VALIDATION OF AN ACTUAL SIMULATED MOVING BED UNIT TOWARDS ITS AUTOMATION CONTROL AIMING TO SEPARATE PRAZIQUANTEL ENANTIOMERS

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ABSTRACT: This work has as its main goals the validation of an actual SMB unit and to get preliminary information that are going to be useful to update the SMB mathematical model to be used in the MPC strategies. Its verification consisted in simple tests of separation of a praziquantel (PZQ) racemic mixture in the isotherm linear region (diluted concentrations). The volumetric flow rate of the pumps and the switching time (the same to all valves - classical operation mode), were calculated in the light of the triangle theory. This racemic mixture was chosen, because it is largely used to fight against schistosomiasis. The separation of these enantiomers is fundamental to formulate pediatric medicines for children under 5 years old. The great challenge is the separation taking into account some performance parameters. This challenge is going to be overcome by using advanced control strategies like MPC (Model Predictive Control).

KEYWORDS: Simulated Moving Bed, racemic mixture separation, chromatography process automation and control

1. INTRODUCTION

Praziquantel is an excellent anthelminthic against a broad spectrum of parasitic trematodes and cestodes (REICH, GOVINDARAJ et al., 1998). Thanks to this particular feature, this substance is included into the “WHO Model List of Essential Medicines” (WHO model list of essential medicines, 2018). Besides this efficiency in dealing with parasitic diseases, it is important to highlight that its administration is oral (i.e., tablet form). Unfortunately, tablet form does not include all group of humans in the regular treatment, preschool aged children (under 5 years of age) are not able to swallow these tablets. It is convenient to remember that the current commercial tablets contain the racemic mixture (The pediatric formulation, 2018). The levopraziquantel is the active principle, while the dextropraziquantel not only confers to the medicine a very strong bitter taste, but also it does not have the ability to kill parasitic worms, it just enlarges the tablets. The main idea behind new attempts to develop pediatric formulations is the separation between the levopraziquantel (L-PZQ and D-PZQ, respectively). The most common technology to separate racemic mixtures since 1990s is the Simulated Moving Bed (SMB) chromatographic process (HENNER SCHMIDT-TRAUB, 2012). Separation itself is not the biggest challenge, but separation of that mixture in a large scale and at the same time minimizing cost and maximizing profit and yield is the biggest challenge. As it is going to be formally presented latter (Section 2), the chromatographic process used to separate the racemic mixture of PZQ has some particular features that make any control strategy an open
issue that has been attracting many research groups around the world. This work intends to validate the actual SMB unit constructed in our lab. This step composes one of many steps to be accomplished towards the control of an actual SMB unit.

1.2. Main objective
Study of different control strategies in a semi-preparative real Simulated Moving Bed (SMB) unit, in order to separate the racemic mixture of praziquantel as convenient (i.e., many different concentrations).

1.3. Specific Objectives
Aiming to accomplish the main objective, the specific objectives are:
- Design and construction of a real SMB chromatographic unit in a semi-preparative scale;
- Validation of the actual SMB unit; and
- Study of different control strategies in the constructed SMB unit to produce continuously L-PZQ as near as possible to some optimal operating point.

2. SIMULATED MOVING BED (SMB) CONCEPT

It is didactic to start explaining the SMB process by making an analogy between the True Moving Bed (TMB) and SMB process. The TMB process has many disadvantages coming from the solid motion, for instance, increase in pressure drop, extract stream contamination by the solid phase, etc (GOMES, MINCEVA e RODRIGUES, 2006). Fortunately, a revolutionary patent (BROUGHTON e GERHOLD, 1961) came to overcome the limitations caused by the solid phase movement of the TMB process. The main idea coming from this patent was the existence of only the liquid phase movement, while the solid phase was kept with no motion. A relative movement between both phases was still experienced, as long as the inlet and outlet liquid streams were switched periodically in the same sense and direction of the liquid phase, so the solid-phase movement was simulated (that is why the *simulated* word is present in the process name). This patent was the very beginning of the SMB process era in the chromatographic separation processes. This approach allowed to overcome all the serious limitations related to TMB process. From that moment on, the SMB process started to be used in many industrial segments which required difficulty tasks of similar compounds separation, like petrochemical, pharmaceutical and sugar industries (RAJENDRAN, PAREDES and MAZZOTTI, 2009). Figure 1 and Figure 2 can clarify some important aspects of both mentioned process, like TMB solid movement and SMB switching streams, respectively. The valves responsible to switch the streams were not illustrated in the Figure 2, just for simplicity. In both processes, a zone is limited by process inlet and outlet streams. For instance, *zone 1* begins with solvent inlet stream and ends with the extract outlet stream; *zone 2* begins with extract outlet stream and ends with racemic (or feed) solution inlet stream, and so on until *zone 4*. A zone must have at least one chromatographic column.

Figure 1. TMB simplified scheme with four chromatographic columns.

Observing Figure 2, one can see just one column per *zone*, totaling 4 columns in this process. Furthermore, the switching streams, after a certain amount of time, promote a permanent
transient behavior to the process. This characteristic makes any control and optimization strategy much more complex, especially if the instantaneous concentration is taken into account. But fortunately, after a certain operation time the transient behavior starts to repeat over the time in a cyclic behavior, which is called Cyclic Steady State (CSS), (see Figure 3). Thanks to this cyclic behavior, it is possible to make a different approach based on the average concentration and not on the instantaneous one. This approach makes things easier, once a classical approach based on ordinary steady state behavior could be done. Thanks to the complexity involving a SMB process and, in order to get L-PZQ continuously from its racemic mixture without any unpredicted interruption, it is indispensable a good control strategy applied on the process (see Section 3).

2.1. Triangle theory

A common design method used to get preliminary flow rates and switching time for a specific SMB unit is the triangle theory. Its basis relies on the calculation of the liquid flow rate in each zone $j (Q_{TMB}^j)$ and the solid flow rate ($Q_{solid}$) both in the equivalent TMB. In the sequence, the ratio between them ($m_j$) are plotted:

$$m_j = \frac{Q_{TMB}^j}{Q_{solid}}$$  \hspace{1cm} (1)

where $j$ represents zone 1, 2, 3 and 4.

![Figure 2. SMB simplified scheme with four chromatographic columns. The locations of the inlets and outlets are illustrated in the (a) first, (b) second, (c) third and (d) fourth switching time.](image)

![Figure 3. Cyclic Steady State (CSS) behavior evidenced by the extract stream.](image)

The separation region has the shape of a triangle (that is why the name is triangle theory) and the regeneration region has a rectangular shape. It is pertinent to mention that the vertex 1 (see Figure 4) represents the point of maximum productivity, but it is important to remember that this theory was conceived with some strong consideration in mind, like linear adsorption isotherm, dispersion effects throughout the column ignored and instantaneous equilibrium between phases. Hence, the most powerful feature of this theory relies on given good preliminary flow rates. To operate in the vertex 1 is not a good choice (RODRIGUES, PEREIRA, et al., 2015), that is why control on the process is of utmost importance. Every process suffers influence from
the surrounding environment; therefore the variables of the process have a natural oscillatory behavior. Bearing that in mind, control strategies need to be developed in order to allow the best performance as possible. Reinforcing, therefore, the main goal of this work.

3. SMB PROCESS CONTROL

Usually the works focused on control issues of a SMB plant need to improve one of the blocks represented in Figure 5. Specially the one called “SMB Model + optimizer”. This block is the core part of a MPC, so it is not coincidence that many works tried to improve mainly this block (e.g., (KLOPPENBURG e GILLES, 1999) (ABEL, ERDEM and AMANULLAH, 2005) (ERDEM, ABEL and AMANULLAH, 2004) (GROSSMANN, LANGE and MAZZOTTI, 2010)).

![Figure 4. Separation regions.](image)

Nowadays, it is common to operate SMB units not in the optimal operating point, but at a reasonable distance from it, thanks to control difficulties (RAJENDRAN, PAREDES and MAZZOTTI, 2009) (SONG, LEE, et al., 2006a). Some studies have been done using different control techniques. In the following paragraphs some of the main works were shortly presented.

A model-based control to separate C8 aromatic substances made by KLOPPENBURG and GILLES (1999) used an interesting control strategy, which consisted in sampling the data just once in the middle of each switching interval and then sending them to controller. This approach allowed hiding the cyclic nature of SMB from the controller, which was a TMB model-based and a detailed SMB model represented the real plant. TMB model was used because of its continuous nature, which better suited control purposes. It is worth to mention that the considered SMB process had 24 columns and it is known that SMB processes with an elevated numbers of columns can be well described by TMB models (RODRIGUES, PEREIRA, et al., 2015). The extract purity and production of p-xylene were chosen as controlled variables and the extract and raffinate flows were chosen as manipulated variables. The main conclusion of this work was the successful controller performance for some proposed disturbances, but experimental validation is still necessary. It is appropriate to mention that a SMB 8 columns was also tested with this controller and, despite a quite different result, the controller strategy was also successful according to authors.

Another possible approach is using SMB model, instead of TMB model to represent a SMB process, but this approach often requires complex implementation and/or high computational costs. Song, et al. (2006a) proposed an identified model in order to overcome the above cited drawbacks and separate a racemic mixture of 1-1’-bi-2-naphthol. The controlled variables were the extract and raffinate purities averaged over one switching time and the flow rate ratios in zone 2 and 3 were the manipulated variables. As a result of these choices, a MIMO (2 by 2) system was constituted. A state-space model was used as an
identified model and the operation region explored was close to the optimal operating point calculated from the triangle theory. The achieved results were considered excellent by the authors, because the proposed set-point tracking and disturbances rejections were satisfactorily accomplished. An extension of this work was proposed by Song, et al. (2006b), in which productivity and solvent consumption were added as controlled variables and now flow rate ratio related to zone 1, 2, 3 and 4 were used as manipulated variables. The compounds to be separated were still racemic mixture of 1-1’-bi-2-naphthol. This new approach using this identified model was successful in pursuing the maximum of productivity and the minimum of desorbent consumption, as well as the disturbance rejection and set-point tracking.

Another interesting work complementing the above works was done by Song, Amanullah, et al. (2006), in which an actual laboratory scale SMB unit was used to test control strategies quite similar to strategies used by (SONG, LEE, et al., 2006a) and (SONG, LEE, et al., 2006b), but now to separate the nucleosides uridine and guanosine and not 1-1’-bi-2-naphthol as the formers. The results were very promising, but the tested strategies still need to be validated by an actual industrial SMB unit. Neural network has also been used as an identified model in some works as well. Wang, et al. (2003) work was carried out at nonlinear adsorption isotherm regions and long-range prediction performance was achieved for the proposed disturbances. But experiments in actual SMB units are required to confirm them. Other works related to identified models could be found at KLATT, et al. (2002) and in the references therein.

RMPC (Repetitive Model Predictive Control) was a strategy adopted by some authors. For instance, ABEL, et al. (2005) proposed a controller based on a simplified SMB model, because RMPC was able to handle significant uncertainties in the model parameters. The separation using this control strategy was successful and the fact of compounds uridine and guanosine present a linear adsorption behavior in the conditions studied helped a lot. The internal flow rates were the manipulated variables and the concentration in the outlet streams (extract and raffinate) were the controlled variables. It is important to notice that actual SMB unit was used and not a detailed SMB model instead. ERDEM et al. (2005) also used the RMPC concept, but the actual SMB plant was substituted by a detailed SMB model and the isotherm was in the linear region. The capability of controlling the unit in some optimum point was assessed by using a linearized state-space model in the optimization step. Furthermore, the manipulated variables were the four internal flow rates and the controlled variables were the concentration in the outlet streams. This study was purely theoretical and no specific substances were handle at all, they were named just species A (more-retained) and B (less-retained). ERDEM, et al. (2004) was an extension from the previous work, but now the SMB was running in the non-linear region of the isotherm, just the information provided by the Henry coefficients were used.

NETO, et al. (2016) proposed a nonlinear model based on first principles to predict the SMB behavior. The nonlinear model predictive control (NMPC) was tested in different scenarios and a good performance was observed. The SMB plant was represented by the same model used in the NMPC, but with a mismatch in the Henry coefficients, in order to simulate estimation errors, temperature fluctuations, and so forth that could culminate in thermodynamic changes during the separation. Despite the excellent results, the studies were carried out just in the linear region of the isotherm. And experimental verification is still needed, as the results were obtained from a virtual plant.

If someone goes deeper into the SMB literature, it shall be noticed that there is a lack of experimental works on SMB studies, especially in the nonlinear region of the isotherms. Working at the nonlinear region (high concentrations) would be preferable to linear regions (diluted concentrations) of the isotherms, because the productivity would be higher and solvent consumption lower.

4. RESULTS AND DISCUSSION

4.1. Validation of the actual unit

As mentioned earlier in Subsection 2.1, the triangle theory has been largely used as the first
approximation to calculate the flow rates and switching time to run the SMB unit. But it is important to keep in mind that the triangle theory takes into account just thermodynamic effects, leaving aside mass transfer ones. Furthermore, the analogy between the SMB and an equivalent TMB, considers that the SMB should have infinity columns per zone, that is the price paid to take advantage on its simplicity. Moreover, an actual SMB process suffers many disturbances, like kinetic effects (e.g., axial dispersion, diffusion in the stagnant liquid film surrounding the solid particles), variation of the adsorption equilibrium thanks to room temperature changes, fluctuations of the flow rate delivered by the pumps, extra column dead volume (thanks to tubing, valves and pumps), asymmetries in the switching time of each valve (ABEL, ERDEM and AMANULLAH, 2005) (GOMES, 2009). These are just a few of the phenomena not included in the triangle theory, but it still gives a good starting point to work. The validation of this unit in the light of the triangle theory has two main objectives:

• unit validation; and
• extracting crucial information that would help to update the model of the SMB, aiming to use it in advanced control strategies.

The validation started with four experiments that were situated in four different strategic areas of the triangle theory (see Figure 6). And, in the sequence, analyzing them in the light of the existed concepts related to SMB.

The flow rate in the zones 2 and 3 were responsible for separating the racemic mixture of praziquantel (PZQ) coming from the feed stream, that means, they were responsible for directing the more-retained substance, D-PZQ (from now on represented by the letter A), to the extract stream and the less-retained substance, L-PZQ (from now on represented by the letter B), to the raffinate stream, according to the area of separation considered in Figure 6 (A, B, C or D). It is of utmost importance to notice that behind the so-called triangle theory, there is the rectangle theory responsible to regenerate both phases (i.e., the liquid and solid phases). This rectangle area is represented by the letter E in Figure 6. All the experiments were conducted keeping the pair of flow rate ratios \( m_1 \) and \( m_4 \) fixed inside this area E. While the pair of flow rate ratios \( m_2 \) and \( m_3 \) were varied, in order to purposely direct the experiments to some desired area (e.g., areas A, B, C or D).

The results coming from the run 1 (see Table 1) were in agreement with the triangle theory and the simulation. Once the conditions chosen were supposed to keep the SMB far from the border, the separation in this condition should not be a surprise. But as mentioned earlier, it was a valuable result, bearing in mind that it helped to validate the constructed SMB unit.

In the sequence, the run 2 was carried out, and the results were shown in Table 1. In this run, the triangle theory, the simulation and the actual SMB unit seemed to show good agreement among them, despite the discrepancy of the purities in the raffinate stream. A comparison with the raffinate stream coming from the actual SMB related to the simulated data reveals that the raffinate was more contaminated by the more-retained species (A). Therefore, in the point \( P_1 \) the produced raffinate stream should be less contaminated by the species A, than in the point \( P_2 \). Bearing that in mind, the raffinate stream produced by the actual

Figure 6. Location of the experiments according to triangle theory. A: separation region, B: pure raffinate, C: pure extract, D: contaminated extract and raffinate, E: solid and liquid phase recovery, F: liquid phase not recovered and G: solid phase not recovered.
SMB unit seems to be in an upper position, if compared with the ideal situation.

The next proposed experiment, *run 3*, intended to direct the SMB to the region of pure raffinate, this region was represented by the letter B in Figure 6. The simulated data showed an ideal situation, where the raffinate stream should be purified and the extract should be contaminated by the species B.

**Figure 7.** Lines PP₁P₂ and PP₃P₄ indicate paths toward a more impure raffinate stream and extract stream, respectively.

In Figure 7, if an experiment in the SMB unit walks on the line PP₃, from the point P to point P₄, the extract stream becomes more contaminated by the less-retained species (B). Therefore, in the point P₃ the produced extract stream should be less contaminated by the species B, than in the point P₄ (the explanation is similar to the *run 2*).

Observing the previous *runs*, the results coming from the experiment called *run 4* (the blue square one), could be easily predicted. As illustrated in the Figure 8, after the triangle shifting, the square point starts to be located in the region C (*i.e.*, pure extract and contaminated raffinate).

**Table 1. Results of the outlet streams.**

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Simulated</th>
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<tbody>
<tr>
<td></td>
<td>Extract</td>
<td>Raffinate</td>
</tr>
<tr>
<td><strong>Purity (%) – run 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purₐ</td>
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<td>0</td>
</tr>
<tr>
<td>Purₐ</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><strong>Purity (%) – run 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purₐ</td>
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<td>30</td>
</tr>
<tr>
<td>Purₐ</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td><strong>Purity (%) – run 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purₐ</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>Purₐ</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td><strong>Purity (%) – run 4</strong></td>
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<tr>
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<td>21</td>
</tr>
<tr>
<td>Purₐ</td>
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<td>79</td>
</tr>
</tbody>
</table>

The results of *run 4*, shown in Table 1 confirm the location of the experiment in the region of pure extract and contaminated raffinate, as predicted.

**Figure 8.** Proposed shifting of the triangle of separation after the *run 1*, 2 and 3.
5. CONCLUSIONS

The validation of the SMB process, situated at LABCADS/LADEQ/EQ/UFRJ, was successfully accomplished. The experiments pointed out that the triangle of separation predicted by the triangle theory has been shifted thanks to some non-ideality existent in the actual SMB unit. There are literature mentioning mass transfer effects and/or switching time asymmetries as the main non-idealities that could be accounted for in mathematical models of SMB. The next step of the work is going to consist in identify the main non-idealities of the unit.

6. BIBLIOGRAPHIC REFERENCE

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