Recent developments in preparative chromatographic processes

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Abstract

Preparative chromatography is an indispensable separation process in the food, pharmaceuticals and fine chemical industry. The aim of this work is to summarize developments in preparative chromatographic processes in the period 2009 to 2012. Particular attention is paid to new developments in the fundamental understanding of chromatography, novel configurations and integrated processes.

Key words:

Preparative chromatography; Continuous processes; Supercritical fluid chromatography; Integrated processes; Simulated moving bed chromatography

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1. Introduction

Preparative chromatography has had significant impact on the separation of pharmaceuticals, food, sugar and petrochemical intermediates and products. While it has been traditionally used, in fairly large scales, for the separation of isomers and sugars, the single most important development in the last 20+ years has been its scaling-down for separation of pharmaceutical ingredients. The value addition achieved by chromatographic purification, particularly in the food and pharmaceutical industries, has justified the use of complex processes and expensive stationary phases. Naturally, the availability of a wide variety of stationary and mobile phase combinations, ease of scale-up and equipment robustness have contributed the rapid acceptance of the technology. It is worth noting that chromatography is one of the few unit-operations that has been commercially used for purifications ranging from a few micrograms, e.g., in bio-pharmaceuticals, to hundreds of tonnes per day, in petrochemicals. Preparative chromatography has played a pivotal role in pharmaceutical purifications [1, 2]. Both single and multi-column processes have been used and applied at appropriate stages of manufacturing. Table 1 provides a qualitative overview of the suitability of various processes for different scales of manufacturing. In the recent years, the technology has seen rapid developments, particularly in the areas of novel process configurations, new applications and novel materials. In this article, which is not intended to be a exhaustive literature review, we focus on the recent developments, i.e., between the years 2009 and 2012, and limit ourselves to process aspects alone. The reader may refer to books and review papers to obtain a better understanding of the topic [3, 4, 5, 6, 7, 8, 9].

2. Fundamentals and modeling

Measuring and describing, both single and multi-component, adsorption equilibria is a continuing adventure. For single component adsorption equilibria, dynamic measurements have now become fairly standard [10]. Interesting advances in the recent years include the development of a calibration-free inverse method [11], extension of the elution-by-characteristic points to more complex isotherms [12] and the use of discrete equilibrium data to represent single-component adsorption [13]. Methods for rapid evaluation of mixture adsorption from single component adsorption isotherms using the ideal adsorbed solution (IAS) theory have also been proposed [14]. The generalized Langmuirian isotherm- a formalism to account for the four possible combinations of competitive, and cooperative adsorption of a binary system opens up a way to characterize [15] and describe the chromatographic behaviour [16] of many systems that are encountered in practice. The discovery of a new composition front, termed as the "delta shock" [17], and its experimental observation [18] demonstrates that even a rather "mature" technology like chromatography continues to reveal new phenomena.

Progress in mathematical modelling and optimization techniques have been driving the understanding of existing processes and the development of new ones [19, 20, 21]. Advanced numerical techniques [22, 23] and stochastic optimization, combined with accessibility to inexpensive computational power have made it possible to optimize processes, using detailed models, in a matter of few hours. While mathematical modelling has been more of an academic exercise, some recent developments have increased their industrial application. The "Quality-by-design (QbD)" initiative advocated by regula-

tory bodies such as US Food and Drug Administration (US FDA) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) emphasizes that quality should be incorporated into processes right from the design stage [24, 25]. It encourages the use of statistical methods to obtain better understanding of how process variables affect the product quality. As a result pharmaceutical manufacturers can perform parametric sensitivity studies over a wide operating range and submit the findings for regulatory clearance. Once this is done, any future variation, within this operating space, is not considered as a digression thereby avoiding a lengthy re-approval process. It is important to note that this evaluation can now be performed using validated mathematical models and computer simulations. These initiatives encourage the use of systematic approaches such as design of experiments, process optimization to be routinely incorporated into the design of chromatographic processes [26, 27, 28]. These advances are expected to have a deep impact on the industrial practice of chromatography.

3. Single-column chromatography

Single column chromatography continues to be the workhorse for small (g to kg scale) and medium-scale (kg to 100s of kg scale) purifications. The main advantages are its simple configuration and operation, potential to perform multi-component separations and ease of scale-up from analytical chromatography. Single-column batch chromatography has reached a high level of maturity and is regularly used in the industry. Although very versatile, batch chromatography has limited productivity and consumes large quanti-

ties of solvents. The performance of a single-column process can be improved by adding a recycle step. Here, the pure fractions are collected as products, while the overlapping portion of the elution profile is recycled repeatedly until the desired separation is achieved. This process, called steady-state recycle (SSR), allows for improved yields and reduced solvent consumption compared to classical batch process. Sainio and Kaspereit proposed design methods for both ideal (zero dispersion and mass transfer resistance) [29] and non-ideal systems [30]. They also showed that the mixed-mode SSR process, in which the recycled portion is collected as a mixed fraction prior to re-injection has a productivity equal to that of batch, but at reduced solvent consumption. Lee and Wankat studied two different modes of recycling: desorbent; and feed-recycle; for ternary and pseudo-ternary mixtures obeying Langmuir isotherms, where the middle-eluting component is the product of interest [31, 32]. They showed by a combination of numerical simulations and optimization that the feed recycle strategy in which the unresolved feed is recycled offers superior performance compared to the other case. Interesting variations of the SSR include the use of initial gradients [33] and concentration by solvent-removal [34, 35] have also been reported.

Chromatography has been traditionally used to obtain very high purity products. In many hybrid processes, as discussed later, chromatography is used as an enrichment step while the final polishing is achieved by crystallization. Hence, it is important to understand how to effectively operate both single and multi-column processes under reduced purities ($< 100\%$). This area has been often neglected and deserves attention. Recently, Siitonen et al. described "bypass chromatography", where the idea is to over purify a

portion of the feed and blend the product to the feed in order to obtain the desired purity level [36]. This process, which is commercially employed in the production of high-fructose corn syrup, has the potential to significantly reduce equipment size, especially when the purity demands are less-stringent.

Preparative supercritical fluid chromatography (SFC) is a technique that has seen significant advancements in the recent years [37, 38]. The use of high-pressure CO_2 as a mobile phase results in improving column efficiency, increasing speed and above all, reducing organic solvent consumption. Enantiomer separation for pharmaceutical applications represents the largest beneficiary of this technology [39]. The mobile phase, is typically a mixture of CO_2 and an organic modifier, has interesting phase behaviour and gives rise to phenomena that is not observed in high performance liquid chromatography (HPLC) [37, 38]. Axial pressure drop, associated with high flow rates used in preparative SFC, results in severe efficiency loss; a phenomena that has baffled scientists for a long time. In the recent years, through a combination of experiments and modelling, it is becoming increasingly clear that the pressure drop generates radial temperature gradients that translate into gradients in velocity and retention. These effects manifest themselves as efficiency losses [40, 41, 42, 43]. The use of isopycnic plots, i.e., plots of constant density, help in simplifying the complex thermodynamic behaviour of the mobile phase and can help understanding some key phenomena that are observed in SFC [44, 45, 46, 47]. In the area of preparative SFC, detailed modelling and optimization studies, validated by experiments, revealed that SFC can result in high productivity with very low solvent consumption [48]. Finally, although many examples of multi-column SFC processes are available in the

literature [8], their scale-up for tonne-scale manufacturing remains doubtful given the high investment costs involved in high-pressure vessels [49].

4. Multi-column processes

Multi-column chromatography (MCC), a concept that gained prominence in the 1960s, provides an avenue to realize countercurrent contact, at least in a simulated manner, between the stationary and mobile phases. This allows continuous introduction of the feed, the possibility to obtain high purities, also from low-efficiency columns, and results in improved productivity and reduced solvent consumption compared to single-column processes, both batch and SSR. The simulated moving bed (SMB) originally developed for xylene separations and later scaled-down for small molecule purifications continues to be the show-stopper [2, 3, 5, 8]. In this process, by using a discrete column/port- switching methodology, the fluid is routed in a manner that simulates the counter-current movement of the solid phase. Appropriate purification targets can be achieved by tuning the flow rates of the mobile phase, using pumps, and/or the flow rate of the solid, by varying the frequency of port-switching [50]. Although, the discrete switching allows only a simulated (not true) countercurrent movement, it however, facilitates the synthesis of complex column arrangements and switching configurations that are not possible in a true countercurrent process. These new variants aim to reduce the usage of (expensive) stationary phase material and to boost productivity. The key developments in the recent years are summarized in Table 2.

Recent developments in bio-based pharmaceuticals have provided the mo-

tivation to develop continuous processes for the separation of multi-component mixtures, invariably using gradients [51]. A key innovation in this space is the multi-column solvent gradient process (MCSGP), which in its original design, involved switching a set of 6 columns alternating between a continuous line and a batch line. Recent developments include process configurations with reduced number of columns, control strategies [52, 53] and the tandem use of chromatography, also for a capture step upstream of the MCSGP [54].

5. Chromatography in integrated processes

While chromatography itself can produce very high purity products, combining it with other unit operations, such as crystallization is gaining increased attention. In pharmaceutical production, the final product is often required in the solid form. This can be achieved in two ways: obtaining target purities using a single/multi-column chromatographic process and then crystallizing the product; or by performing a partial enrichment using chromatography and then use crystallization to simultaneously purify and obtain the product in a solid form. The second path aims to exploit the higher productivities that are possible when purity requirements are relaxed. However, this hybrid process cannot be advocated for all separations as its deployment depends on the solid-liquid phase behaviour, particularly the composition of the eutectic point, and the possibility of using the same solvent (or to be able to recover and reuse the solvent) in both processes. While the concept has been discussed for some time, recently the potential of such a process was demonstrated for purifying upto 600g of the (R) enantiomer of bicalutamide through a SMB+2-step crystallization process [55]. A combination of chro-

matography and crystallization, now combined with racezimization of the undesired enantiomer, using a homogenous catalyst, was employed to separate 100s of grams of (S)-2',6'-pipecoloxilidide [56]. Nimming and Kaspereit demonstrated the coupling of chromatography and racemization coupled with in-situ solvent removal through nanofiltration [57]. The concept of combining SMB resolution with enzymatic racemization was successfully demonstrated for the production of rare-sugars [58]. This process resulted in a dramatic improvement of the yield from a previous best of 25 to 100% with product purities exceeding 99.5%. A particularly interesting concept of combining continuous-flow reactor with SMB was demonstrated for the production of (S)-2',6'-pipecoloxilidide [59]. This study is expected to open up interest in combining continuous chromatography and flow-synthesis.

Finally, with several options available to obtain a product, the natural question to ask is which route should be chosen. This was recently addressed by Kaspereit et al. who considered possible combinations of chromatography, crystallization and racemization for the production of enantiomers [60]. Although they considered an ideal situation where the same solvent can be used for all operations, the conceptual optimization is an important step. By using simple design methods and cost-factors typical in the pharmaceutical industry, they solved a mixed integer non-linear programming (MINLP) problem. Through this study, they demonstrated that hybrid processes indeed expand the range of operations possible and that it is possible to make objective decisions about optimal process choice.

6. Other related developments

Outside the realm of process design, there have been significant developments in the area of stationary phase design. Two major advances are the widespread use of sub-2μm particles and the advent of sub-3μm core-shell particles [61]. Both approaches aim to reduce mass transfer resistance and increase column efficiency. This would mean that shorter columns can used resulting in shorter analysis times. These have had enormous impact on analytical chromatography where the focus is on increasing speed and resolution. However in preparative chromatography one of the main aims is in the improvement of productivity and the reduction of solvent consumption. Many studies in the past have addressed the optimal particle size and have concluded that there is a trade-off between the improvement in column efficiency offered by reduced particle sizes and the detrimental effect of pressure drop which limits the maximum permissible flow rate. Hence, it is indeed doubtful if these near-micron particles would find applications in preparative separations.

7. Conclusions

Over the last years, chromatography has been developed into a mature separation process. Although it's shortcomings such as product dilution, increased solvent-usage, are often cited as reasons for avoiding it in the manufacturing process, its versatility, and ease of scale-up has often made it a convenient choice. This is especially true when separations are made under tight constraints of time, e.g., in early stages of pharmaceutical drug discovery process. With the development of novel stationary phases, new processes,

design methods and examples of commercial success, the technique has seen rapid growth in the past two decades. Multi-column chromatography originally considered as binary separation process, is now being increasingly used for ternary separations; integrated processes are being keenly studied; and supercritical fluid chromatography is now considered an essential tool in the preparative chromatographers arsenal.

In the recent years, it will not be exaggeration to say that mathematical modelling and associated optimization tools have driven the development of new processes. While many fundamental aspects, such as mass transfer and equilibrium continue to be challenging phenomena to be modelled in a strictly predictive way, we have gained a high level of confidence in modelling the dynamics of chromatographic columns and in synthesizing processes . The widespread use of these techniques have provided the practitioner with tools to reliably develop new processes and objectively compare them to others. As we have argued earlier [8], users will certainly benefit from commercial systems that incorporate optimization algorithms in the form of easy-to-use software; robust monitoring and control systems; and quick reconfigurable plumbing to take full advantage of the host of new process configurations. Although most novel processes described in the literature certainly improve performance compared to classical operations such as batch, SSR and SMB, very few offer improvements that are commensurate with the increased complexity. Engineers and scientists need to pay particular attention to this trade-off in developing new processes. In addition to this, further demonstrations of hybrid processes and optimization of the overall process are needed to explore how chromatography can be integrated seamlessly into the manufac-

turing process. Although chromatography demonstrates several advantages, it continues to face the continued criticism of excessive usage of solvents. Future efforts, either by developing phases that can use more environmentally benign solvents or less energy intensive methods for solvent recycle, e.g., membranes are needed to extend the reach of process chromatography.

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Process	Adv/ Disadv	kilo-Lab [few kgs]	Multi-purpose plant [100 kgs]	Large-scale dedicated plant [Tonnes]
HPLC	+	• Versatility • Easy development • Multi-component separations possible	• Versatility • Easy development • Good if associated with solvent recycling	• Easy to scale-up • Robust operation
	-	• Low productivity • Handling large solvent volumes	• Low productivity	• Low productivity • High solvent consumption
SFC	+	• High productivity • Low organic solvent consumption • Easy development • Multi-component separations possible	• High productivity • Low organic solvent consumption	• High productivity • Low organic solvent consumption
	-	• Limited versatility (normal-phase separations) • Limited solubility	• Limited application • CO_2 consumption can be high owing to loss in collected fractions	• Very high investment costs linked to high-pressure operations • Solvent management requires additional infrastructure
SSR	+	• High productivity • Low solvent consumption	• Good trade-off between performance and investment costs.	• High productivity • Low solvent consumption
	-	• Complex to design and implement • Typically limited to binary separations	• Complex to design and implement • Typically limited to binary separations	• Less robust compared to SMB and HPLC
MCC	+	• Very high productivity • Very low solvent consumption	• Very high productivity • Very low solvent consumption • High robustness	• Low production costs • High robustness at this scale
	-	• Complex equipment • Multi-component separations are complicated • Method development and optimization is time consuming	• Complex equipment • Multi-component separations are complicated	• High investment costs

Legend	Appropriate	Not appropriate

Table 1: A qualitative comparison of various preparative chromatographic processes and their suitability for use in various scales. Symbols '+' and '-' refer to advantages and disadvantages, respectively.

Name of operation	Main contributors and Reference	Characteristics	Remarks
Intermittent SMB (I-SMB)	Mazzotti et al. [62, 63, 64, 65]	The switch time is divided into two intervals. In the first interval the unit is operated as a conventional SMB and in the second, section 4 is removed and the inlet/outlet ports are closed while maintaining desorbent flow.	I-SMB outperforms the SMB by achieving high purities especially when working with fewer columns.
Two column processes	Mota et al. [66, 67, 68]	These processes aim to limit the number of columns to two. Intermittent product collection, feed introduction and internal recycling is used to approach the performance of the SMB.	Key advantage is the reduction in capital investments, e.g. pumps, valves etc.
Partial feed and partial extract collection (PF-PCE2)	Mun [69, 70, 70]	Developed especially for 5-column three-component separations where the feed and extract ports are closed for a portion of the switch.	The process is promising for systems where it is difficult to obtain baseline separation between the intermediate and heavy components.
Fractionation and feedback SMB (FF-SMB)	Seidel-Morgenstern et al. [71, 72]	Portions of the extract and raffinate streams that do not meet purity specifications are recycled to the feed.	FF-SMB, as expected, shows advantage over conventional SMB for difficult separations, using very low efficiency columns.
Parameter estimation	Engell et al. [73, 74]	Describes optimization control methods to estimate adsorption isotherm parameters by monitoring concentration profiles at the outlet ports.	
Optimization of operation and processes	Seidel-Morgenstern et al. [75, 76], Kawajiri et al. [77]	Publications describe options to reduce start-up times and to compare different process configurations	Methods are particularly useful in large campaigns where large quantities of product might not meet purity specifications until cyclic steady-state is reached.
Control of SMB	Morbidelli et al. [78, 52]	Experimental demonstration of control system that uses offline HPLC analysis for purity monitoring.	For systems requiring high-purity products, very often online monitoring tools are accurate enough. The "cycle-to-cycle" control strategy overcomes this by using more accurate offline HPLC analysis.

Table 2: A summary of some recent developments in MCC processes