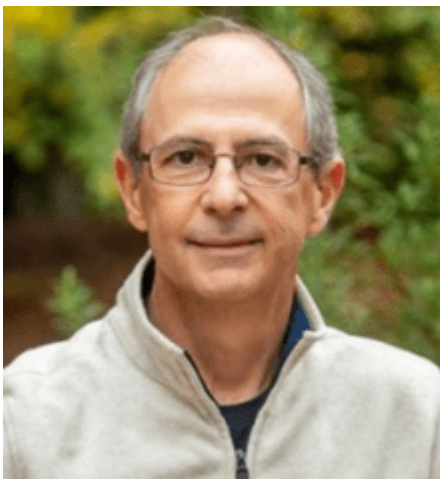
New look at Chiral SMB with Dr. Olivier Dapremont

Olivier Dapremont earned his Ph.D. in chemical engineering and applied chemistry from the University of Pierre & Marie Curie in Paris in 1997. There, he worked on the development of SMB technology in collaboration with Prochrom (Nancy, France). Shortly after, he moved to Chiral Technologies Europe (Strasbourg, France) where he oversaw the kilo scale separation service using SMB technology. In 2001, Dr. Dapremont joined Aerojet Fine Chemicals, now AMPAC Fine Chemicals, to manage all chromatography processes. Dr. Dapremont's role encompasses the development of SMB separations using multiple SMB units from 4.6 mm to 1 m in diameter, as well as developing continuous processes for the manufacturing of APIs. During his career Dr. Dapremont has built several SMB units and developed many chiral and achiral separations. Dr. Dapremont is co-author of several publications in scientific journals and magazines and has multiple patents related to SMB technologies, as well as several chapters in scientific books.

Dr. Dapremont will be one of our esteemed speakers at this year's North American PhenoPrep Seminar in Princeton, NJ, October 19th, discussing large scale chiral separation using SMB. We were given the opportunity to meet up with Dr. Dapremont and ask him a few questions regarding **Chiral** SMB.

Since you are one of the world leaders in simulated moving bed/multicolumn chromatography (SMB/MCC), could you outline the key milestones for the development of this technology?



Simulated Moving Bed technology (SMB) is in fact a fairly old technology developed in the early 1960's by UPT for the purification of xylenes. The technique was based on the concept of continuous distillation columns using liquid/solid equilibrium instead of liquid/ vapor equilibrium. Since the solid (packing material) cannot be moved without issues, the idea of

simulating the movement of the solid against the flow was developed. The concept was implemented by using a very large multi-port valve that allowed the movement of the inlet and outlet ports, “simulating” a counter current of solid and liquid. This counter current significantly increases the performance of the packing material and permits a drastic reduction in eluent consumption making the process economically attractive.

As a result, the technique spread rapidly to other applications, such as the purification of sugar molasses using very large ion exchange columns. But we had to wait for the early 1990s for the transfer of this efficient technology to the pharmaceutical industry. Companies like UOP, Prochrom, and Novasep were intensively working on adapting the technology to the purification of small molecules using high pressure columns. Few kilo scale units were produced in the 1990s, yet finally the first commercial scale SMB unit with 300mm diameter columns was installed in the mid-1990s at a pharmaceutical company. Since then, several very large-scale units (450, 800, 1000 and 1200mm in diameters) have been installed for commercial production. About a dozen APIs are manufactured using a SMB step in the process. Ampac Fine Chemicals (AFC) installed its first three units in 1999: the 8×50 for kilo scale separation, the 8×200 unit for pilot scale (hundreds of kilograms) and the 6×800 unit for commercial scale (multi tons). Since then, we added two bench top units for process development, a small kilo unit for products requiring high containment, and a 1000mm unit for multi ton commercial production of APIs. More units are likely to come as the need for capacity increases.

What are the advantages of SMB versus batch chromatography?

First, SMB is a continuous process, so there is a continuous flow of product entering the unit for separation. While in batch there is a dead time between each injection, waiting for the product to elute off the column. Because the SMB process is a counter current of liquid and solid, the packing material is used more efficiently, so the column load in terms of grams of product per grams of packing material is typically 3 to 5 times higher than batch. Since a complete separation in SMB is not necessary to achieve high purity and recovery, it is possible to either load more, leading to a huge overlap of the peaks, or to use other eluent conditions that will result in faster processing (lower viscosity solvent for example, such as ACN, can result in a higher throughput vs. a separation with pure IPA by allowing higher flow rate for the same operating pressure even if the separation selectivity is much lower). SMB

can be considered as the ultimate “shave recycling” process.

This is a process where overloaded injections are performed and only the front and the back end of the peaks are collected where the product is pure. The middle fraction containing the mixture is reinjected in the column or in SMB stays inside the column arrangement. A small amount of feed is continuously added to compensate for the product taken off the columns. However, to be able to achieve this level of performance, some concessions have to be made. The SMB is a binary separation tool and complex separations are not straightforward. Recovering the middle peak of a three-peak feed will require two SMB units in series for example. Also, because of the nature of the system, it is imperative that the feed be diluted in the eluent used for the separation so there is no possibility for a gradient as in batch separations, SMB is not the sole solution for all the separation problems; each problem needs to be addressed with all the tools available to find the most economical process.

Though continuous techniques such as SMB can show excellent economics, why are there relatively few largescale continuous processes established in the industry? Are you seeing an increase in multi-column continuous chromatography compared to batch chromatography processes? What is the biggest challenge in SMB chromatography that needs to be overcome to make it a more widely used technique?

There are many factors that influence the acceptance of SMB in the pharmaceutical industry. The first one is knowledge; even if chromatography is intensively used in the early stages of the discovery at very small scale (mg/g quantities), it is common to hear that the chromatography step needs to be removed from the process. This is mostly due to the limited knowledge of **preparative chromatography** by chemists developing synthetic routes. Most of the chromatography used at small scale by synthetic chemists is a simple open glass column with a “simple” solvent gradient.

This type of chromatography is very inefficient and does not scale well, but it gets the job done at the scale it is used. When the process needs to be scaled-up the column step needs to be thoroughly optimized. For example, a high pressure prep column needs to be used with solvent recycling strategies to minimize operating costs and reduce cycle time. This requires the good understanding of the technology, knowledge that is not always available in house

and thus all efforts are put into completely removing the chromatography step from the synthetic route, which may lead to a more expensive process. So to date, there have been a limited number of commercial projects with a chromatography step imbedded. However, the SMB technology is perceived differently than batch chromatography by most process chemists. We see a steady increase in companies willing to try the technology for their product. The driving force being that it takes very little time to develop a chiral SMB separation (a couple of weeks) and a few more weeks to get the first kilograms of product with a very scalable process. So speed to market is the major driving force and this is the second factor in acceptance of the technology.

The idea remains to "fix" the process later by finding an alternate route to eliminate chromatography, but with regulatory and financial pressure, it may be more and more difficult to switch the process later, unless there is a significant reduction in processing costs. The final factor in my view is related to the complexity of the equipment and the price barrier. It is obviously more expensive to install a large SMB unit for manufacturing than a train of reactors for asymmetric synthesis or chemical resolution. So companies are reluctant to invest in equipment if there is no long term contract, especially these days when corporations demand ROIs of a few years. Since it is a more "complex" technology, there is a need to have a resident expert within the company to help manage and troubleshoot the separation when problems arise. These very specialized experts are difficult to find as there are not many universities offering this type of education and thus it is more of a "on the job" training that takes place. Finally, from the supply chain risk management, there is a limited number of CMOs offering the technology, so this can have a big influence on the choice of the manufacturing process.

There are a limited number of companies in Europe, America, and Japan offering SMB services under cGMP conditions. Do you see cGMP competition increasing from countries like India and China?

Since SMB is quite an expensive technology, the threshold to get in is pretty high, so in parts of the world where labor is still quite inexpensive, the manufacturing choice remains with processes that utilizes existing cheaper assets, such as large volume reactors. Since there is still little pressure in these parts of the world to implement greener processes, there are fewer concerns with solvent intensive processes, such as chiral resolutions for example.

However, we are seeing an increase in the number of scientific publications from Asia on the subject of continuous chromatography. A scientific knowledge base is being built there and it is just a question of time before we see large scale SMB units operating in this part of the world as well. In terms of competition, I think it will help the development and the acceptance of the technology, which is a good thing. But I don't think that in terms of price there will be a huge difference compared to western companies since SMB is a highly automated process, the contribution of the manpower cost to the overall cost remains fairly small. The advantage of less expensive manpower in these parts of the world will not weigh as much in the balance.

Simulated Moving Bed technology (SMB) is the technique of choice for large scale separation of enantiomers. What is your general approach and key step to developing a chiral purification by SMB?

Chiral separations are indeed the main application so far on SMB because they are true binary separations. Since there is no predictive tool yet, we have to proceed with the screening of multiple CSPs with multiple combinations of solvents and this can be time consuming. All our screenings are geared toward SMB, so we look at very specific parameters. First, we evaluate the solubility and the stability of the sample in various potential solvents. Then, we screen for conditions that will give us the best selectivity within 8 minutes of separation on a 4.6mm x 250 column at 1mL/min with the simplest possible solvent system. Then, we screen all the CSPs we have in the lab. We have basically a three stage screening. For the first stage, there are traditionally 4 main CSPs that we evaluate. We use mixtures of alcohols and hydrocarbons for this screening. In the second stage, we look at the immobilized CSPs with more exotic solvents such MTBE, ethyl acetate, acetonitrile, etc. If we still do not have a satisfactory separation, then we look at other phases from as many suppliers as we can, including the **Phenomenex Lux®** series. Overall, we test between 25 and 30 chiral phases. Please note that we only test phases that are available at commercial scale using the particle size that will be used for the separation – i.e. 20 or 16 µm.

Do the chiral stationary phases, which are available on the market, satisfy the customer needs in terms of variety? What products would you like to see from chiral stationary phase manufacturers to make your work easier in the development of a chiral separation?

If you look at a separation from the analytical point of view, we can probably cover 95%+ of the chiral separations needed with 4 CSPs developed in the last 25 years. However, if you look at the separation from a productivity perspective, we need to find THE CSP that will give the highest throughput. With the launch of the immobilized CSPs by Daicel in the last 15 years, we have seen a significant increase in the average productivity reported; fifteen years ago, a productivity of one kg of feed per day per kg of stationary phase (kkd) was considered a good separation. Nowadays, since we can use less viscous solvents with higher solubility power, we regularly see productivity north of 3 kkd.

This means that with the same equipment, I can process 3 times more material in a day! This has a huge impact on the cost of the process. Since the operating costs are fixed, the cost of the molecules in $/kg is significantly reduced. So if packing manufacturers had stopped innovating we would have fewer chances today to see a SMB separation at commercial scale. We are always on the lookout for new chiral phases that could give us the extra productivity for the separation to achieve better economics. We understand that packing manufacturers cannot come up with hundreds of phases that they can support commercially, but please keep bringing new chiral selectors to the market, we will add them to our screening. In terms of particle size, we typically like to run with 20 µm because this size offers a good compromise between efficiency and back pressure. Much larger particles require a lot longer column which may become impractical. Maybe a 25 or 30 µm particle could provide some added benefit but this remains to be tested.

Today, SFC is used primarily at lab scale. How do you foresee the development of this technology? When do you think that this technology will become a production scale technology and can SMB chromatography be performed under SFC mode?

SFC is indeed finding a premium place in most separation labs for small scale quantities. The speed of development, the lower solvent consumption and the ease to recover the product post separation make this technology very attractive for early discovery support. As we have seen at conferences, major pharma companies use SFC to purify libraries of compounds and isolate a few mg/g quantities in record time. So, this technology has found a very good niche. Fundamental work is ongoing at universities and this work is extremely important to better understand the process and support the development of larger scale separations. Isotherms are the heart of chromatographic processes and there are still too many unknowns about the

behavior of the isotherm in SFC as the pressure changes. This fundamental work will be used for the modeling of SFC processes, which will result in the development of larger scale units. On paper, SMB-SFC seems to be a great combination. However, I think there are many challenges to solve before we can see a unit in operation. Pressure swings in the SMB-SFC unit are difficult to control and the switch time will be extremely short therefore pushing the equipment to the limit with increased wear and tear. So, the complexity of the equipment may overshadow the productivity gains. But with the improvements we have seen on equipment in the last 20 years, it is not excluded that an SFC-SMB unit will be manufactured for large scale separations.

How important is the "Green Chemistry" concept and what impact does it have on the overall chromatography market?

The green chemistry concept is not totally new, but it has been pushed forward by the supporters of SFC. Surprisingly chromatography is a wonderful tool to help improve the sustainability of a chemical process. In a published chapter in a book edited by W. Zhang and B. W. Cue Jr. (Wiley) in 2012 called "Green Techniques for Organic Synthesis and Medicinal Chemistry", Chapter 22: Preparative Chromatography, the authors looked at the chromatographic process as a way to reduce the carbon footprint compared to other approaches. Chromatography can be used to recover product from waste streams for example (SMB mining™). Chiral separations by SMB can also provide a significantly lower carbon footprint compared to a classical resolution step thanks to the high recycling rate of the solvent at commercial scale for an SMB unit (greater than 99.98%). Therefore, chromatographic processes can be extremely "green". At AFC, we support a holistic approach of the synthetic route that allows the synthesis of a desired molecule at the lowest possible cost with the lowest possible impact on the environment. I think this is something that every chemist and engineer should look into and promote.

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?

The objective for preparative chromatography is obviously not the same as analytical chromatography. The use of smaller particles is really to increase the efficiency between

closely eluting impurities for resolution purpose. But smaller particle size usually corresponds to much higher operating pressure, so superficially porous or core-shell types mitigate this by increasing the efficiency while maintaining a reasonable pressure drop. In large scale prep, what matters is how much product can be processed in the shortest possible amount of time (throughput! throughput! throughput!). Of course, this is done with the final product meeting the stringent quality requirements. So, any new packing material with high loading capacity will be considered for prep applications. Unfortunately, this is not always the case with the core-shell or the fully porous packing.

How do you see the future of hybrid silica based reversed phase media (stable from pH 1-12) and can it compete with polymeric media?

These phases are very interesting as they can provide unique selectivity for some applications. Being able to use lower and higher pH is clearly of great interest in the bio-molecule world. The packing can be “cleaned” with minimum risk, substantially increasing the life time and hence reducing the operating costs (less packing/unpacking columns, less media to purchase). But outside of this, I can see hybrid silica media being used for small molecules. I believe that QC groups will find it very interesting to use columns that can be cleaned without risk, thus reducing operating costs (consumables).

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

There is a clear push for higher throughput in the labs and in cost reduction. By increasing the automation in the lab, higher throughput can be achieved with less manpower. This can be done by adding more SFC or **UHPLC units** and by adding “smart” prep systems. These are systems with fraction collection controlled by MS for example. I also expect to see more “hybrid” systems; systems combining analytical and prep functions. These already exist but remain marginal. We should see more of these in the near future. Automatic screening with system experts will also have an increased presence in the discovery labs. All of this can potentially cut the development costs by increasing the throughput and by reducing the cost associated with manpower (less highly paid “experts” will be needed but this may come at a loss of the in-house knowledge). I see also a push to use or re-use consumables in an attempt to cut operation costs. Sales of more robust columns (like immobilized phases for CSP or

hybrid packing for reversed phase) should increase. For kg to commercial scale, there is a definite trend to outsourcing to specialized CMOs and chromatography is following this trend. Large corporations are reducing the size of their development groups and their manufacturing sites (becoming “virtual” companies). As a result, they increase their outsourcing to support their product portfolio. So, companies like AFC benefit from this trend and we have been growing at a steady pace in both the process R&D and the manufacturing departments (including QC and QA).

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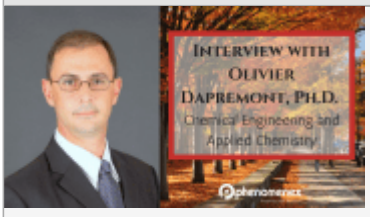
Summary



Article Name Chiral SMB Perspectives with Dr. Olivier Dapremont Description Dr. Olivier Dapremont answers the biggest questions those in prep chromatography ask regarding Chiral Simulated Moving Bed technology or SMB