Manufacturing

MIP-Based Processing

Molecularly imprinted polymers (MIPs) enable unwanted contaminants or high-value desirables to be efficiently extracted from processes, resulting in a decreased number of purification cycles and a more cost-efficient process.

In the development and manufacturing of active pharmaceutical ingredients (APIs) and their intermediates, purification consumes the bulk of the processing time and cost. Burgeoning technological advances in analysis, which make detection of impurities at ever-lower levels possible, exacerbates the time and cost demands. At the same time, there is a growing expectation among patients regarding the efficacy, safety and purity of medicines. These trends have created an urgent need for new molecular purification technologies in pharmaceutical production.

This article reviews a novel polymer technology – molecular imprinting – that makes the creation of artificial receptor sites within stable polymer materials possible, enabling the provision of innovative solutions for the separations market. The market for the technology covers a wide range of activities, from analytical solid phase extraction (SPE) products through to large-scale solutions for selective extraction on an industrial scale.

MIP TECHNOLOGY
Molecularly imprinted polymers (MIPs) are highly cross-linked polymer-based molecular recognition elements that have been engineered to bind one target compound or a ‘class’ of structurally related target compounds with high selectivity. This selectivity is introduced during synthesis when a template molecule – designed to mimic the analyte – guides the formation of specific cavities or imprints that are sterically and chemically complementary to the target molecule(s) (see Figure 1). Unlike most separation particles, MIP particles have a selective synthetic recognition site (or imprint); MIP interactions thus mimic antibody or receptor binding and are stronger than interactions obtained with conventional separation materials.

MIPs are able to bind analytes even when these are present in complex matrices such as process solutions, and their key strength is an ability to bind to trace levels of the target analyte in the presence of a large excess of other compounds that have similar physico-chemical properties. They are economical and fast to produce, are robust and stable under storage, and can be used at elevated temperatures, in organic solvents and at extreme pH values. They also display a higher sample load capacity than is typical for immunoaffinity-based sorbents, making them particularly suited to semi-preparative or preparative scale separations.

PROCESS SCALE
MIPs enable unwanted contaminants or high-value desirables to be efficiently extracted from processes, resulting in more efficient production and cleaner products. MIP-based process materials introduce selectivity into the separation/extraction process and can be engineered for a large variety of molecules including:

Figure 1: The synthesis of MIPs
A template molecule – designed to mimic the analyte – guides the formation of specific cavities or imprints that are sterically and chemically complementary to the target molecule(s).
Small molecules
Chiral compounds
Proteins (via epitope imprinting)
Peptides
Carbohydrates

It is possible to extract unwanted chemical compounds from complex mixtures, leading to a significantly increased productivity by decreasing the number of purification cycles, which in turn leads to a more cost-efficient process. MIPs can thus dramatically increase the productivity of a process due to their selectivity compared with conventional resins. Figure 2 shows a 25-times higher product capacity in unit mass/litre per hour using a MIP phase compared with a conventional resin. The MIP process is particularly advantageous in the intermediate and/or polishing steps of the purification cycle, where resolution is an important factor.

As MIP materials are cross-linked, they typically exhibit high stabilities and are known to withstand organic solvents, extreme pH and elevated temperatures without loss of selectivity. Furthermore, they are compatible with most process matrices and the polymer constituents can be engineered to meet regulatory requirements.

The benefits of MIP-based process materials can be summarised as follows:

- Increased productivity at reduced cost
- A large variety of target molecules
- Compatible with most process matrices
- Stable material and a robust format
- Particularly advantageous in the intermediate and/or polishing steps

In one example of the use of MIPs for a process scale application, a group of contaminants needed to be removed from a crude mixture, while a structurally related compound needed to be retained in the mixture using a process scale solid-phase extraction method. The contaminants were present at a concentration 10,000 times lower than the compound to be retained. Using the selective MIP extraction material, around 90% of the contaminants was removed, whereas only 14% of the compound that should be retained was co-extracted.

COMMERCIAL DEVELOPMENT

At MIP Technologies, we have pioneered the commercial development of molecularly imprinted polymers (MIPs), hold important patents on the technology and maintain cutting-edge research activities in the area. Our mission is to provide innovative products based on molecular imprinting that serve the industry’s needs in analytical, preparative and process-scale selective separations.

We develop and produce material from the mg scale up to multi-kilogram scale in-house; for larger quantities, up to the ton scale, we have partnerships with ISO- and GMP-certified polymer producers. Our separation and extraction materials for process scale applications can be developed in order to operate in different separation/extraction formats (for example, HPLC, SMB, LPLC or non-chromatographic batch type). In the development phase, we work closely with partners to engineer a material that will meet demanding separation or extraction challenges. In the earliest phase, we start with a screening protocol where polymerisation parameters are varied using statistical models (for example, experimental design) in order to find a selective MIP in the most efficient manner possible. We then provide sufficient material for evaluation and approval, before proceeding to the pilot scale phase (see Figure 3); our pilot scale facility currently allows production of up to 10kg per week and has environmental permission to produce up to 500kg MIP material annually.

In order to ensure high reproducibility of our products we work according to ISO 9001:2000. Our quality control laboratories ensure a high product quality and low batch-to-batch variations. Physical and chemical characteristics, as well as performance of the MIP sorbents, are carefully checked and reported with each batch supplied.

Currently, we have four major projects with blue chip companies targeting selective separation challenges in the food, diagnostic, commodity and biopharma industries. Some of these projects have already entered scale up stages, where MIPs or other selective separation materials have been produced at up to the 100kg scale.
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TECHNOLOGY DEVELOPMENTS

With a new proprietary technology, known as ‘Grafting’, MIPs can be directed to the surface of porous silica particles, resulting in the production of solid phase materials – called thin-layer MIPs – that have large surface areas (up to 1,000 m² per gram) and improved mass transfer properties (see Figure 4). This is particularly important where separation of similar molecules (for example, enantiomers) is required, or fast kinetic resolution is desirable.

Another new technology is hierarchical imprinting, whereby the template is immobilised onto a support material during polymerisation, after which the support is removed. The polymers obtained – called surface imprinted MIPs – then have binding sites that are highly accessible to molecules that are much larger than the imprinted template. This is particularly relevant for epitope imprinting of proteins and similar applications where a fragment of the target is sufficient to form a specific cavity into which the whole molecule (for example, a protein or peptide) can then bind.

CURRENT RESEARCH PROJECTS

In May 2007, MIP Technologies received SEK4 million from the Swedish Governmental Agency for Innovation Systems (VINNOVA) for the process development of a new, patented separation material for the biotech industry. The project – to develop a production process for a novel controlled pore size separation material – was projected to last for 18 months, after which it would be commercialised. The company already had performance proof of concept for this new material and its entry into the market is expected by the end of 2008. The approach to purifying API intermediates. The project aims to offer a powerful and unique solution to the purification of active pharmaceutical ingredients by combining Organic Solvent Nanofiltration (OSN) with MIPs, and will focus on the removal of contaminant organic compounds from APIs. The NEMOPUR network consists of three universities, two small- and medium-sized companies (including MIP Technologies), and four end-users; Hovione SA, UCB Pharma SA, GlaxoSmithKline Ltd and Lonza Ltd, who will provide input on the choice of purification systems and validation of the purification methods developed.

In November 2008, we received funding from the EU-funded New Molecular Purification Techniques for API Intermediates (VINNOVA) for a four-year project, including funding for a three-year PhD position. The overall goal of NEMOPUR is to make a paradigm shift in the approach to purifying API intermediates. The project aims to offer a powerful and unique solution to the purification of active pharmaceutical ingredients by combining Organic Solvent Nanofiltration (OSN) with MIPs, and will focus on the removal of contaminant organic compounds from APIs. The NEMOPUR network consists of three universities, two small- and medium-sized companies (including MIP Technologies), and four end-users; Hovione SA, UCB Pharma SA, GlaxoSmithKline Ltd and Lonza Ltd, who will provide input on the choice of purification systems and validation of the purification methods developed.

At MIP Technologies, we believe that MIPs constitute a powerful technique for the highly selective removal of impurities from API solutions, and that developments such as this research programme will further facilitate the creation of novel MIP materials for large scale processes, particularly important in the pharmaceutical and biopharma industries.

Figure 4: Grafting

A thin film of MIP (dark blue) is grafted onto a porous silica base material, forming a highly accessible set of binding sites into which small or large molecules may bind, depending on the template used.

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Figure 4: Grafting

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Template
Monomer
Crosslinker
Polymerisation
Product capacity (unit mass/litre/hour)

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