as much as 5 mL, depending upon the elution and binding strengths (28–30).

The excellent cleanup obtained with molecularly imprinted polymer-based SPE columns can be explained by the fact that little discrimination will occur between individual components of the same polarity when using conventional SPE materials, whereas matrix components with the same polarity will be washed away with the molecularly imprinted polymer phase because they lack the same spatial arrangement of functional groups present in the analyte that causes selective recognition.

In the development of an analytical method, such as a high performance liquid chromatography (HPLC) method, most researchers focus their efforts on separating the analyte from the nearest eluted components. When these components already are partially removed in the sample pretreatment step, HPLC method development becomes simpler.

Using molecularly imprinted polymer-based SPE will limit the presence of new potentially interfering components in extracts and may avoid redevelopment of analytical methods for drug development applications, matrix changes, or samples with co-medications. The cross-reactivity observed for structurally related components is strongly dependent upon the structure and functional groups of the template molecule used for making the molec-

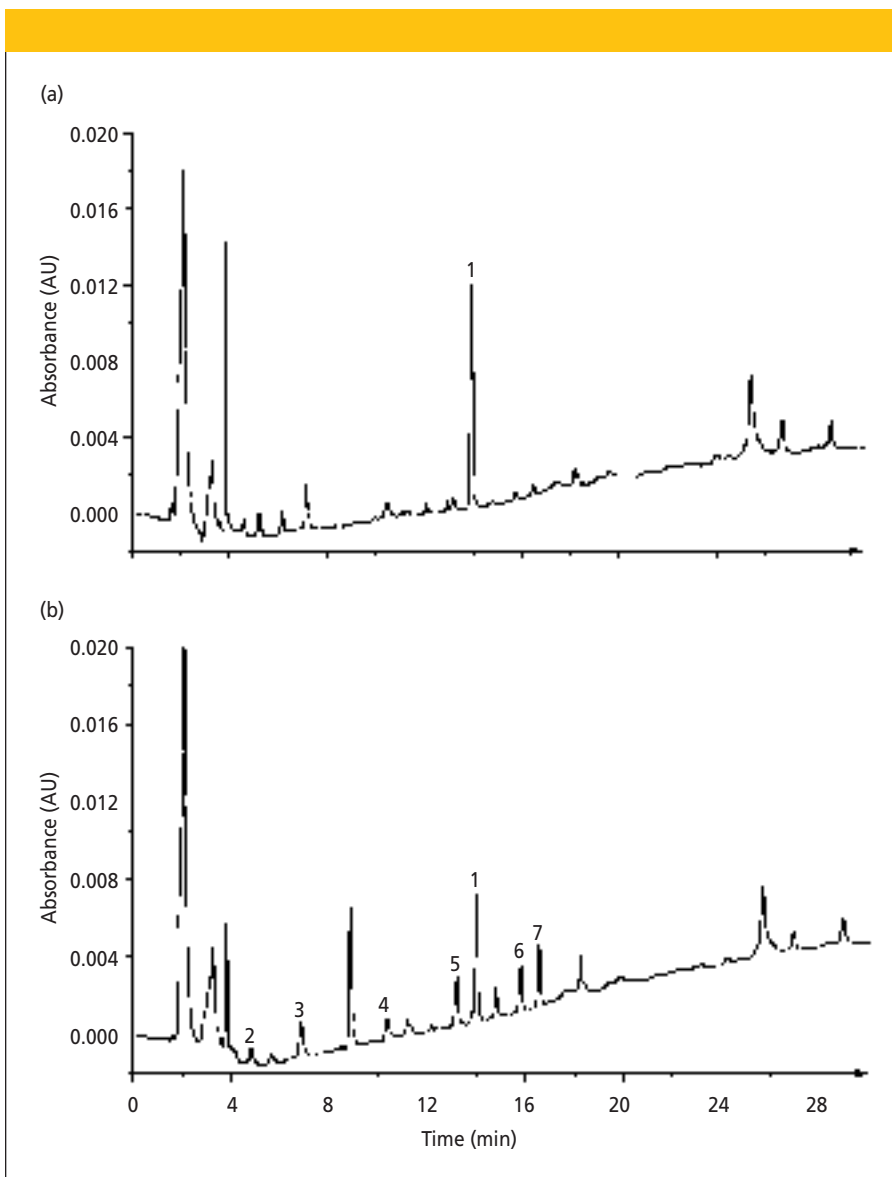


Figure 2: LC chromatogram obtained after preconcentration of a 100-mL groundwater sample spiked at 1 $\mu\text{g/L}$ on (a) a nonimprinted polymer and (b) terbuthylazine-imprinted polymer. Washing solvent: methylene chloride; detector: diode array; detection wavelength: 220 nm. Peaks: 1 = diuron (internal standard), 2 = deisopropylatrazine, 3 = deethylatrazine, 4 = simazine, 5 = atrazine, 6 = propazine, 7 = terbuthylazine (template). (Reprinted from reference 16 with the permission of the American Chemical Society.)

ularly imprinted polymer. It is essential that the functional group types of the template and their 3-D orientation be very similar to those of the target analytes to obtain cross-reactivity. Furthermore, the noninteracting remaining functional groups in the analytes should be similar in size or smaller than the corresponding functional groups of the template molecule (14).

As a rule of thumb, the binding capacity for the analyte of interest often is approximately 1 $\mu\text{mol/g}$ using 3–100 μmol tem-

plate/g. A 100–1000-fold excess in binding sites is needed for near-quantitative recoveries (31).

Examples of the Use of Molecularly Imprinted Polymers

During recent years, several publications have described the use of SPE that incorporates molecularly imprinted polymer technology for extracting drugs and pollutants from different matrices (16,26, 28–30,32–48). Table I provides an overview of examples (16,28–30,32–47).

Andersson (49) published a well-written review about the use of molecularly imprinted polymers for the analysis of biological samples that illustrates the technology's sample cleanup efficiency. He examined an optimized and validated gas chromatography (GC) method for sameridine using liquid–liquid extraction and SPE with molecularly imprinted polymers. As Figure 3 shows, virtually all matrix components present in the liquid–liquid extract that are coeluted in the same time frame as the analyte and internal standard are absent in the extract using the molecularly imprinted polymer (49). This cleaner chromatogram implies that the chromatographic conditions can be adjusted to reduce the analysis time by a factor of at least 2.

However, it is important to note that one major extra peak from the template molecule originates from the molecularly imprinted polymer. Residues of this template molecule, which differs from the analyte molecule only in the size of the alkyl chain, remain present in the polymer and slowly leach out during their use in SPE.

The analysis of clenbuterol in urine and liver illustrates that workers can extract an analyte from either liquid or solid samples using molecularly imprinted polymers (41,45). Urine was loaded directly onto a

Nonselective and Selective Adsorption of Molecularly Imprinted Polymers for SPE

Nonselective Adsorption of Molecularly Imprinted Polymers for SPE

- Apply an aqueous sample on a conditioned molecularly imprinted polymer column. The analyte will be *nonselectively* retained by ion-exchange or hydrophobic interactions.
- Wash a column with a solvent that contains little or no modifier. The analyte will be *selectively* retained, and the matrix compounds will be eluted.
- Wash a column with a solvent that contains a high amount of modifier. The analyte will be eluted.

Selective Adsorption of Molecularly Imprinted Polymers for SPE

- Transfer an analyte into an organic solvent. Use liquid–liquid, support-coated liquid–liquid, or solid-phase extraction with organic eluting solvent. Dissolve the freeze-dried sample residue in an organic solvent.
- Apply an organic extract on a conditioned molecularly imprinted polymer column. The analyte will be *selectively* retained, and parts of the matrix compounds will be eluted.
- Wash a column with a solvent containing little or no modifier. The matrix compounds will be eluted.
- Wash a column with a solvent that contains a high amount of modifier. The analyte will be eluted.

Table I: Examples of applications of molecularly imprinted polymers for SPE

Compounds	Applications	References
Bentazone	Water	39
Clenbuterol	Animal feed	46
	Liver	45
	Urine	41
Darifenacin	Serum and urine	38
7-Hydroxycoumarin	Urine	33
Nicotine and analogs	Chewing gum	28
Nitrophenol	Water	42
Pentamidine	Urine and serum	41
Propranolol	Plasma, urine, and bile	37,44
Sameridine and analogs	Plasma	35,40
Tamoxifen	Plasma and urine	34
Theophylline	Serum	29
Tramadol	Serum	47
Triazines	Apple extract and urine	30
	Liver	36
	Sediment	43
	Water	16,32

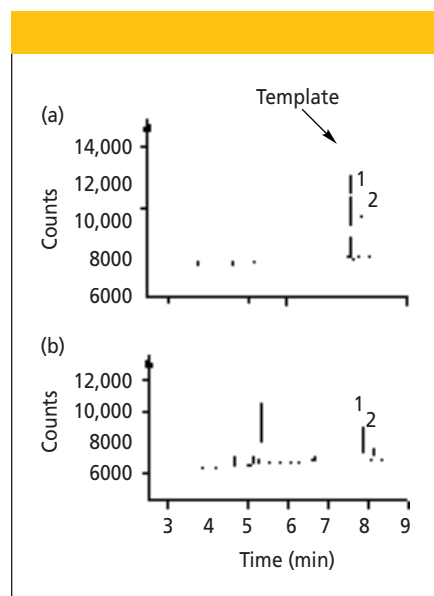


Figure 3: Representative GC traces of spiked human plasma samples subjected to (a) molecularly imprinted polymer-based SPE and (b) liquid–liquid extraction only. The samples were spiked with 66.8 nmol/L of sameridine and 50.2 nmol/L of internal standard. The injection volume was 5 μL . Peaks: 1 = sameridine, 2 = internal standard. (Reprinted from reference 49 with the permission of Elsevier Science Publishers.)

molecularly imprinted polymer column that was previously imprinted with a struc-

tural analog. Clenbuterol first was retained nonselectively on the polymer. Washing it

with acetonitrile that contained 1% acetic acid induced selective binding of the analyte to the molecularly imprinted polymer and removed most matrix components. For the liver sample, clenbuterol was eluted from a matrix-dispersion SPE column, which contained a mixture of liver and C18 sorbent, with acetonitrile that contained 1% acetic acid so that the analyte was retained directly by selective binding. The matrix components passed through the molecularly imprinted polymer column. Figure 4 shows chromatograms of a liver extract blank and the liver extract spiked with 1 ng of clenbuterol per gram of liver (45).

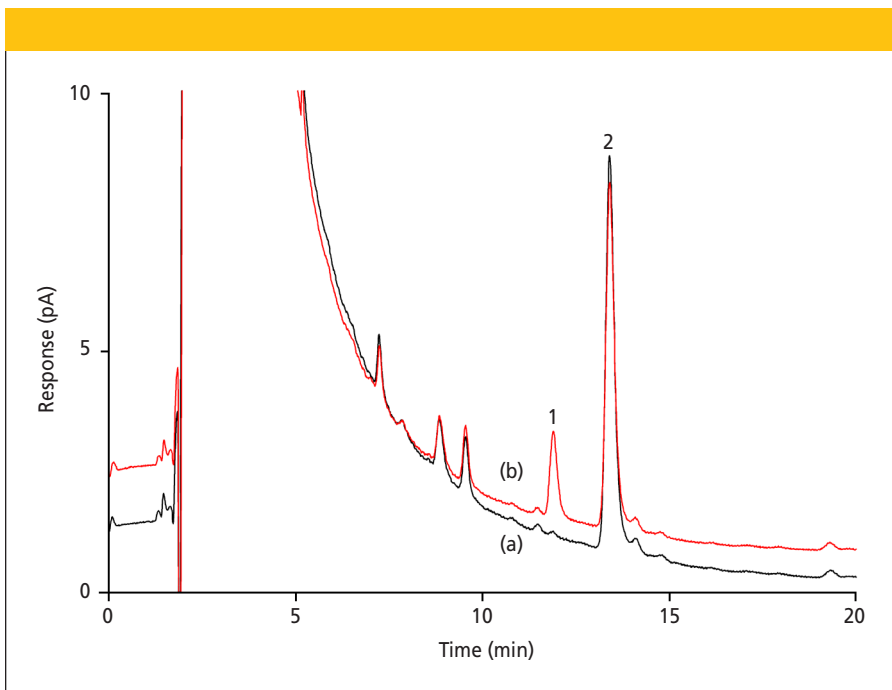


Figure 4: LC chromatograms of (a) blank and (b) spiked (1 ng/g) beef liver extracts. Detector: electron capture; injection volume: 50 μ L. Peaks: 1 = clenbuterol, 2 = bromoclenbuterol (template bleeding). (Reprinted from reference 45 with the permission of the American Chemical Society.)

Discussion

Molecularly imprinted polymers can provide a strong contribution to the selectivity and sensitivity of analytical methods. Theoretically, they can solve a given selectivity problem, reduce method development time, reduce analysis time, and, possibly, allow the use of more conventional detectors. The last aspect can save money and facilitate method transfer to quality control laboratories and contract research organizations.

From a practical point of view, developing a molecularly imprinted polymer sorbent is much quicker than developing biological antibodies (that is, weeks versus one

year). However, compared with conventional SPE sorbents that can be purchased off-the-shelf, molecularly imprinted polymers must be synthesized for each new

analyte or class of analytes. If specialty molecularly imprinted polymer phases can be produced for specific analytes or classes of analytes such as drugs of abuse or environmental pollutants, then this disadvantage disappears. One issue that can limit the use of molecularly imprinted polymers is related to the availability, cost, and toxicity of template molecules. Tables II–IV assess the advantages and disadvantages of immunoaffinity, molecularly imprinted polymer, and conventional SPE columns.

Despite the similarity of handling molecularly imprinted polymers and conventional SPE sorbents, users must have a basic understanding of how to make and break selective interactions of an analyte using the polymers to benefit from their theoretical advantages and obtain rugged methods. Training in developing molecularly imprinted polymers and methods based on their use might be crucial for the success rate of these phases. A professional society — the Society for Molecular Imprinting — for molecularly imprinted polymers already has been established in Europe for those interested in developing and further understanding this new class of selective phases. The web site for this society is <http://www.ng.hik.se/-SMI/SMIbase.htm>.

The fast-growing research activities in molecular imprinting may contribute to the development of faster screening procedures for new molecularly imprinted polymers, reduced template consumption, and a higher success rate because of the availability of more highly developed polymerization protocols. Time will tell if a large range of imprints for biomarkers, toxins, and drug residues will become available. The upcoming development techniques for affinity phases based upon phage display (50) or recombinant-type antibodies might remove a principal advantage of molecularly imprinted polymers in time, though these biomolecules will not reach the same chemical stability as those polymers. The development of cheap and very selective mass spectrometers could be seen as a threat to the use of molecularly imprinted polymers for several applications, but molecularly imprinted polymers also can remove matrix components that affect the ionization and identification of the target analytes in mass spectrometry.

Conclusion

Molecularly imprinted polymers may have a place in analytical chemists' toolboxes (51). At this stage, molecularly imprinted

Table II: Solid-phase extraction with immunoaffinity columns

Advantages	Disadvantages
Excellent selectivity	Custom-made products must be developed for new analytes
Works best in aqueous environment	Analytical applications should be transparent to permit development of an antibody with the desired selectivity profile
Proven technology for analysis of complex matrices	Unstable with organic solvents, pH extremes, and at higher temperatures
	Nonselective interactions of carrier material with analytes and matrix components
	Developing antibodies may take as long as one year
	Different immunizations will yield different antibodies

Table III: Solid-phase extraction with molecularly imprinted polymers

Advantages	Disadvantages
Highly selective for individual compounds and compound classes	Custom-made products must be developed for new analytes
Works best in organic solvent	Analytical application should be transparent to permit development of a molecularly imprinted polymer with the desired selectivity profile
Fast development of rugged methods	If polymer swells and shrinks, it may disrupt integrity of sorbent bed and preclude repeated use
Stable to pH extremes and organic solvents and may be heated to 120 °C	Difficult to remove template from polymer
Low cost relative to immunoaffinity columns, which allows single use	Possible leaching during use
Production period of weeks (versus one year for immunoaffinity columns)	

Table IV: Conventional solid-phase extraction with modified silicas and polymers

Advantages	Disadvantages
Off-the-shelf availability of wide variety of sorbent chemistries	Properties of sorbents based upon the same chemistry vary between distributors
Low cost, which allows single use	Modified silicas not resistant to pH extremes
Low levels of extractable compounds	Coextraction of analogs with different polarities such as parent drug and metabolites is difficult
Simple to use, well-known technology	Less selectivity than molecularly imprinted polymer-based SPE and immunoaffinity columns
Wide variety of consumable formats	Potential need to redevelop analytical method when changing matrix containing same analytes

polymers are still considered as the last option to solve a given analytical problem. However, we anticipate that the initial successful use of molecularly imprinted polymers in some laboratories will demonstrate such strong advantages in facilitating method development and providing very rugged methods that other laboratories may be inspired to try them. Limitations in the selectivity of an analytical method become apparent only when the method is in use, and added selectivity through sample pretreatment using molecularly imprinted polymer SPE should be welcomed.

Although it is possible that users can synthesize their own molecularly imprinted polymers, it is more likely that those interested in this technology initially will work with a partner that specializes in molecularly imprinted polymer synthesis and manufacture. The commercialization of molecularly imprinted polymer technology has already begun. At least four companies — Aspira Biosystems, Inc. (San Francisco, California), Ellipsa AG (Berlin, Germany), Instruction AG (Ludwigshafen, Germany), and MIP Technologies AB (Lund, Sweden) — are producing molecularly imprinted polymers for various uses. Synthesis services are based upon clients providing the template molecules and by working closely with the vendors to produce usable molecularly imprinted polymers.

References

- (1) R.E. Majors, *Current Trends and Developments in Sample Preparation, LCGC May 1998*, S8–S15 (1998).
- (2) E.S.P. Bouvier, P.C. Iraneta, U.D. Neue, P. McDonald, D.J. Phillips, M. Capparella, and Y.-F. Cheng, *Current Trends and Developments in Sample Preparation, LCGC May 1998*, S53–S58 (1998).
- (3) N. Delaunay-Bertoncini, V. Pichon, and M.-C. Hennion, *LCGC Eur.* **14**(3), 162–172 (2001).
- (4) J.G. Rollag, M. Beck-Westermeyer, and D.S. Hage, *Anal. Chem.* **68**, 3631–3637 (1996).
- (5) S. Ouyang, Y. Xu, and Y.H. Chen, *Anal. Chem.* **70**, 931–935 (1998).
- (6) J. Cai and J. Henion, *J. Chromatogr. B* **691**, 357–370 (1997).
- (7) F. Lanza and B. Sellergren, *Chromatographia*, in press, 2001.
- (8) K. Ensing and T. De Boer, *Trends Anal. Chem.* **18**, 138–145 (1999).
- (9) B. Sellergren, Ed., *Molecularly Imprinted Polymers: Manmade Mimics of Antibodies and Their Application in Analytical Chemistry: Techniques and Instrumentation in Analytical Chemistry* (Elsevier Science, Amsterdam, The Netherlands, 2001), p. 355.
- (10) C. Dauwe and B. Sellergren, *J. Chromatogr.* **753**, 191 (1996).
- (11) M. Quaglia, K. Chenon, A.J. Hall, E. De Lorenzi, and B. Sellergren, *J. Am. Chem. Soc.* **123**, 2146 (2001).
- (12) G. Wulff, D. Oberkobush, and M. Minarek, *Tetrahedron Lett.* **44**, 4329–4332 (1973).
- (13) L. Ye, P.A.G. Cormack, and K. Mosbach, *Anal. Commun.* **36**, 35–38 (1999).
- (14) B. Sellergren, M. Lepistö, and K. Mosbach, *J. Am. Chem. Soc.* **110**, 5853–5860 (1988).
- (15) K. Yoshizako, K. Hosoya, Y. Iwakoshi, K. Kimata, and N. Tanaka, *Anal. Chem.* **70**, 386–389 (1998).
- (16) I. Ferrer, F. Lanza, A. Tolokan, V. Horvath, B. Sellergren, G. Horvai, and D. Barceló, *Anal. Chem.* **72**, 3934–3941 (2000).
- (17) A. Ellwanger, C. Berggren, S. Bayouduh, C. Crescenzi, L. Karlsson, P.K. Owens, K. Ensing, P. Cormack, D. Sherrington, and B. Sellergren, *Analyst* **126**, 784–792 (2001).
- (18) Y. Chen, M. Kele, P. Sajonz, B. Sellergren, and G. Guiochon, *Anal. Chem.* **71**, 928 (1999).
- (19) D. Kriz and K. Mosbach, *Anal. Chim. Acta* **300**, 71–75 (1995).
- (20) M.W. Polyakov, *Zh. Fiz. Khimii.* **2**, 799 (1931).
- (21) F.H. Dickey, *Proc. Nat. Acad. Sci.* **35**, 227–229 (1949).
- (22) F.H. Dickey, *J. Phys. Chem.* **59**, 695–707 (1955).
- (23) G. Wulff, W. Grobe-Einsler, W. Vesper, and A. Sarhan, *Macromol. Chem.* **178**, 2817–2825 (1977).
- (24) G. Wulff, T. Gross, and R. Schönfeld, *Angew. Chem.* **18**, 1962–1964 (1995).
- (25) O. Ramström, L. Ye, and K. Mosbach, *Chem. & Biol.* **3**, 471–477 (1996).
- (26) B. Sellergren, *Anal. Chem.* **66**, 1578–1582 (1994).
- (27) K. Ensing and C. Berggren, “Molecularly Imprinted Polymers for Solid Phase Extraction,” paper presented at the First Senspol Workshop, Alcalá de Henares, Spain, 9–11 May 2001.
- (28) A. Zander, P. Findlay, T. Renner, B. Sellergren, and A. Swiedow, *Anal. Chem.* **70**, 3304–3314 (1998).
- (29) W.M. Mullett and E.P.C. Lai, *Anal. Chem.* **70**, 3636–3641 (1998).
- (30) B. Bjarnason, L. Chimulka, and O. Ramström, *Anal. Chem.* **71**, 2152–2156 (1999).
- (31) K.J. Shea, D. Spivak, and B. Sellergren, *J. Am. Chem. Soc.* **115**, 3368–3369 (1993).
- (32) J. Matsui, M. Okada, M. Tsuruoka, and T. Takeuchi, *Anal. Commun.* **34**, 85–87 (1997).
- (33) M. Walshe, J. Howarth, M.T. Kelly, R. O’Kennedy, and M.R. Smyth, *J. Pharm. Biomed. Anal.* **16**, 319–325 (1997).
- (34) B.A. Rashid, R.J. Briggs, J.N. Hay, and D. Stevenson, *Anal. Commun.* **34**, 303–305 (1997).
- (35) L.I. Andersson, A. Paprica, and T. Arvidsson, *Chromatographia* **46**, 57–62 (1997).
- (36) M.T. Muldoon and L.H. Stanker, *Anal. Chem.* **69**, 803–808 (1997).
- (37) P. Martin, I.D. Wilson, D.E. Morgan, G.R. Jones, and K. Jones, *Anal. Commun.* **34**, 45–47 (1997).
- (38) R.F. Venn and R.J. Goody, *Chromatographia* **50**, 407–414 (1999).
- (39) C. Baggiani, G. Giraudi, C. Giovannoli, A. Vanni, and F. Trotta, *Anal. Commun.* **36**, 263–266 (1999).
- (40) L.I. Andersson, *Analyst* **125**, 1515–1517 (2000).
- (41) C. Berggren, S. Bayouduh, D. Sherrington, K. Ensing, *J. Chromatogr. A* **889**, 105–110 (2000).
- (42) N. Masqué, R.M. Marcé, F. Borrull, P.A.G. Cormack, and D.C. Sherrington, *Anal. Chem.* **72**, 4122–4126 (2000).
- (43) J. Matsui, K. Fujiwara, S. Ugata, and T. Takeuchi, *J. Chromatogr. A* **889**, 25–31 (2000).
- (44) P. Martin, I.D. Wilson, and G.R. Jones, *J. Chromatogr. A* **889**, 143–147 (2000).
- (45) C. Crescenzi, S. Bayouduh, P.A.G. Cormack, T. Klein, and K. Ensing, *Anal. Chem.* **73**, 2171–2177 (2001).
- (46) G. Brambilla, M. Fiori, B. Rizzo, V. Crescenzi, and G. Masci, *J. Chromatogr. B* **759**, 27–32 (2001).
- (47) C.T. Fleischer, K.-S. Boos, F. Lanza, and B. Sellergren, *J. High. Resolut. Chromatogr.* **23**, 284 (2000).
- (48) J. Ølsen, P. Martin, and I. Wilson, *Anal. Commun.* **35**, 13H–14H (1998).
- (49) L.I. Andersson, *J. Chromatogr. B* **739**, 163–173 (2000).
- (50) D.J. Rodi and L. Makowski, *Curr. Op. Biotechnol.* **10**, 87–93 (1999).
- (51) B. Sellergren, Ed., *Molecularly Imprinted Polymers: Manmade Mimics of Antibodies and Their Application in Analytical Chemistry: Techniques and Instrumentation in Analytical Chemistry* (Elsevier Science, Amsterdam, The Netherlands, 2001).

Kees Ensing is marketing director of MIP Technologies AB, Research Park Ideon, SE-223 70 Lund, Sweden, e-mail info@mip.ideon.se. He also is managing director of Merska Receptor Screening Methodologies in Groningen, The Netherlands. Christine Berggren is managing director of MIP Technologies AB in Lund, Sweden.

Ronald E. Majors

“Sample Prep Perspectives” editor
 Ronald E. Majors is business development manager, consumables and accessories business unit, Agilent Technologies, Wilmington, Delaware, and is a member of LCGC’s editorial advisory board. Direct correspondence about this column to “Sample Prep Perspectives,” LCGC, 859 Willamette Street, Eugene, OR 97401, e-mail lcgedit@lccmag.com.

