*Iranian Journal of Chemical Engineering*
*Vol. 15, No. 4 (Autumn 2018), IAChE*

# Design and Fabrication of an Improved Single-Column Chromatographic Separation Process

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**ARTICLE INFO**

**Article history:**
*Received: 2018-07-28*
*Accepted: 2018-09-22*

**Keywords:**
*Chromatographic Separation,*
*Process Design,*
*Monitoring,*
*Guaifenesin*

**ABSTRACT**

*In this work, an improved single-column chromatographic (ISCC) separation process is proposed. The term "improved" represents both conceptual and physical modifications compared to the available single-column processes, including a novel fraction collection scheme and allowing overlapped peaks from adjacent cycles. In addition, the fraction collection mechanism was modified in order to facilitate online monitoring. Another advantage of the ISCC process is that its large degree of freedom as injection volume, cycle time, solvent flow rate, feed concentration, and fraction-collection intervals can all be decision variables in this process. The experimental implementation and validation are covered in this work. The results indicate the successful operation of the ISCC process and accompanying peripherals for the separation of guaifenesin enantiomers. In particular, the tests confirmed the integrity of the online monitoring system and proved the capability of the process for 98 % purification of the tested enantiomers with an advantageously shorter cycle time, resulting in higher productivity.*

## 1. Introduction

Despite the high value of products produced by chromatographic separation, fixed and working capitals are important factors in the profitability of such production plants. Usually, the fabrication costs are minimized by modification of the process design, while the working capital is minimized by the optimization of the process conditions.

Continuous chromatographic separation is the preferred method for large-scale production due to its higher productivity and robustness [1-3]. Simulated moving bed (SMB), introduced in 1960 [4], has become the benchmark in this regard. Although single-column chromatography does not appear to be highly competitive, it is still attractive due to higher flexibility and lower capital investment [5, 6].

In this work, an improved single-column chromatographic (ISCC) separation process is developed to eliminate the inefficiencies of the usual stacked injection chromatography [7], i.e., low productivity and high solvent (desorbent) requirement, while utilizing its inexpensive and simple design. The term

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"improved" represents both physical and conceptual improvements in the process; the feed injection and fraction collection mechanisms of commercial high-performance liquid chromatography (HPLC) units were modified to facilitate the mode of operation and online monitoring. The process performance is also improved by several factors including allowing overlapped peaks from adjacent cycles, dividing the elution profile into four fractions, and variable cycle times and injection volumes.

It must be mentioned that there are other competitive process designs available in the market, which deserve attention. In fact, closed-loop recycling (CLR) chromatography [8] and steady-state recycling (SSR) chromatography [9] have certain similarities with the ISCC process. However, in the CLR process, one injection is resolved multiple times by recycling a portion of the elution profile in contrast to the intermittent feeding in the ISCC process. On the other hand, while overlapping is the essential part of the ISCC processing method, in the SSR process, overlapping is not allowed, particularly due to difficulties occurring in the mathematical formulation [10].

Developing an efficient online monitoring system, especially for chiral separation, is still an open challenge [11]. A novel online monitoring system, which operates on a cyclic basis, was developed in this work. This is intended to return average purity/recovery measurements for product quality control and closed-loop automatic operation. Two HPLC units, each comprising a pump, an analytical column, a UV detector, and an injection valve, are the main components of the proposed online monitoring system. This arrangement improves the sampling rate and increases the accuracy of analysis. In addition, two customized intermediate vials are designed and realized to connect the online monitoring system to the fraction collection mechanism, as described in Section 2.1. The role of the intermediate vials is to obtain the average concentration of products per every cycle of operation/analysis. Therefore, they are made in such a way that perfect mixing is achieved, and cross-contamination between collection cycles is minimized.

This study focuses on the process design and fabrication and presents the results of preliminary experimental works carried out by the ISCC process. Other studies have described process optimization and control elsewhere [12-14]. The process was realized on a laboratory scale with a semi-preparative chiral stationary phase (CSP) column as the heart of the separation process. The operating parameters are implemented through a dedicated human-machine interface (HMI) software package developed for this process on site. It is also in charge of automatic injection and fraction collection. The integrity of the process, the online monitoring system, and the HMI were validated in practice for steady-state runs.

## 2. Process description

It is well known that batch chromatography, even at its best (i.e., stacked injections), suffers from both low productivity and high solvent consumption [7]. Accordingly, one of the reasons is the tailing effect of nonlinear isotherms, causing very low concentration spread over a long portion of the collection cycle. Such tails can be truncated with low costs by allowing overlapping profiles from the same or adjacent cycles and discarding or recycling the corresponding fractions. This manifests itself as a reduction in the cycle

time for the same feed throughput and purity requirement. As a result, productivity can increase, and solvent consumption can decrease. The former parameter implies higher production income, while the latter one implies the reduction of production costs. This is, in fact, the primary advantage of the ISCC process. A schematic of this mode of operation is given in Figure 1.

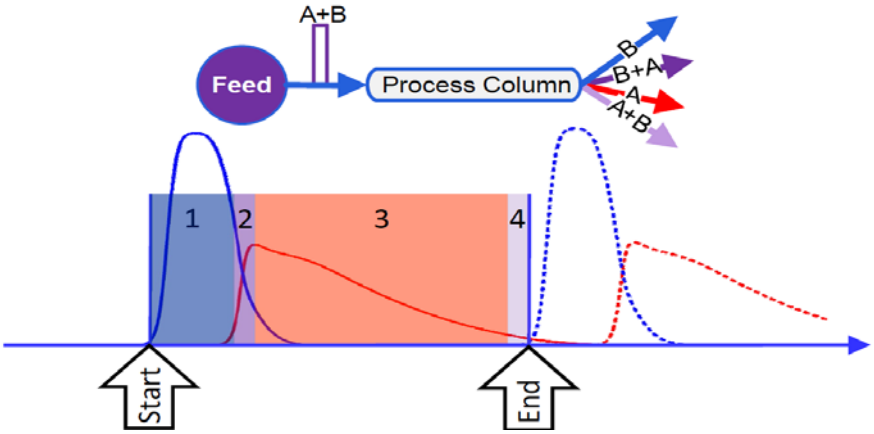


**Figure 1.** Conceptual operation of the ISSC process.

Implementing such a mode of operation requires major modifications in injection, fraction collection, and online monitoring systems. Moreover, as the process description suggests, a larger degree of freedom is advantageously achieved in this mode of operation, which is important regarding process optimization. However, it complicates process design and control inevitably. With overlapping profiles, as cycle time decreases, the time window available for measurements also decreases. This necessitates employing a faster online monitoring system. Therefore, an online monitoring system is designed and fabricated for this process based on a combination of two customized HPLC systems, fitting the fraction collection mechanism, too.

The complete process of the flow diagram is given in Figure 2. In the forthcoming paragraphs, the item numbers refer to those given in Figure 2. To deliver an accurate feed flow rate, the feed is injected by the arrangement of an HPLC pump (P1) and an 8-port and 2-position switching valve (V1). The arrangement replaces conventional autosamplers and reduces sample injection time by delivering the feed as a train of consecutive pulses. In addition, it allows modulation of injection volume in a gradual manner by partial loop filling, which is necessary for the implementation of the optimal point in the entire range of injection volumes. The second HPLC pump (P2) is used to deliver the solvent. The solvent flow rate is limited by the maximum allowable pressure drop that the stationary phase can withstand.

A semipreparative column (C1) is used as the core of the separation process. The process column is followed by an ultraviolet (UV) detector (D1), which monitors the concentration change in outlet stream, as shown in Figure 3a. Since it is unable to differentiate the two enantiomers, this detector provides supervisory information for monitoring the overall process condition, for example, to set the time to start the fraction collection.

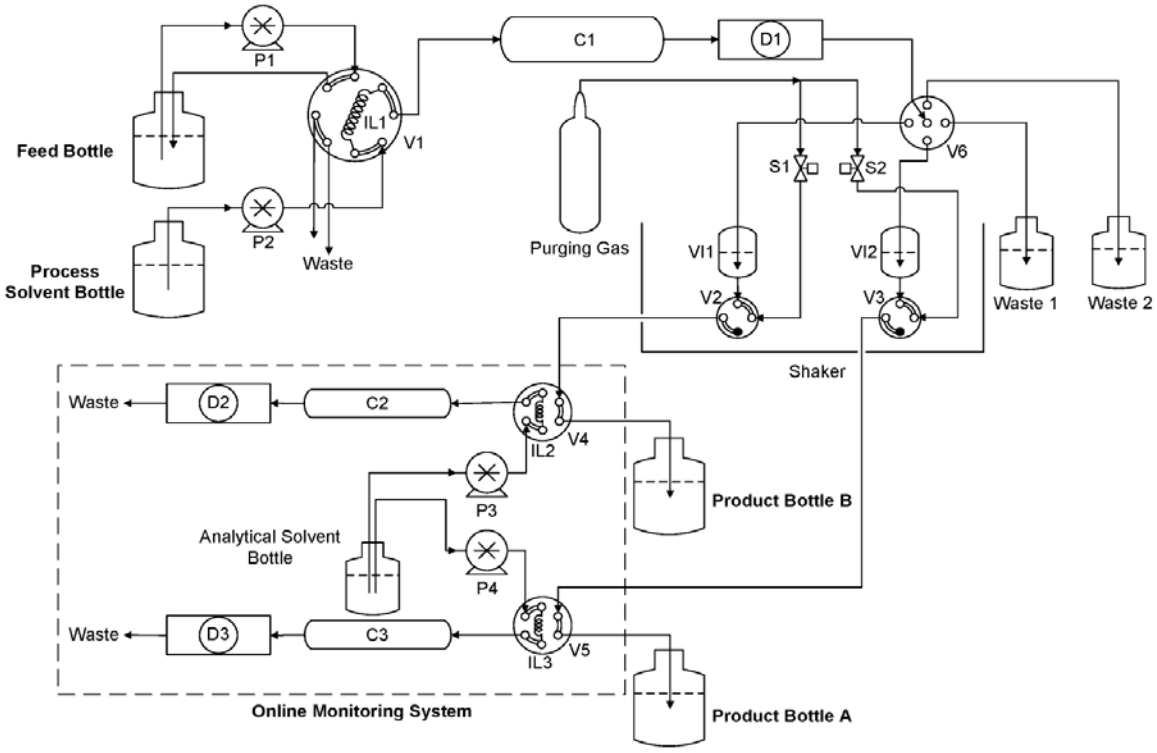


**Figure 2.** Process flow diagram.

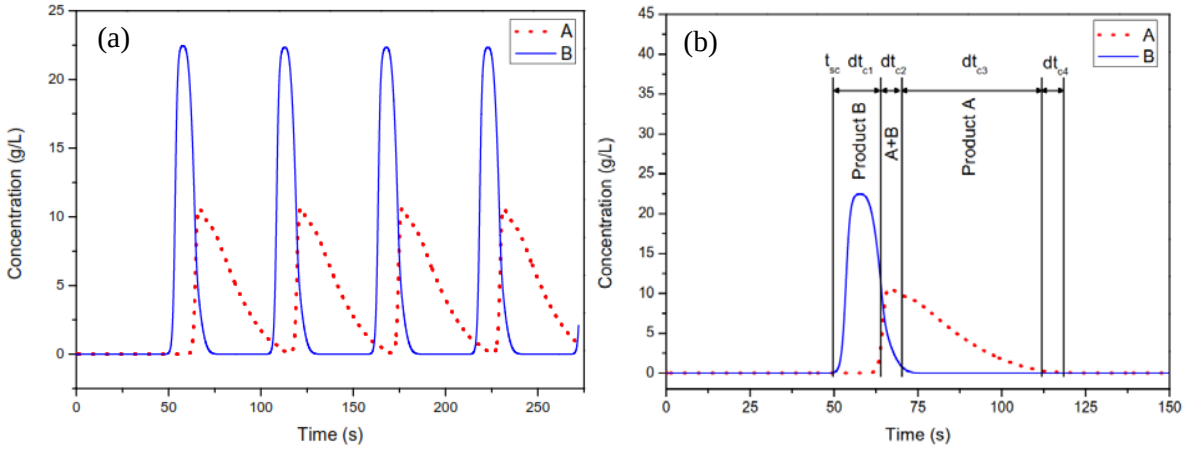


**Figure 3.** Typical elution profiles: (a) train of overlapped peaks; (b) allocation of cut intervals and fractions.

The chromatogram obtained over one cycle is divided into four fractions based on the target products, as shown in Figure 3b. The start of the first cycle is detected after a threshold by the rising shoulder of the first eluted peak. In the steady-state mode of operation, the starting points of consecutive cycles are simply assigned with respect to this point. In the dynamic mode, however, the actual cycle time may change due to a change in the solvent flow rate, feed concentration, or other factors. Therefore, the new fraction collection strategy was devised based on peak detection techniques, as described elsewhere [13, 14]. The conventional fraction collection is revised both conceptually and practically. A 5-port, 4-position valve (V6) is used as a fraction collector, as shown in Figure 2. The

fraction collector mechanism incises the elution profile of every injection into four fractions: the first portion is typically rich in the less retained compound, which is called compound B in this work. The third portion is typically rich in the more retained compound, called compound A here. The second and fourth portions are mixtures of A and B (see Figure 3b). Of note, the concentrations of the second and fourth fractions are not identical. For a Langmuir type isotherm, the fourth fraction is usually very diluted, that is, its total concentration is by far less than the second one. Therefore, these two mixtures are collected separately for further processing or recycling. Of course, recycling the second fraction has more potential to be economical as compared to the fourth fraction.

### 2.1. Intermediate vials

After fractioning each chromatogram, the product streams are sent to two intermediate vials (VI1/VI2), where the contents in the vials are well mixed so that they represent average concentration of respective fractions. The natural circulation of the mobile phase is not enough to provide the perfect mixing. Therefore, vials are designed and fabricated to enhance mixing. In addition, the vials and their accompanying switching valves are mounted on a variable-speed external shaker, facilitating an orbital movement at a rotational speed of $\omega$ for better mixing.

The schematic drawing of the vials is given in Figure 4. The main part of each intermediate vial is a Swagelok sampling cylinder [15]. It is necessary to make major modifications in order to achieve desirable results. For instance, a proprietary insert was designed to minimize the dead volume of the outlet port. Additionally, as the purging gas (helium) enters from the lower nozzle, the upward flow of gas also blocks the flow of liquid downward and, hence, isolates dead volumes under the outlet nozzle. This is a major difference compared to the normal way of purging liquid-filled vessels. It must be emphasized that the primary purpose of gas filling is to pressurize the vial and regulate the purging speed. Moreover, a small piece of tubing is used to create a deep-jet nozzle. The length of tubing is selected in such a way that the inlet liquid is injected far beneath the liquid level, causing additional mixing. The tubing used as the deep-jet nozzle is slightly tilted. Therefore, it acts as a baffle and further boosts the mixing.

### 2.2. Online monitoring system

After sufficient mixing, the two product fractions are purged from the intermediate vials to the product bottles by means of the purging gas. During purging, a small portion of each product is withdrawn by a switching valve (V4/V5) from each vial and sent to the online monitoring system for analysis. The online monitoring system comprises two pumps, two analytical chiral columns, and two injection valves followed by two UV detectors. This mode of using HPLC modules for online monitoring is similar to what was suggested by other researchers [16-18]. However, for the current system, the way the products are collected and directed to the online monitoring system is an innovative approach. Moreover, compared to conventional low-frequency online HPLC detection, this system works at a moderate sampling frequency as the two fractions can be analyzed simultaneously, reducing time delay to analyze two products in one cycle. The entire laboratory-scale process setup is shown in Figure 5.

| No. | Description |
|---|---|
| 1 | Swagelok sampling cylinder |
| 2 | Deep-jet injection tubing/Liquid inlet |
| 3 | Insert for reducing internal diameter |
| 4 | Male nut |
| 5 | Reducing union |
| 6 | Liquid outlet/Gas inlet |

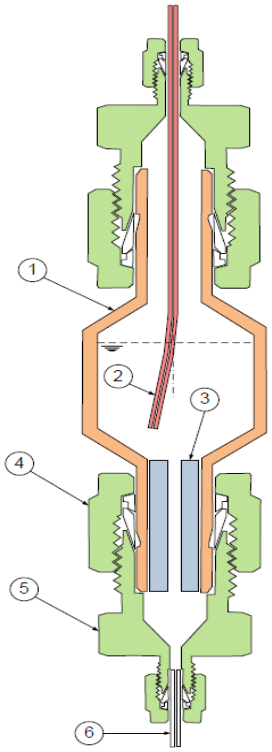


**Figure 4.** Cross-section of a customized intermediate vial.

**Figure 5.** Laboratory process setup displaying HPLC modules, fraction collection, online monitoring, and the HMI system.

### 2.3. Human machine interface

A human machine interface (HMI) is essential to communicate with the process components, automate, and interface with the user. The backbone of the communication system is National Instruments software and hardware products (National Instruments, Singapore). The LabVIEW development software package was employed as a programming environment, and various hardware products were used as input/output devices. The HMI features manual, semiautomatic (steady-state automation), and fully automatic (controlled) modes of operation. It also includes data logging, emergency interruption, startup, and shutdown procedures. The main menu of the HMI system is shown in Figure 6.

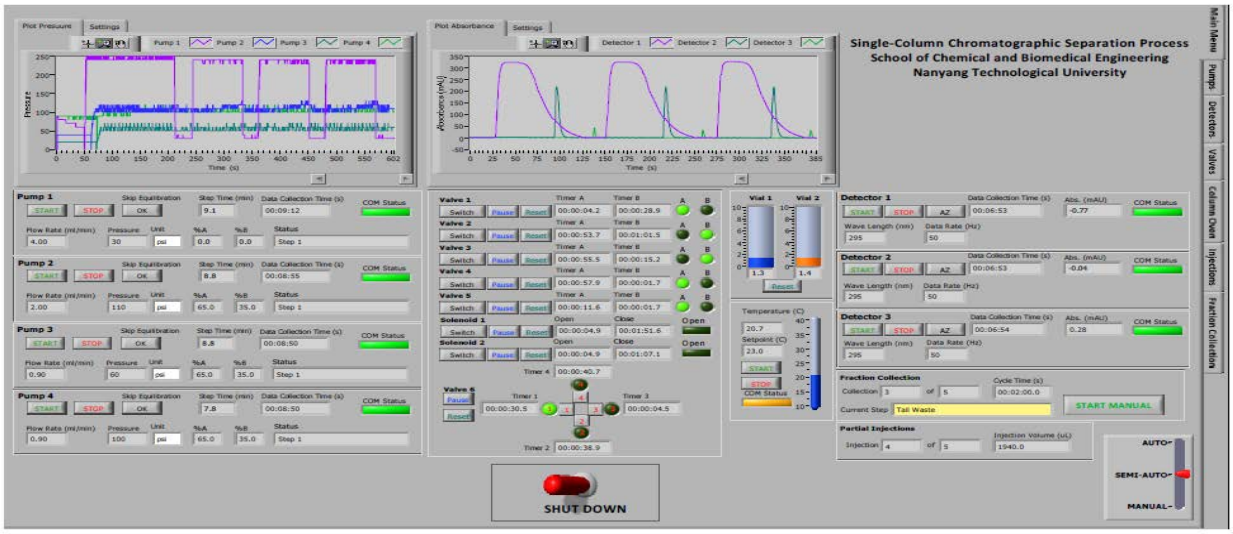


**Figure 6.** A snapshot of the main menu of the process HMI.

## 3. Experimental section

### 3.1. Materials

Racemic guaifenesin, obtained from Fludan (Vankleek Hill, Canada), was used as a solute. (S)-(+)-Guaifenesin is the more retained enantiomer denoted by A, and (R)-(−)-guaifenesin is the less retained enantiomer denoted by B throughout this paper. A mixture of chromatography-grade heptane and ethanol, obtained from Sigma-Aldrich (Singapore), was used as a mobile phase. A cellulose-based chiral stationary phase (cellulose tris (3,5-dimethylphenylcarbamate) coated on silica) was used as the stationary phase in the preparative column (Chiralcel OD, 10 cm × 1 cm i.d., particle size 20 μm) and the two analytical columns (Chiralcel OD-H, 15 cm × 0.46 cm i.d., particle size of 5 μm). All the columns were purchased from DAICEL, Singapore.

### 3.2. Process equipment

The ISCC process comprises various building blocks of conventional HPLC modules. The modules (i.e., pumps, UV detectors, oven, and degassers) were purchased from PerkinElmer (Singapore). The switching valves were purchased from VICI (Schenkon, Switzerland).

## 4. Results and discussion

### 4.1. Testing the intermediate vials

The objective of this experiment is to evaluate the mixing and cross-contamination in the vials. The test is based on checking the material balance through absorbance analysis. Any biased deviation from the mass balance or sporadic response is a sign of imperfect mixing or cross-contamination, while the latter problem can be readily detected by blank injections.

The mass injected as feed can be related to the concentration in the liquid holdup. Theoretically, considering density as a constant, the concentration in the vial liquid holdup is:

$$c_H^t = \frac{c_T^F V_{inj}^F}{V_H} \qquad (1)$$

where $c_T^F$ is the feed concentration, and $V_{inj}^F$ and $V_H$ are the volumes of the feed injected and the liquid holdup, respectively. On the other hand, experimentally, the concentration in the vial liquid holdup is:

$$c_H^e = \frac{A_S}{A_F}\frac{c_T^F V_{inj}^F}{V_{inj}^S} \qquad (2)$$

where $A_F$ and $A_S$ are the areas under

absorbance curves of the feed injected and the sample taken from the liquid holdup, respectively. $V_{inj}^{S}$ is the volume of the sample taken from the liquid holdup. It must be noted that this formulation is based on the assumption of the linear response of the UV detector, which is valid when the concentration is low.

The mixing effectiveness factor is defined as follows:

$$\alpha = \frac{C_H^e}{C_H^t} \qquad (3)$$

where $\alpha$ must be unity for perfect mixing and, in the case of blank injections, must be zero for no cross-contamination. A typical case of analysis is given in Figure 7. In this test, similar to the normal operation, yet without any HPLC column used, a diluted pulse of feed is injected into the vial. Similar to the procedure explained in Section 2.1, the vial is then pressurized, and sufficient time is given until perfect mixing has been achieved. Then, a small sample of the vial contents is withdrawn for analysis. This sample is directly injected into a similar stream of clean mobile phase and, then, is analyzed using a UV detector. Finally, $\alpha$ is determined by the experiments. The values of the parameters involved in this test are given in Table 1. The $\alpha$ values are given in Table 2. Note that the last run is for a blank injection.

For a majority of runs, $\alpha$ is very close to unity, which means that the measured concentration is a good representative of the average concentration. On the other hand, it is clear that there is minor cross-contamination between consecutive runs. However, if we inject the second blank, no peak can be identified within the sensitivity of the UV detector. This means that contamination is only carried to the very next cycle. In other words, this monitoring system has a dynamic behavior with a one-cycle transient response until it gives accurate readings, which is acceptable for continuous operation.

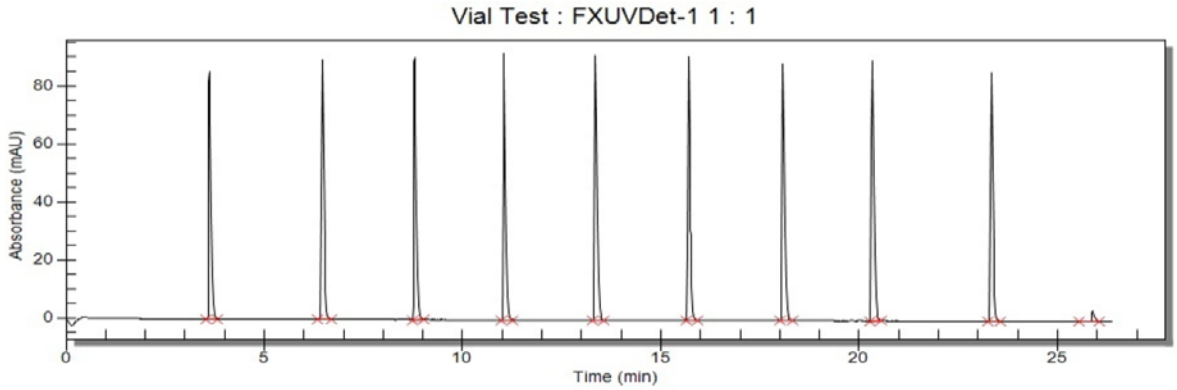


**Figure 7.** Testing mixing and cross-contamination in the intermediate vial.

**Table 1**
Values of the parameters involved in the vial test.

| Parameter | Value |
|---|---|
| $c_T^F$ | 10 g/L |
| $V_{inj}^F$ | 50 µL |
| $V_{inj}^S$ | 20 µL |
| $V_H$ | 2 mL |
| $\omega$ | 150 rpm |

**Table 2**
The results of testing mixing and cross-contamination in an intermediate vial (Note: the last run is a blank injection).

| Run | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| $\alpha$ | 0.94 | 0.98 | 0.98 | 1.01 | 0.99 | 0.99 | 0.96 | 0.97 | 0.93 | 0.04 |

### 4.2. Separation of guaifenesin enantiomers

The purpose of this open-loop operation is to test and verify the separation performance of the ISCC process and the integrated online monitoring system without imposing any controller. The operating parameters for the experiments are summarized in Table 3. After the feed injection step, the separation performance is monitored by observing the elution profile on the process UV detector (Figure 8). Products are collected in the intermediate vials and analyzed in the analytical HPLCs, as described earlier.

**Table 3**
Operating parameters for the open-loop operation of the ISCC process.

| Parameter | Value |
|---|---|
| $c_T^F$ | 10 g/L |
| $Q^D$ | 4 mL/min |
| $t_{cy}$ | 175 s |
| $dt_{c1}$ | 75 s |
| $dt_{c2}$ | 5 s |
| $dt_{c3}$ | 90 s |
| $V_{inj}^F$ | 2 mL |
| $\lambda$ | 295 nm |
| $Q_{ana}^D$ | 0.9 mL/min |
| $\lambda_{ana}$ | 255 nm |
| $V_{inj}^S$ | 20 µL |
| $\omega$ | 150 rpm |

In this case study, the objective is to achieve 98 % purity for both products. The steady-state elution profile of this experiment is shown in Figure 8. For the sake of brevity and clarity, only a part of the elution profile is presented here. Figure 8 indicates a successful separation of the enantiomers with considerable intraprofile and profile-profile overlaps. The less retained compound (product B) was collected in Vial 1, and the more retained compound (product A) was collected in Vial 2. The chromatograms of the online monitoring system are shown in Figure 9. The analytical response of the products in Vial 1 (Figure 9a) shows that there are small peaks of the more retained compound (product A), indicating a separation under reduced purity (~98 %). Similar observations were made for the product in Vial 2 (Figure 9b).

It is apparent that when overlapping of the adjacent cycle is employed like the case studied here, the actual cycle time is decreased, which implies processing the same amount of feed at a shorter interval. This is simply translated into higher productivity compared to the stacked injection scheme, which was theoretically investigated in our previous studies [12, 19].

## 5. Conclusions

In this work, after a brief comparison of the available single-column chromatographic separation processes, The ISCC process was described in detail and in technical terms. We discussed how the online monitoring system proposed in this work is different from available instruments. After elaboration on the importance of mixing in the intermediate vials, their integrity was confirmed and shown that, in practice, this system is viable. The process was run qualitatively to ensure that all sections can operate seamlessly. The process is superior to the stacked injection method since a shorter cycle time can be

employed for the same feed throughput, showing higher productivity.

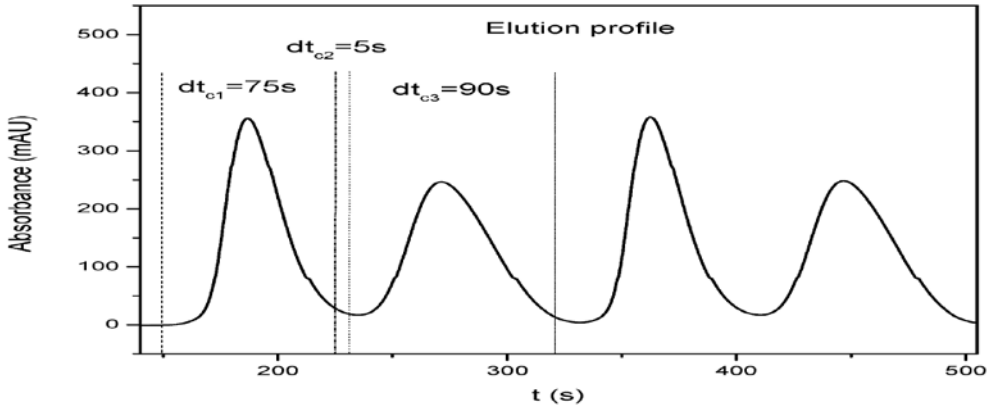


**Figure 8.** Elution profile of the steady-state operation of the ISCC process as seen on the detector D1.

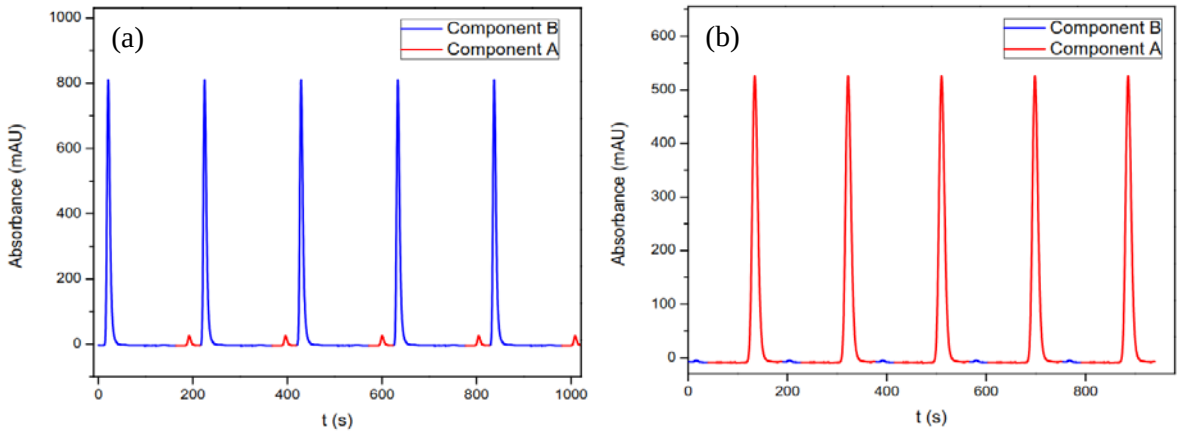


**Figure 9.** Products analysis via the online monitoring system: (a) vial 1; (b) vial 2.

There are several operational considerations regarding the process and online monitoring system design; partial loop filling may be a major source of irreproducibility. This can be avoided using a loop volume much larger than injection volume and synchronization of software, pump, and switching valve to ensure loading of an accurate amount of feed. Tubes with a smaller diameter are favored for injection loop to minimize axial dispersion during injection and achieve an ideal rectangular pulse feed delivery. Axial dispersion in the injection system may cause long tails in the elution profile, resulting in poor resolution. However, pressure drop limits the smallest diameter that can be used for this purpose. Furthermore, proper mixing in the intermediate vials is essential for online monitoring of the products concentration profiles. For large molecules or for viscous fluids, mixing must be enhanced. In general, vial volume, gas inlet pressure, mixing time, and shaker speed must be adjusted to achieve proper mixing. Use of a transparent material for the vials allows a visual inspection of the mixing patterns.

A short measurement time for the products' concentration values is necessary for high-frequency feedback information to the controller. This is, however, dictated by the maximum allowable pressure drop of the stationary phase of the analytical column. Selection of the column length, stationary phase, and analysis operating conditions (e.g.,

flow rate, mobile phase composition, and temperature) must take place such that analysis time is minimized along with baseline separation with some room for flexibility to account for process variations.

Of note, although the ISCC process and its online monitoring system are designed for binary separation, they can be extended for multi-component separation with appropriate modifications.

**Acknowledgment**

The experiments were carried out at the School of Chemical and Biomedical Engineering (SCBE), Nanyang Technological University under Grant No. RG24/07 for which the authors thank Singapore's Ministry of Education. We would also like to acknowledge the help of many school's staff in accomplishing this project, especially Mr. Lim Beng Chong from the SCBE mechanical workshop who helped the authors with the design and fabrication of laboratory equipment and intermediate vials.

**Nomenclature**

| | |
|---|---|
| A | area under absorbance curve [mAU.s]. |
| $c_F^T$ | total feed concentration [g/L]. |
| $dt_{ci}$ | cut intervals [s]. |
| $Q^D$ | solvent flow rate [mL/min]. |
| $t$ | time [s]. |
| $t_{cy}$ | cycle time [s]. |
| $t_{sc}$ | start of cycle [s]. |
| $V_H$ | holdup volume of the intermediate vial [μL]. |
| $V_{inj}^F$ | feed injection volume [μL]. |
| $V_{inj}^S$ | sample injection volume [μL]. |
| $\alpha$ | mixing effectiveness factor. |
| ω | shaker speed [rpm]. |
| $\lambda$ | wavelength [nm]. |

**Superscripts and subscripts**

| | |
|---|---|
| ana | analytical. |
| cy | cycle. |
| D | solvent (desorbent). |
| e | experimental. |
| F | feed. |
| H | holdup. |
| inj | injection. |
| S | sample. |
| t | theoretical. |
| T | total. |

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