Interview with Dr. Aline Devoille

Preparative Industry and Instrument outlook from Novasep

Aline Devoille received a Master degree in Organic Chemistry and Chemical Engineering from ECPM (European Engineering School of Chemistry in Strasbourg, France) and a Master degree in Molecular and Supramolecular Chemistry from the University of Strasbourg, France. She obtained a PhD in Inorganic and Coordination Chemistry from the University of Edinburgh, UK. Through her studies, she has worked as medicinal chemist for GSK in Harlow, UK for a year. She has joined Novasep in 2011 where she is in charge of Marketing for the Synthetic Molecules business.

Dr Devoille is the author or co-author of several peer-reviewed articles and has given lectures at several scientific conferences.

INDUSTRY

Phenomenex:
How do you view the current state of preparative HPLC?

Dr. Aline Devoille:
Some applications, such as insulin, require ever bigger columns. The biggest columns to date feature a 1600 mm internal diameter and can handle a pressure of 70 bars. For other applications, like the manufacture of peptides or the purification of fermentation products, HPLC is a must and cannot be avoided because it allows for the isolation of a product in very high purity starting from a very complex mixture. The same is true for high potency active pharmaceutical ingredients (HPAPIs) for which chromatography also presents the advantage of minimizing the handling of the highly potent compound.

Phenomenex:
Considering the state of the economy, what trends do you expect to see in purification by HPLC?

AD:
Industrial preparative HPLC remains a niche market and is not strongly impacted by the global economy. The trend we observe, however, is the ever increasing complexity of the new molecules reaching the market. Over the years, they have become more challenging to synthesize and purify.

This has impacted on our customer's expectations, they need chiral separation, purification of molecules that are insoluble in organic solvents, thermally labile, contain sensitive functionalities or closely related impurities, cannot crystallize, etc. This need to separate complex mixtures—like natural extracts, enantiomers or to ultra-purify a compound—really shows the current need for advanced purification technologies in general and for large scale preparative chromatography in particular.

Phenomenex:
What is the biggest challenge in Preparative HPLC chromatography that needs to be overcome to make it a more widely used technique?

AD:
For chromatography to be a competitive technology, smart solvent recycling has to be integrated within the process. Preparative chromatography has long suffered from the misconception of being costly due to high solvent consumption. While solvents are usually not recycled at lab scale, state-of-the-art process scale chromatography systems now integrate efficient solvent recycling units which reduce costs dramatically and also renders the technology very eco-friendly. For instance, even in reverse phase, 99% of the solvents are routinely recycled nowadays.

Phenomenex:
Which industry are you seeing the most growth, Pharma, BioPharma or Food and Bio-industries and why?

AD:
The biggest growth is observed in the Biopharma industry. Patents of very successful drugs are expiring and many players want to step on this fruitful market, hence the development of biosimilars is booming. In particular, the strong development of diabetes treatment in the BRIC countries currently drives the big increase of insulin production, the purification of which is realized by chromatography. Chromatography technologies are well adapted for the purification of biosimilars since the use of semi-continuous or continuous chromatography increase the productivity drastically. The use of advanced simulation tools also allows for rapid and direct scale-up, including the transfer from batch to continuous/semi-continuous process.

Phenomenex:
What are the major purification cost cutting efforts you think corporations will focus on in the coming years?

AD:
As mentioned earlier, solvent recycling is the major point that needs to be efficiently tackled for a cost-effective chromatographic process. State-of-the-art purification systems already integrate efficient recycling units and the performance of these is definitely the key to costs reduction since solvent consumption and waste treatment are both very expensive.

Phenomenex:
How have you seen growth in SFC equipment?

AD:
Preparative SFC has become a very popular technology in the industry because it presents strong advantages intrinsically linked to the nature of the eluent, supercritical CO_2. High mobile phase velocity can be reached with SFC, which improves both the separation and process throughput. A simple pressure drop off induces the evaporation of CO_2, resulting in a rapid, straightforward concentration of the sample and a dramatic reduction of the costs and time associated with solvent evaporation. In comparison to HPLC, the purification time by SFC is also dramatically reduced. As batch techniques can be rapidly developed, SFC is usually the optimal option for moderate scale productions, from a few grams to a few kilograms and we see a strong demand for these applications. However, the technology is not very well suited to larger productions since the risks associated with the use of gas under high pressure (typically a few 100s of bars) increase with the scale. These large volumes are therefore advantageously tackled with continuous technologies such as the SMB/Varicol® processes, which are in demand at the moment too.

Phenomenex:
What do your customers expect from a stationary phase manufacturer in terms of availability, choice of phase, delivery time, and financial stability?

AD:
Indeed, these are all important factors to assess for our clients. Two characteristics are essential when considering a phase for a commercial, large scale production. First, it needs to be commercially available in large enough quantities: when a phase needs to be renewed, our clients will typically expect its production to be able to cover their need rapidly, without resorting to stocks. The second and also most important characteristic is the reproducibility. For a process to be commercially viable, the phase has to be robust enough for the purification to be reproducible, batch after batch (or to be stable in time for continuous processes). This is a prerequisite to secure the high quality of the products but also has important financial implications since stationary phases can be costly to replace (especially for chiral applications) and because industrial applications require much larger volumes of phase than for analytical applications.

Phenomenex:
Analytical chromatography is moving toward smaller particles with fully porous as well as core shell types of particles. Do you see this trend moving into preparative chromatography?

AD:
The use of smaller particles is indeed a successful way to promote better separations at analytical scale: it allows for shorter bed length and the use of higher pressure promotes more efficient separations and increases productivity at comparable resolution. As far as technology considerations are concerned, state-of-the-art chromatography systems currently available for large scale production can definitively handle these constraints. However, the potential gain in productivity and operating costs remains to be demonstrated at large scale.

Phenomenex:
What particle size solutions do you see customers settling on over the next three to five years in chiral separations?

AD:
At large scale, chiral separations are best tackled by continuous processes and are usually carried out with SMB/Varicol® technologies which allows for an optimal use of the chiral stationary phase. Complete resolution of the peaks is not necessary in continuous chromatography so larger (less efficient) size particles can routinely be used: this enables to run the system at a higher flow rate without the building up of very high pressure; therefore the use of larger particles increases the productivity. Typical SMB/Varicol® stationary phase particles are 20-30 micron in diameter. For moderate scales such as the ones required during the product development phases, batch (SFC and HPLC) technologies are more advantageous than continuous chromatography. Here the peak resolution needs to be reached, hence smaller particles and consequently higher pressure are used, typically around 10 microns.

INSTRUMENTS

Phenomenex:
Where are preparative instruments moving in terms of performance and pressure?

AD:
In terms of pressure, equipment handling 100 bars is becoming a standard nowadays and columns are also getting larger. Standard preparative HPLC columns can reach up to 1200 mm of internal diameter, both for batch and continuous systems. In terms of continuous chromatography, Varicol® systems are typically equipped with 5 to 6 columns which affords the optimal efficiency (more columns would not bring more efficiency; the key factor is the optimization of the process). The current batch HPLC productivities typically reach a few tons per year and SMB/Varicol® processes can produce up to a few 100s of tons per year.

Phenomenex:
How often are customers able to recycle more than 97% of their solvent?

AD:
An efficient recycling of the solvent is definitely considered as a must, especially for large scale productions. Except in very particular cases, the cost of solvent and of waste treatment implies that an economically and ecologically sound process must include solvent recycling. For this reason, integrated solvent recycling units are usually included within the equipment offered by Novasep, they most often allow for the recycling of 99% of the solvent, even for reverse phase processes – where the eluent is aqueous – as already mentioned.

Phenomenex:
Are you seeing an increase in multi-column continuous chromatography compared to batch chromatography process?

AD:
Very often, the SMB/Varicol® processes are seen as the technology of choice for enantiomeric resolutions since they are intrinsically well suited to the separation of binary mixtures and we still see a strong demand for this application in the pharma industry but also in other markets, such as the agro or cosmetic ones. However, SMB/Varicol® is becoming more and more popular for the purification of multicomponent complex mixtures. Indeed, the continuous nature of the technology makes it very cost-effective. For large productions we observed that a purification in two steps on continuous SMB/Varicol® systems can be advantageous compared to a batch process. The construction of the biggest API purification system worldwide announced by Novasep earlier this year illustrates this trend. Two Varicol® 5-1200 systems, equipped with 5 columns of 1200 mm internal diameter each, will serve the purification of a highly purified omega 3 API from a complex mixture and at a scale of 100s of tons per year.