

# SupelMIP™ Solid Phase Extraction

**SUPELCO**  
Analytical

Molecularly Imprinted Polymers for the Highly Selective  
Extraction of Trace Analytes from Complex Matrices



**MIP**  
Technologies

- **NEW** SupelMIP Phases and Applications
- Achieve Lower Detection Limits
- Reduce Time and Costs
- Improve MS-Compatibility
- No Method Development Required

**SIGMA-ALDRICH**®

## Supelco Partners with MIP Technologies AB

MIP Technologies AB, Lund, Sweden, is a world leading company in the development of molecularly imprinted polymers (MIPs). The company is a pioneer in the commercial applications of MIPs, holds important patents, and maintains cutting-edge research activities in the area. The company's mission is to provide innovative products based on molecularly imprinted polymers that serve industry's needs in analytical, preparative and process scale 'selective separations'.

Supelco and MIP Technologies has entered in a collaborative agreement in which, as of December 2006, Supelco has assumed the exclusive global distribution of MIP Technologies' patent protected molecularly imprinted polymers for sample preparation, analytical, and preparative applications. The companies will collaborate on the development of new products while MIP Technologies will continue to separately develop its process scale separations business.



Supelco, Bellefonte, PA, USA

MIP Technologies AB, Lund, Sweden

*"With molecularly imprinted polymer technology, analysts can reach a level of sample prep extraction selectivity that could not be achieved by conventional means. With the widespread advent of mass spec technology, more and more methods are requiring lower limits of quantitation when analyzing difficult and dirty sample matrices. Improvements in selectivity during sample preparation are absolutely critical," said An Trinh, Product Manager, Supelco.*

*"By merging the strengths of both organizations in this collaborative effort, a new generation of innovative molecularly imprinted polymers and applications will emerge."*

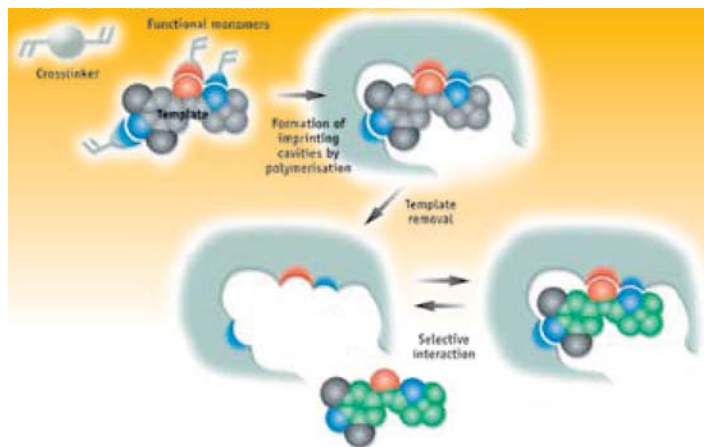
## What are Molecularly Imprinted Polymers?

Molecularly imprinted polymers (MIPs) are a class of highly cross-linked polymer-based molecular recognition elements engineered to bind one target compound or a class of structurally related target compounds with high selectivity. Selectivity is introduced during MIP synthesis in which a template molecule, designed to mimic the analyte, guide the formation of specific cavities or imprints that are sterically and chemically complementary to the target analyte(s).

As illustrated in Figure 1, MIPs are prepared by first mixing a template molecule that consists of a structural analog of the analyte(s) of interest with one or more functional monomers. The monomers form spontaneous complexes around the template. Upon complex formation, cross-linking monomers are then added with a suitable porogen (solvent that aids in the role in pore formation) to drive polymerization. An extensive wash procedure is used to

remove the template from the polymer, leaving imprints or binding sites that are sterically and chemically complementary to the template.

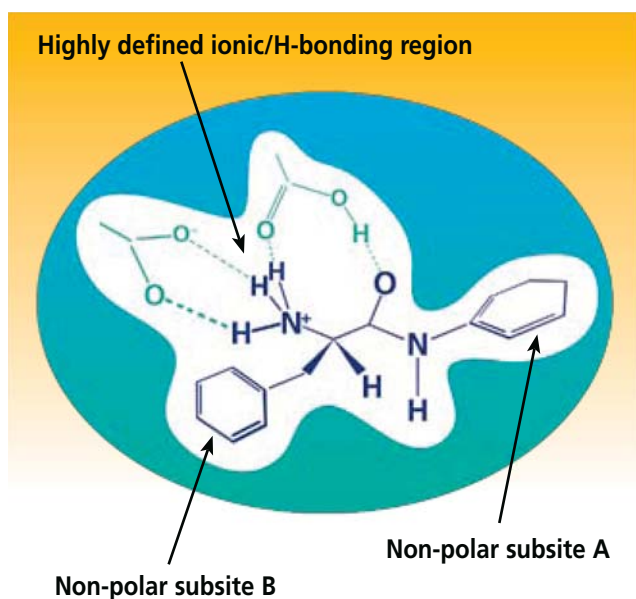
Figure 1. Formation of MIPs



SupelMIP is a trademark of Sigma-Aldrich Biotechnology LP, Inc. SupelMIPs have been developed by MIP Technologies AB.

# How is Selectivity Improved Using SupelMIP SPE?

Figure 2. Visual Depiction of a Typical MIP Binding Site



By careful design of the imprinting site, either by molecular modeling, experimental design, or screening methods, the binding cavities can be engineered to offer multiple interactions with the analyte(s) of interest (Figure 2). Multiple non-covalent interaction points (ion-exchange, reversed-phase with polymer backbone, and hydrogen bonding) between the MIP phase and analyte functional groups allow for stronger and more specific analyte retention. Improved selectivity is then introduced through the use of harsher wash conditions during sample prep methodology (Figure 3). Because extraction selectivity is significantly improved, lower background is observed allowing analysts to achieve lower detection limits relative to other less selective sample prep techniques (Table 1).

### Did you know?

Did you know that SupelMIP SPE scored perfectly (z-score of 0) for the FAPAS (Food Analysis Performance Assessment Scheme) proficiency test for chloramphenicol in prawns? FAPAS is the largest international analytical proficiency testing program since 1990. See the press release at [sigma-aldrich.com/supelmip](http://sigma-aldrich.com/supelmip) for more information.

Figure 3. Overview of a Typical SupelMIP SPE Procedure

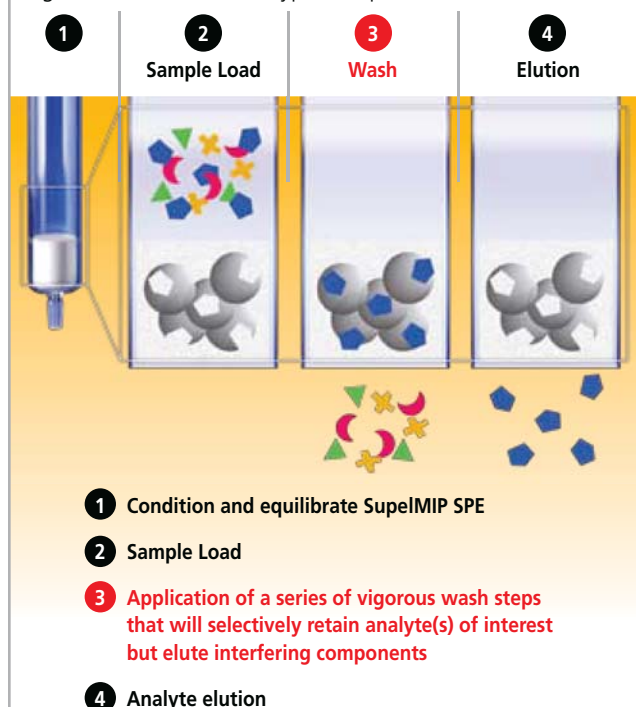


Table 1. Relative Selectivity of Various Sample Prep Techniques

Non-Selective	Dirty Extracts
Protein Precipitation	
Liquid-Liquid Extraction	
Hydrophobic Resin SPE	
Supported LLE	
C18-C2 Silica Based SPE	
Mixed-Mode SPE	
<b>SupelMIP SPE</b>	
Highly Selective	Clean Extracts (Lower LODs/ LOQs)

**Key Features & Benefits of SupelMIP:**

**Achieve lower detection limits through superior selectivity**

Reduce ion-suppression

Save time and reduce cost via robust and rapid methodology

Minimal to no method development required

Stable at broad pH ranges and high temperatures

Stringent quality control conditions

## Achieving Lower Detection Limits Through Superior Selectivity

**Chloramphenicol** is a broad spectrum antibiotic that has recently been determined as a causative agent of aplastic anemia and possible carcinogen in humans. Because of these health concerns, the EU, US and Canada have banned the use of chloramphenicol in food-producing animals and live stock.

In this application, the extraction of 15 ng/mL of chloramphenicol from milk using a SupelMIP SPE – Chloramphenicol cartridge was compared against a published method using a conventional hydrophilic polymer SPE phase (P.A. Guy et al. in J. Chromatogr. A 1054 (2004) 365-371). Note that unlike the SupelMIP SPE – Chloramphenicol protocol (included with the product), the conventional polymer method required a protein precipitation/filtration and three liquid-

liquid extraction steps in addition to SPE cleanup. Using the SupelMIP SPE – Chloramphenicol phase, the total sample handling time is significantly reduced.

In Figure 4, we see that LC-MS signal/noise ratio for the hydrophilic polymer SPE method was double that of the SupelMIP ion-chromatograms (320-323 m/z range); and blank milk samples processed using the SupelMIP were free of interfering responses in the elution area of chloramphenicol. In Figure 5, a significantly cleaner mass spectra is observed for the SupelMIP SPE extract relative to the conventional hydrophilic polymer extract.

For additional information regarding this application, please refer to Supelco Reporter 25.1; or European Reporter, Issue 26, May 2007, available at [sigma-aldrich.com/supelmip](http://sigma-aldrich.com/supelmip)

Figure 4. Chloramphenicol Spiked Milk Samples Extracted on SupelMIP SPE vs. Conventional Hydrophilic Polymer SPE

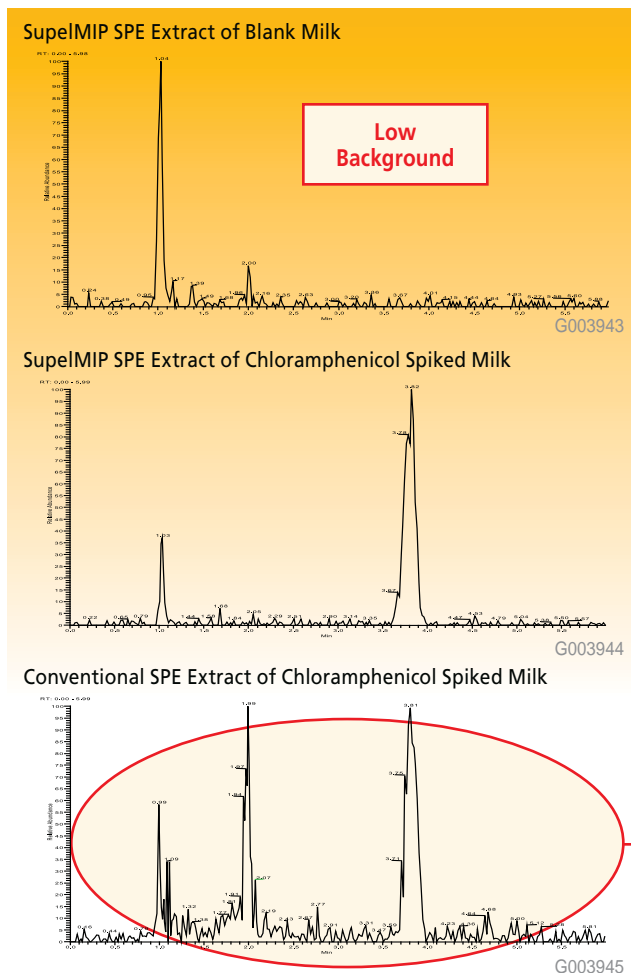
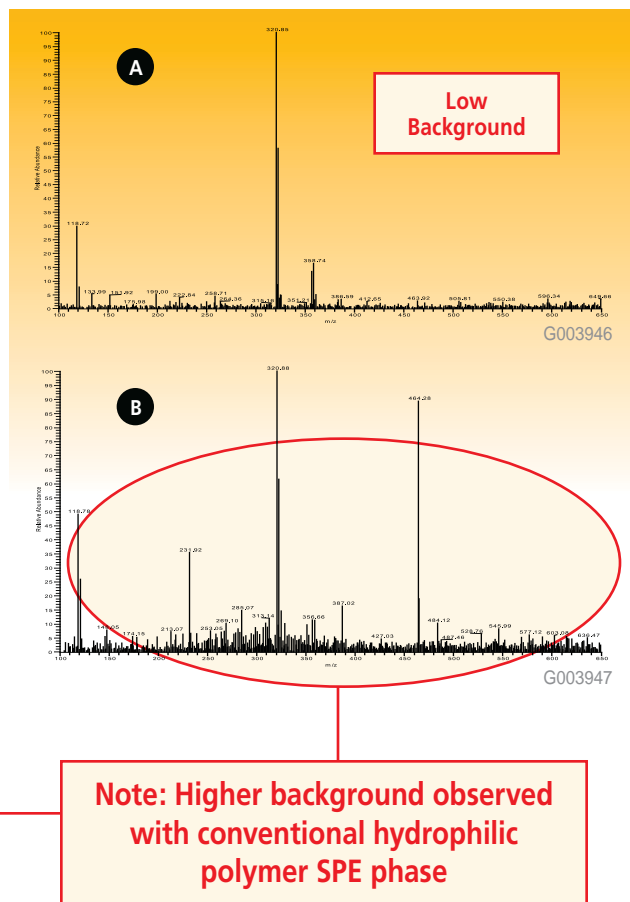


Figure 5. Mass Spectrum of Full Ion-Chromatograms (3.65- 4.00 min.) of the SupelMIP SPE Extract (A) and the Hydrophilic Polymer SPE Extract (B)



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**Clenbuterol** is a beta-agonist known for its growth-promoting properties in which use of the drug induces significant weight gain by increasing the proportion of muscle mass to fat. Although the US Food and Drug Administration, US Department of Agricultural and European Union have banned the use of clenbuterol for humans and livestock, illegal use of the drug still readily occurs.

In this application, 0.1-1.0 ng/mL clenbuterol was extracted from human urine using a SupelMIP SPE – Clenbuterol cartridge. The SupelMIP method was compared against a published method using a conventional hydrophilic polymer SPE phase (M. Joseffson, et al., J. Chromat. A., 2006, 1120:1-12.). The extracts were analyzed via LC-MS/MS analysis.

In Figure 6, blank urine samples extracted with the SupelMIP protocol offered low background. In contrast, the conventional hydrophilic polymer SPE procedure co-extracted matrix interferences resulting in a high background response within LC elution area of clenbuterol (1-2 min.). This can potentially lead to lower assay reproducibility, accuracy and sensitivity thereby elevating lower limits of quantitation. Table 2 lists recovery values for clenbuterol using both sample prep procedures. Note that at the lowest spike levels tested (0.1 ng/mL), SupelMIP recovery was 99% whereas the hydrophilic polymer phase yielded a recovery of 8%.

For additional information regarding this application, please refer to Supelco Reporter 25.2; or European Reporter, Issue 25, March 2007, available at [sigma-aldrich.com/supelmip](http://sigma-aldrich.com/supelmip)

Lower Detection Limits

Figure 6. Clenbuterol Spiked Urine Samples Extracted with SupelMIP SPE vs. Conventional Hydrophilic Polymer SPE

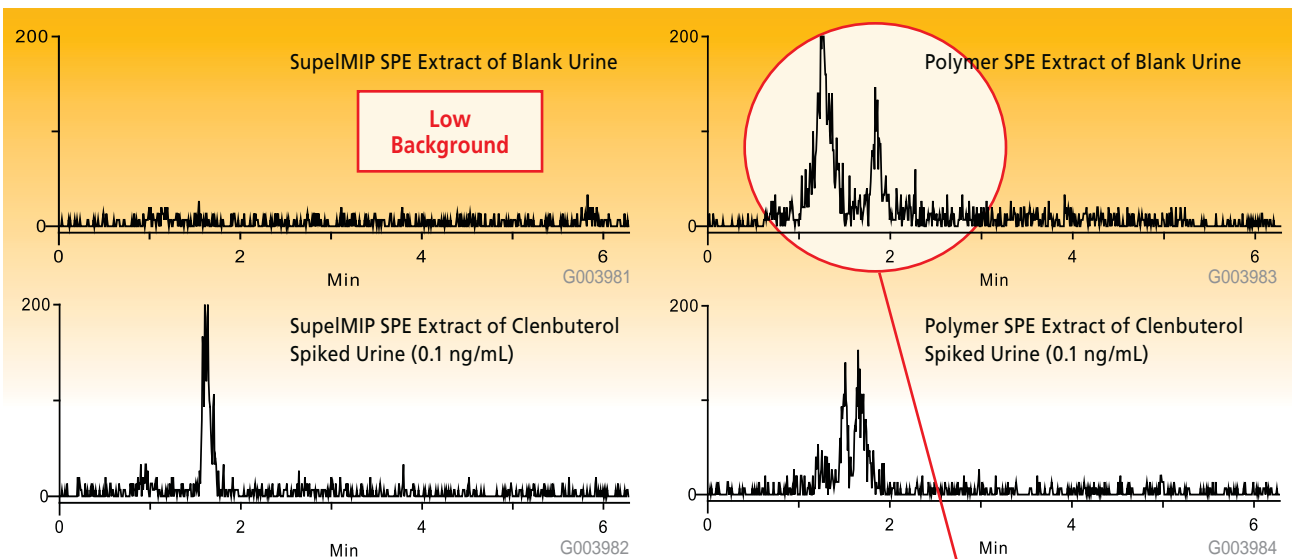


Table 2. Recovery Comparison for Clenbuterol from Urine using SupelMIP SPE and Conventional Hydrophilic Polymer SPE

Spike Level (ng/mL)	% Recovery from Urine	
	SupelMIP SPE - Clenbuterol	Hydrophilic Polymer SPE
0.1	99%	8%
0.5	75%	66%
1.0	75%	69%

**Note: Higher background observed with conventional hydrophilic polymer SPE phase resulted in signal suppression at lower detection levels.**

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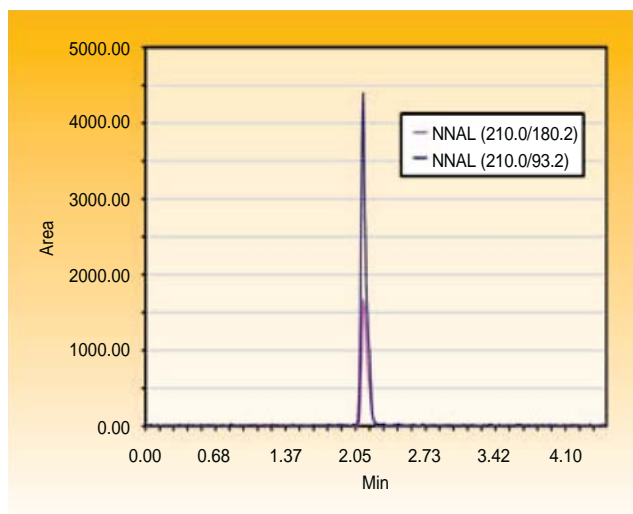
Stringent quality control conditions

**Tobacco Specific Nitrosamines (TSNAs)** are highly carcinogenic and derived solely from tobacco products. They are generated from the fermentation, curing, and burning of tobacco. For example, NNAL is a valuable biomarker in human urine to determine exposure to second-hand smoke. Because TSNAs are often found in very low concentrations in difficult biological matrixes, a highly selective and sensitive assay is required for sample preparation and analysis.

MIP Technologies AB has developed two phases to address this issue. SupelMIP SPE – NNAL is designed for the extraction of NNAL, and SupelMIP SPE – TSNA is a class selective phase developed for the extraction of four different tobacco specific nitrosamines: NNK, NNN, NAB, and NAT.

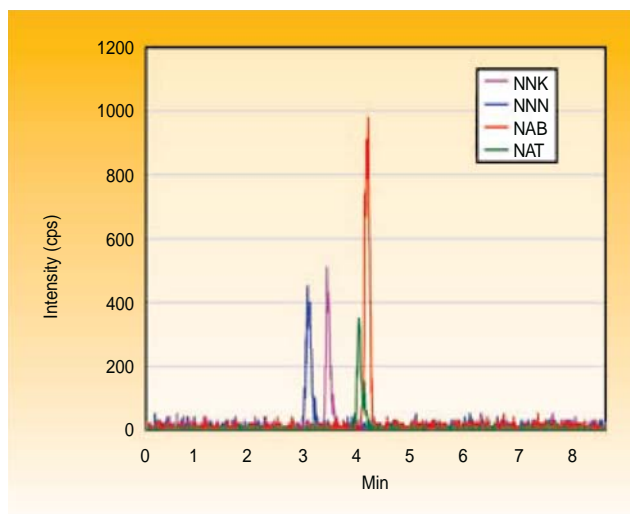
Figures 7 and 8 depict LC-MS-MS chromatograms (MRM) of SupelMIP extracts of human urine spiked with 1 ng/mL NNAL and 25 pg/mL TSNAs, respectively.

Figure 7. Representative LC-MS-MS Chromatogram (MRM) of a SupelMIP SPE – NNAL Extract of Human Urine Spiked with 1 ng/mL NNAL



- SupelMIP SPE – NNAL:**
- Consistent low background
  - Recoveries greater than 90%
  - Achieve LODs of 5 pg/mL
  - Achieve LOQs of 13 pg/mL

Figure 8. Representative LC-MS-MS Chromatogram (MRM) of a SupelMIP SPE – TSNA Extract of Human Urine Spiked with 25 pg/mL TSNAs



- SupelMIP SPE – TSNAs:**
- Consistent low background
  - Recoveries greater than 90%
  - Achieve LODs of 2.5 pg/mL
  - Achieve LOQs of 4 pg/mL

NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol  
 NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone  
 NNN = N-nitrosoanabasine  
 NAB = N'-nitrosoanabasine  
 NAT = N'-nitrosoanatabine

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**Reduce Ion-Suppression**

## Reduce Ion-Suppression

Ion-suppression or ion-enhancement is caused by one or more interfering components/species that co-elute with the analyte(s) of interest during LC-MS analysis. These co-eluting species can affect droplet formation or ionize concurrently resulting in an erroneous decrease (suppression) or increase (enhancement) in signal response. Ion-suppression often leads to poor assay reproducibility, accuracy, and sensitivity, and such deleterious effects are often most notable at the lower limits of quantitation.

In order to achieve adequate lower limits of quantitation when conducting trace analysis of analytes in complex matrices such as biological fluids, it is absolutely critical to procure adequate selectivity during sample preparation. By virtue of molecularly imprinted polymer technology, SupelMIP SPE offers the necessary selectivity and sample cleanup required for achieving ever-decreasing detection limits that are challenging analysts today.

Blank urine samples were extracted with SupelMIP SPE – NNAL and the resulting SPE (post-SPE) eluate was spiked

with NNAL and analyzed via LC-MS-MS. The resulting chromatogram response (peak area) levels generated were compared against external standards (prepared in buffer). The results (Figure 9) show that ion-suppression was nominal (< 4% signal suppression) for the SupelMIP SPE – NNAL urine extract (post-SPE spike) relative to the external standard calibration curve.

In another study, blank urine samples were extracted with SupelMIP SPE Beta-agonists and conventional hydrophilic polymer SPE phases and the resulting SPE eluate was spiked (post-SPE) with metaproterenol at the levels of 0.5, 1, and 5 ng/mL, respectively. Figure 10 compares the response levels and linear relation of known spike concentrations vs. calculated concentrations determined from the signal responses obtained from blank urine extracts spiked post-extraction using both the SupelMIP SPE – Beta-agonist method and conventional polymer SPE method. Increased levels of ion-suppression were observed for the polymer SPE protocol relative to the SupelMIP procedure.

Figure 9. Response Comparison of NNAL Calibration Curve Generated from SupelMIP SPE – NNAL Urine Extract (post-SPE spike) vs. External Standards

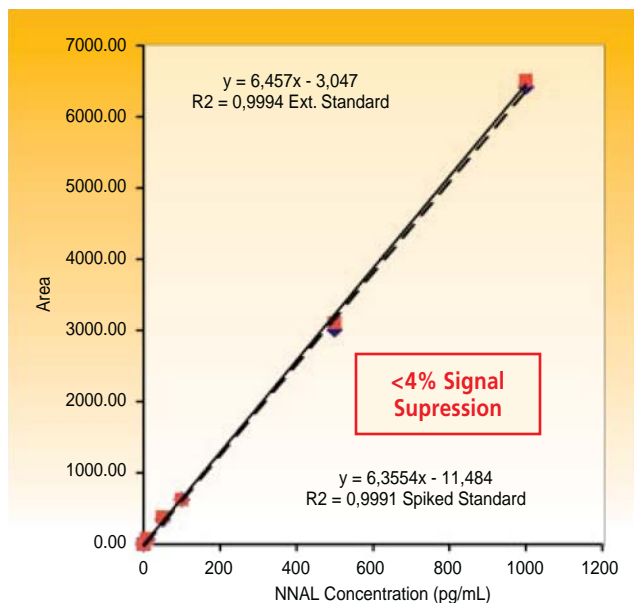
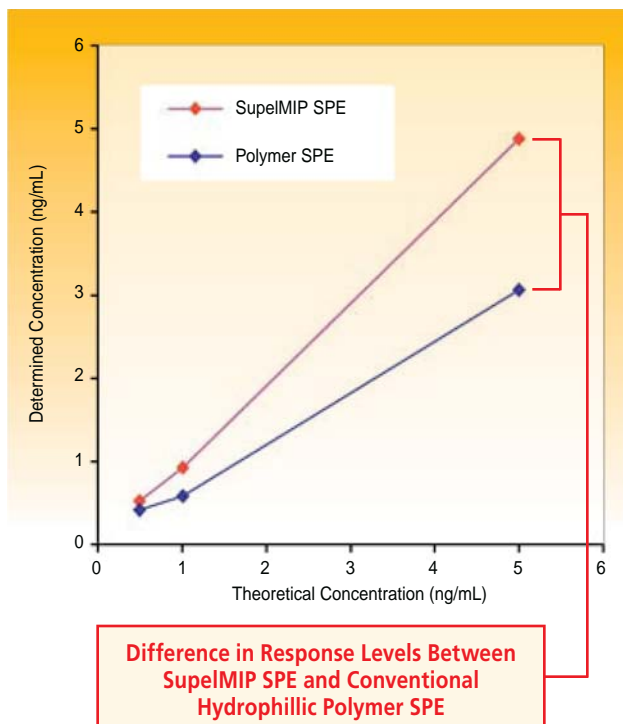


Figure 10. Known Spike Concentration vs. Determined Concentration for SupelMIP SPE Beta agonist and Polymer SPE for Metaproterenol from Urine (Post-Extraction Spike)



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## Save Time and Reduce Cost

Sample preparation is often the rate-limiting step within the analytical process, and can often take up to 10 times as long as the analysis in itself. It is therefore critical for analysts to develop simple, robust, and rapid extraction techniques that are selective enough to achieve sensitivity, precision, and accuracy limits required of the assay.

Table 3 describes the cost difference for the extraction of chloramphenicol using SupelMIP SPE – Chloramphenicol vs.

a conventional sample prep method that utilizes a common commercially available hydrophilic polymer SPE phase (1).

Time data depicted in Table 3 courtesy of Dr. Philippe A. Guy, Nestlé Research Center, Nestec Ltd., Lausanne, Switzerland.

**Total Cost and Sample Prep/Analysis Time Reduced by 75% using SupelMIP SPE - Chloramphenicol.**

Table 3. Comparison of SupelMIP SPE Method and Conventional Method Using a Hydrophilic Polymer SPE Phase

### SupelMIP SPE - Chloramphenicol Method Sample

#### Pre-Treatment:

Whole pasteurized milk (purchased from the local supermarket) was centrifuged for 15 min. at 5k rpm. The aqueous lower layer was spiked with chloramphenicol at the level of 15 ng/mL and 38 ng/mL.

#### SPE Procedure:

SupelMIP SPE – Chloramphenicol, 25 mg/10mL (LRC) (53210-U)

- Condition and equilibrate MIP phase with 1 mL methanol followed by 1 mL DI water.
- Apply 1 mL of the pre-treated milk sample to the cartridge.
- Elute interferences using the following wash scheme:
  - 2 x 1 mL MS-grade water
  - 1 mL 5% acetonitrile in 0.5% acetic acid
  - 2 x 1 mL MS-grade water
  - 1 mL 20% acetonitrile in 1% ammonium hydroxide
  - Dry SPE tubes for 5 min. under gentle vacuum
  - 3 x 1 mL dichloromethane
  - Dry SPE tubes for 1 min. under gentle vacuum
- Elute chloramphenicol with 2 x 1 mL methanol:acetic acid:MS-grade water (89:1:10, v/v/v)
- Evaporate combined eluate to dryness at 50 °C under nitrogen. Reconstitute 150 µL LC mobile phase prior to LC-MS analysis.

### SupelMIP SPE - Chloramphenicol

Sample Prep/Analysis Time: 1.5 hrs.

Sample Prep Analysis Cost (140 EUR/hr.) = 195 EUR

Total Cost of Extraction = 202.5 EUR (275 USD)

### Published Chloramphenicol Method Using Conventional Hydrophilic Polymer SPE Phase

#### Sample Pre-Treatment:

5 mL of milk was spiked with 40 ng chloramphenicol. Proteins were precipitated by the addition of 15 mL 10% trichloroacetic acid in water. The sample was vortexed and heated for 1 hour at 65 °C. After cooling to room temperature, the mixture was centrifuged for 15 min. at 3K rpm. The supernatant was filtered over glass wool, and the filtered was rinsed with 10 mL DI water. The pH of the filtrate was adjusted to pH 5 with 0.1 M sodium acetate.

#### SPE Procedure:

Conventional Hydrophilic Polymer SPE, 500 mg/12 mL

- Condition and equilibrate SPE phase with 3 mL methanol, 4 mL DI water, and 4 mL 10 mM HCl
- Apply the pre-treated milk extract to the cartridge.
- Elute interferences using the following wash scheme:
  - 4 mL MS-grade water
  - 2 mL 5% methanol
  - 2 mL 50% methanol
- Elute chloramphenicol with 2 mL methanol
- Evaporate combined eluate to dryness at 50 °C under nitrogen. Reconstitute 0.4 mL DI water

#### Liquid-Liquid Extraction

- Liquid-liquid extract of reconstituted eluate with 0.6 mL acetonitrile: dichloromethane (4:1, v/v).
- Centrifuge at 7k rpm for 5 min. Transfer upper organic layer to a fresh tube.
- Repeat steps 1 & 2 of the LLE procedure two additional times on the lower aqueous layer.
- Combine all organic layers, evaporate to dryness at 60 °C under nitrogen. Reconstitute with 0.2 mL LC mobile phase and filter through a 0.2 µm nylon filter.

### Published Chloramphenicol Method

Sample Prep/Analysis Time: 6.5 hrs.

Sample Prep Analysis Cost (140 EUR/hr.) = 845 EUR

Total Cost of Extraction = 855 EUR (1,161 USD)



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## High Stability

SupelMIP SPE consists of highly cross-linked polymers that maintain stability when exposed to a broad range of organic solvents, can withstand high temperatures, and can be used over broad pH ranges, without loss of selectivity. Furthermore, they can be stored at room temperatures for prolonged periods of times. This is extremely advantageous over immunoaffinity based products.

## Stringent Quality Control Conditions

SupelMIP SPE phases are manufactured by MIP Technologies AB. Each lot is subjected to stringent QC conditions to ensure low batch-to-batch variation. MIP based SPE technology is currently employed by a number of industrial and regulatory agencies for routine analysis. References from these organizations are available upon request.

## Frequently Asked Questions (FAQs):

### 1. How is sample preparation improved using molecularly imprinted polymer SPE technology?

Because MIPs are tailor-made for individual analytes and analyte classes, analyte retention strength is increased significantly allowing for powerful wash steps within the SPE procedure. This allows for highly selective and simple extractions resulting in lower detection limits and improved MS compatibility (reduced ion-suppression). Each SupelMIP phase also comes with a detailed application specific protocol simplifying the method development process which in turn saves time and cost.

### 2. Are sample packs available?

Yes. Sample packs are available and can be obtained through the SupelMIP website: [sigma-aldrich.com/supelmip](http://sigma-aldrich.com/supelmip). Alternatively, you can also request a sample pack by calling or emailing your local Sigma-Aldrich office and connecting with technical service.

### 3. There is no MIP phase for my application? How do I develop a MIP protocol for my application?

Within the SupelMIP website, [sigma-aldrich.com/supelmip](http://sigma-aldrich.com/supelmip), there is a survey where you can describe your application and needs for MIP based SPE product/procedure. Scientists from both Supelco and MIP Technologies AB will evaluate your application through a short feasibility stage. If your application is prioritized to move through feasibility, the next stages will be development and optimization. The latter two stages can often take up to 8 months; however, we are in the process of streamlining how we develop and approach new SupelMIP applications.

### 4. Are process scale MIP products available through Supelco?

No. Process scale MIP products are not available through Supelco. Please contact MIP Technologies AB directly by visiting [www.miptechnologies.com](http://www.miptechnologies.com)

### 5. Can we use existing or traditional SPE protocols with SupelMIP SPE technology?

No. Existing protocols cannot be used. Every SupelMIP SPE includes a detailed extraction protocol that is analyte and matrix specific. This protocol needs to be used in order to achieve optimal retention during sample load, maximum interference removal during sample wash, and high recoveries during elution.

### 6. What dimensions are available for SupelMIP SPE?

Currently, our standard product consists of 25 mg bed weights (50 mg for SupelMIP SPE – TSNA) packed in 3 mL and 10 mL LRC (large reservoir cartridges) SPE tubes. The phases can be custom packed in all other SPE hardware that Supelco offers (other SPE tube dimensions, glass SPE tubes, 96-well plates, etc.)

# Ordering Information

SupelMIP SPE Cartridges	Sorbent Mass (mg)	Cartridge Volume (mL)	Cartridges per Box	Cat. No.
PAHs	25	3	50	52773-U
Nitroimidazoles	50	3	50	52734-U
NSAIDs	25	3	50	52769-U
NSAIDs	25	10	50	52772-U
Fluoroquinolones	25	3	50	53269-U
Amphetamines	25	3	50	52228-U
Clenbuterol	25	10	50	53201-U
Beta-agonists (class selective)	25	10	50	53202-U
Beta-agonists (class selective)	25	3	50	53225-U
Beta-blockers (class selective)	25	10	50	53218-U
Beta-blockers (class selective)	25	3	50	53213-U
Full Beta Receptor (Beta-agonists and Beta-blockers)	25	10	50	53223-U
Full Beta Receptor (Beta-agonists and Beta-blockers)	25	3	50	53224-U
Chloramphenicol	25	10	50	53210-U
Chloramphenicol	25	3	50	53209-U
NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol)	25	10	50	53206-U
NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol)	25	3	50	53203-U
TSNAs (4 different Tobacco specific Nitrosamines: NNK, NNN, NAB, NAT)	50	10	50	53221-U
TSNAs (4 different Tobacco specific Nitrosamines: NNK, NNN, NAB, NAT)	50	3	50	53222-U
Riboflavin (vitamin B2)	25	10	50	53207-U
Triazines (class selective)	25	10	50	53208-U

For a complete SupelMIP product listing, and to request a SupelMIP sample pack, visit [sigma-aldrich.com/supelmip](http://sigma-aldrich.com/supelmip)

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To learn more about SupelMIP SPE and to download additional literature please visit our website:

[sigma-aldrich.com/supelmip](http://sigma-aldrich.com/supelmip)

## SupelMIP Phases & Methods Available for:

- PAHs in edible oil
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