A New Efficient Fractionation Process: The Simulated Moving Bed with Supercritical Eluent

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1. INTRODUCTION

The development of preparative chromatographic processes in fine chemistry and in pharmaceutical industries is a very important field of research. This new process called SF-SMB (Supercritical Fluid Simulated Moving Bed) is a attempt to optimize preparative chromatography by three ways: the choice of a supercritical CO_2 as eluent, the implementation of the simulated moving bed, and the use of an elution strength modulation in the process, performing a pressure gradient.

If elution and frontal chromatography are still the main implementations used in preparative processes because of the simplicity of their development, processes like true moving bed (TMB) or simulated moving bed (SMB) have been used for about 40 years in large scale separations in petroleum or sugar industries [1,2]. In these processes, a countercurrent between solid and fluid phase is realized (or simulated) in order to improve process productivities and to decrease the eluent consumption. These implementations are now developed for laboratory and small productions and find a lot of applications in pharmaceutical and fine chemistry industries [3,4].

In a lot of industrial adsorption processes like PSA (Pressure Swing Adsorption) or TSA (Temperature Swing Adsorption), a variation of a physical parameter is used to increase the recovery yield of the purified product or to increase the productivity of the process [5]. If such kind of variation is difficult to realize with liquid eluent SMB, the use of supercritical eluent is particularly appropriate to realize an elution strength gradient. In fact, the elution strength of supercritical eluents is varying with pressure and temperature and a lot of simple models describe the retention coefficient variations versus temperature and specific gravity of the eluent [6-8]. If a temperature control is always difficult to handle because of the thermal inertia, this property can be used in SMB performing a pressure gradient between the different zone of the bed [9,10].

After explaining the process concept, this paper presents the two steps of the process development. First a simulation software allows to set the different process parameters and gives an idea of the SF-SMB performances. Then, the pilot plant is described and experimental results confirm the numerical simulation expectations and prove the great interest of this process.

2. PRINCIPLE OF THE PROCESS

The basic principle of a true moving bed is to use a countercurrent contact between solid and fluid phases. The feed to be processed (A + B) is injected in the middle of the column.

The products with lower retention (A) follow the eluent direction enabling recovery at the top of the column. Products with higher retention (B) follow the solid direction where they can be recovered at the bottom of the column.

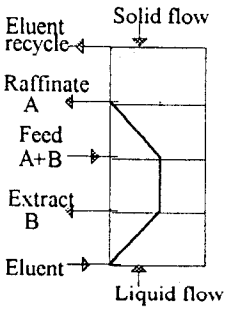
The main drawback of true moving bed is the lack of control of the solid flow. This is why the simulated moving bed implementation is most often used. The system consists of at least 4 columns connected in series. The solid is therefore fixed as a stationary phase in the different columns. The solid flow is only simulated by shifting the injection and collection points. That is, moving fronts of A and B appear in the system owing to elution, and these fronts are followed by shifting the injection and collection points. Consequently, the profiles are continuously moving within the system, but the effluent concentrations appear almost constant because of shifting of the collection points.

It can be shown that the performances of simulated moving beds are equivalent to those of true moving beds [11]. Also, SMB process has a lot of advantages compared to classical elution chromatography. With a continuous process, purified products are recovered at 100% with a low dilution and a low eluent consumption. Moreover, SMB process are not very sensitive to column efficiency and we can obtain very good product purities with even low column efficiencies [11].

The parameter setting of liquid eluent SMB consist in a right and accurate setting of the inlet and outlet flowrates of the system [12]. SF-SMB is more complex and 4 pressure and 4 flowrates have to be set. The idea of SF-SMB concept to perform a pressure gradient in the different zones of the bed is illustrated in figure 1.

The purpose of zone 1 is to stabilize the concentration front of component B in order to prevent B to be sent in zone 4 in the solid phase direction. The use of a high pressure in this zone allow increase the elution strength of the eluent and to decrease the flowrate in zone 1 leading to reduce eluent consumption and to increase the concentration of the extract flowrate.

Compared to an isocratic process where flowrates in zone 2 and 3 are determined by the objective to stabilize A concentration front in zone 2, and B concentration front in zone 3, in order to recover both components pure at the extract and the raffinate, the realisation of a pressure gradient between these two zones allow to decrease Q_{II} and to increase Q_{III} and therefore to increase the feed flowrate Q_f (as $Q_f = Q_{III} - Q_{II}$) and finally the productivity of the system.



Zone	Objective	Elution strength
4	$A_{\downarrow}$	- -
3	$B_{\downarrow}$	-
2	$A^{\uparrow}$	+
1	$B^{\uparrow}$	++

Figure 1 : Explanation of the interest to perform a pressure gradient in a moving bed

3. NUMERICAL PROCESS SIMULATION

Before each separation, process parameters have to be determined through a numerical simulation software. Knowing the size of the system and the adsorption isotherm of the components, the software is able to compute the optimal set of flowrates allowing to perform the separation.

The first step is devoted to the determination of adsorption isotherms. Several adsorption isotherm determination methods have been described [13], and we developed a laboratory apparatus allowing to determine very precise adsorption isotherms in supercritical fluids.

In a second step, we use the thermodynamical data previously obtained, and we compute the SF-SMB separation performances.

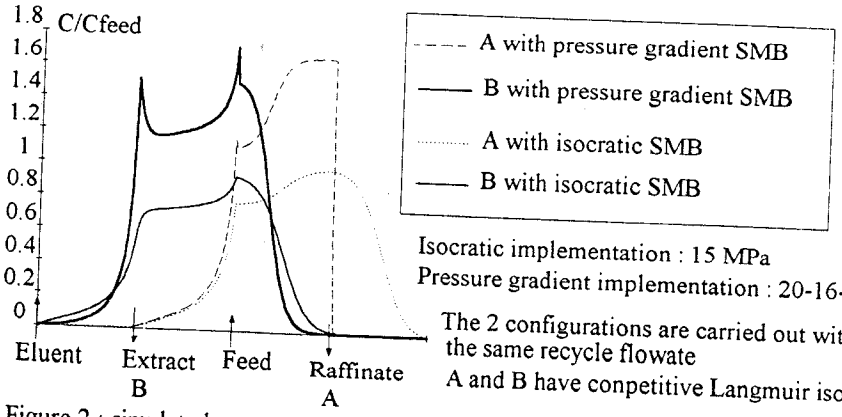


Figure 2 : simulated concentration profile in a TMB with or without a pressure gradient [14]

A first model is used to compute the flowrates allowing to perform the separation with the greatest productivity. Then, the "mixed cell in series" model takes into account thermodynamic, hydrodynamic and kinetic properties of the system and compute the concentration profile inside the columns [14]. In this model, we make the assumptions that the pressure drop inside the column is negligible compared to the pressure drop realized and controlled with the analogical valves, and we model the true moving bed assuming that the performance of SMB and TMB are equivalent. A mass balance equation is written for each stage and a classical Newton Raphson numerical method is used to solve the permanent state of the process [14].

Figure 2 presents a typical exemple of computed concentration profiles obtained with the software using or not a pressure gradient [14].

The production of the pressure gradient implementation is found to be about twice the production that can be achieved by a isocratic implementation (using the same recycling flowrate). This improvement of process separation potential is due to the use of a pressure gradient between the different zones of the bed. If we observe the concentration profile, we see that the mean concentration of the components in the pressure gradient system is higher than the one of isocratic system. The component concentration can even be greater in the column than in the feed. This effect is in fact one of the main limits of pressure gradient because we are obviously limited by the solubility of the solutes in the fluid.

4. PILOT PLANT DESCRIPTION

The pilot plant is composed of 8 columns of 33 mm of internal diameter connected in series. Six automated valves are placed after each column in order to connect the columns to the different inlets and outlets of the process (See figure 3). Analogical valves are located after each column (Un) and are used to control the pressures in the different zones of the process. Five analogical valves control inlets and outlets flowrates.

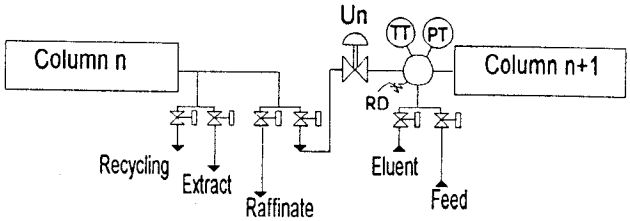


Figure 3: Valve configuration between the columns

Efficient control algorithms based on a representation of analogical valves have been developed in order to control simultaneously the pressure in the four zones and the inlet and outlet flowrates. The eluent pump is filling a high pressure reservoir maintained at constant pressure. The fresh eluent is sent to the eluent inlet and to a mixer M to be mixed with the feed.

The purified products are withdrawn in three separate outlets composed of cyclonic separators connected in series. Pure products, free of eluent are recovered in the bottom of reservoir as the gaseous eluent is easily recycled after being liquefied in a condenser, pumped and heated to the desired temperature and finally sent to R2.

5. EXPERIMENTAL SEPARATION RESULTS

The separation of two fatty ethyl esters (GLA: γ-linolenic ethyl ester and DHA: docosahexaenoic ethyl ester) has been carried out on the pilot plant.

The stationary phase is a C18 bounded silica, granulometry 15 µm LiChrospher E.Merck.

Two experiments will be compared. The first experiment has been carried out in almost isocratic conditions without the system allowing to perform the pressure gradient. The pressure drop in the column is low (15 bar on the 8 columns). In the third experiment, we add a pressure drop between the columns, using analogical valves, in order to obtain a global pressure drop of 90 bar.

a) Isocratic implementation

The pilot plant is carried out about 24 h with the following parameter setting determined with the numerical simulation software:

zone 1	zone 2	zone 3	zone 4
15.8	15.4	15.0	14.6

Pressure setting in the different zones (MPa)

Feed	Extract	Raffinate	Recycle
0.69	1.49	0.67	3.18

Inlet and outlet flowrate setting ($kg.h^{-1}$)

Step time: 694 sec

A system allows to determine the concentration of the components after each column. Figure 4 presents the concentration profile obtained with this configuration.

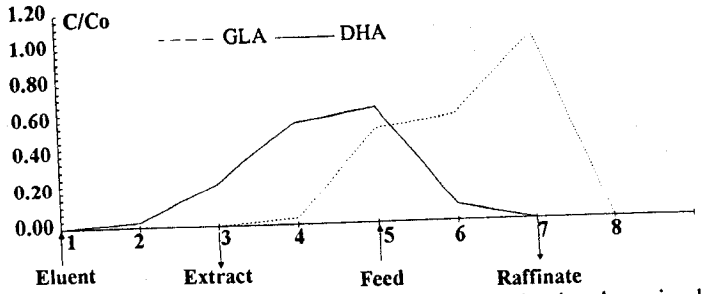


Figure 4: Experimental concentration profile in the simulated moving bed (isocratic implementation)

The purities of the recovered fractions are:

- Extract purity (DHA): 97.8 %
- Raffinate purity (GLA): 97.7 %

The total production of purified oil on the system is 33.1 g/day.

b) Pressure gradient implementation controlled by analogical valves

The new parameter setting determined by the numerical simulation software is :

zone 1	zone 2	zone 3	zone 4
19.5	17.5	12.5	11.5

Pressure setting in the different zones (MPa)

Feed	Extract	Raffinate	Recycle
2.2	1.3	0.79	7.15

Inlet and outlet flowrate setting ($kg.h^{-1}$)

Step time : 276 sec

The purities of the extract and raffinate recovered fractions are :

- Extract purity (DHA): 99.9 %
- Raffinate purity (GLA): 100.0 %
- The total production of purified oil on the system is 122 g/day.

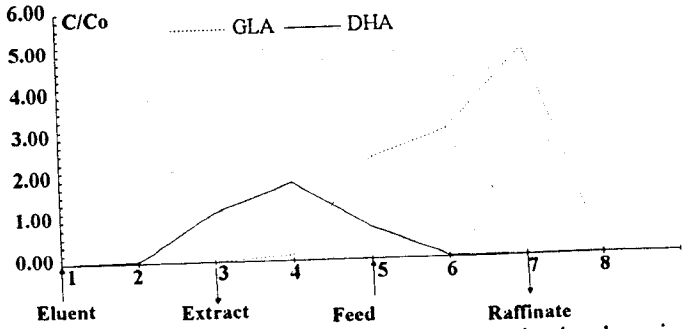


Figure 5: Experimental concentration profile in the simulated moving bed (pressure gradient with automated control through analogical valves)

As it was predicted by the simulation software, the use of a pressure gradient allow to increase process productivity. In this last configuration, the production of the pilot plant is increased about 4 times compared to the first "isocratic" separation. The effect of the pressure gradient on the productivity can be estimated, dividing the experimental production by the

sum of the inlet flowrates in the pilot plant. We compare this way the production for a given amount of stationary phase and a given capacity of the eluent pump. Between the first "isocratic" and the last "pressure gradient" experiments, we increase the productivity of the system more than 2 times.

We also observe that the concentration of the components in the simulated moving bed is higher than it was in the feed. In our case, the main limiting factor of process productivity was the adsorption capacity of the stationary phase, but, when this is the solubility of the solute in the eluent witch is limiting, the pressure gradient has to be set in order to take into account this constraint. In fact, compared to a liquid eluent SMB, SF-SMB improve the process by 2 ways: supercritical eluents allow first to use much more important flowrates, and then, it is possible to perform a pressure gradient witch can increase drastically the productivity of the system.

6. CONCLUSION

A new preparative chromatographic process has been developed. This process combines the advantages of supercritical eluent in chromatography and those of simulated moving bed implementation. This complex process is developed in 2 steps. In a first step, an adsorption isotherm determination and a simulation software allow to give an estimation of process performances. Then, the separation is carried out on a pilot plant with the setting determined on the simulation software. The numerical and experimental results prove that the concept of this new process that is to perform a pressure gradient along the bed, improves drastically the process productivity. Some economical comparisons will certainly confirm the interest of SF-SMB compared to liquid eluent SMB, PSFC or HPLC technologies.

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