Experimental study of optimizing control of continuous chromatographic separation process

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**EXPERIMENTAL STUDY OF OPTIMIZING CONTROL
OF CONTINUOUS CHROMATOGRAPHIC
SEPARATION PROCESS**

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I would like to dedicate this thesis to my loving parents.

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Abstract

As single enantiomeric drugs bring clinical benefits in terms of improved efficacy and more predictable pharmacokinetics, the drug quality regulatory authority, i.e, U.S. Food and Drug Administration (FDA) requires marketing of enantiopure drugs instead of racemic mixture. This has provided a great challenge to the industries and researchers to seek techniques that are efficient, economical and easy to apply for the production of enantiopure products. Chiral chromatography is one of the preferred techniques for this kind of separation due to its cost effectiveness, ease of operation, and flexibility. During past two decades, continuous chromatography has received growing attention of many researchers over batch chromatography, as there is clear scope to increase the efficiency and the performance of the processes. Simulated moving bed (SMB) process has become renowned for large-scale operation as this is supported by rich theoretical background and is benefited by counter-current mode of operations. The complexity and difficulties of SMB designing and controlling lead the researchers to imitate SMB by simpler processes that can harness both the advantages of batch and continuous processes. From this motivation, we developed an economical process, which is simple and easy to handle compared to an SMB process in low to moderate scale of production.

In this project, we proposed an improved single-column chromatographic (ISCC) separation process. The improvements are in physical modifications and conceptual advances making the ISCC process distinct from existing single column chromatography processes. Fraction collection schemes and mechanism are the important features of the improvement. Design of the customized fraction collection system allows accommodation of overlapped peaks from adjacent cycles and reduce the overall time delay of the system. Process design accommodates a wider degree of freedom:

injection volume, cycle time, desorbent flow rate, feed concentration and fraction-collection intervals.

An accurate and robust online monitoring system for continuous chromatography, especially for chiral separation, continues to be a challenge. An automated online monitoring system, which overcomes the existing limitations has been designed. Our online monitoring system comprises two analytical columns along with standard HPLC peripherals. Besides being relatively inexpensive, it offers high frequency and accurate analysis of samples compared to an analytical HPLC or a combination of various detectors. Effectiveness of this customized online monitoring system was demonstrated through implementation with the ISCC process for the separation of guaifenesin enantiomers.

Operational cost and profit maximization play a significant role to evaluate the performance of a process. In ISCC process, these factors are related to several decision variables and constraints. The optimization of this process is not a straightforward solution, as there are numerous opposing effects creating complex functions. Therefore, there may not be a single operating point for the optimal run of the process. We used a multi-objective stochastic optimization technique based on genetic algorithm (GA) to optimize the process performances. The optimization problem was appropriately formulated as a multi-objective optimization problem with the aim of maximization of productivity and minimization of desorbent consumption. A set of optimal operating points were found in the multi-dimensional solution domain constrained by product specifications and hardware limitations of the system. These non-dominated points along with the contribution of the decision variables were presented using Pareto fronts.

Detector calibration is in general a prerequisite for isotherm determination. This posed a challenge due to high nonlinearity of the response of the detector. This has been overcome by adopting a new method for simultaneous calibration of detector and determination of adsorption isotherm. The nonlinear direct inverse method developed in this study can readily be used for a mixture of enantiomers under base line separation

or overlapping of elution profiles. This is a relatively fast and economical techniques compared to existing alternatives.

A robust and efficient optimizing control scheme is sought for continuous operation of the ISCC process that guarantees product and process specification and at the same time optimize the process performance. The performance of the ISCC process was also compared with a similar SMB process. This study provided the basis for reaping the full potential benefits of a single column process that adopts cyclic injection. Besides, relative contribution of the decision variables were ascertained through the study of their effects on the performance indicators. A ‘cycle to cycle’ model predictive control (MPC) scheme for the ISCC process was developed earlier in-house to meet this need. This control scheme was able to satisfy the constraints and achieve optimized profitability as was demonstrated through simulation studies. Besides, MPC has the advantage of efficient set-point tracking and disturbance rejection.

Finally, the cycle-to-cycle optimizing controller developed for the ISCC process for the separation of a mixture of guaifenesin enantiomers. Key implementation issues were accuracy of the online measurement system and integration and automation of the ISCC process with online measurement system and controller. This was achieved by designing and developing a human machine interface (HMI) that was able to effectively communicate among the three essential components of the control loop. The performance of the controller was tested for set point tracking and disturbance rejection. Results indicate that the controller was able to deliver product specifications, and at the same time, optimize the process performance.

In this work, we developed and realized an improved single-column chromatographic (ISCC) separation process to eliminate the inefficiencies of usual stacked injection chromatography that is, low productivity and high desorbent requirement while utilizing its inexpensive and simple design. I also developed an optimizing controller based on strong mathematical modeling, robust online monitoring system and offline optimization of the ISCC process. Our contribution is not limited to

the physical improvements in the separation process. Moreover, the improvement in the fraction collection concept, which allows overlapping of two adjacent cycles, is also an important contribution to the separation technology.

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Chapter 1

Introduction

The history of optical activity is not new; Biot first noted it in early 1800s. Pasteur established the concept of optical isomers in 1848. Emil Fisher's Nobel Prize winning work in chemistry regarding the configuration of (+)-glucose was one of the major steps of stereochemistry. Continual work in the field of stereoisomer moves relatively at a snail's pace until about 1980 when the selective physiological activity of the different optical isomers of drugs became renowned. Workings on stereoisomer become a high priority by the impact of the Thalidomide disaster. The United States Drug Administration mandated the testing of the optical isomers of all drugs that could exist in enantiomeric forms. Thus, the demand for analytical techniques to separate enantiomeric drugs increases. Optically active compounds also find applications in agrochemicals, flavour and fragrances, foodstuffs, liquid crystals and non-linear optical materials, electronics, biochemicals, polymers and other areas.

Today, approximately 80% of chiral intermediates and related products go into the pharmaceuticals market, and it is expected that in the future, pharmaceuticals will remain the key driver for chiral chemistry development (1). Chiral drugs comprise more than half the drugs approved worldwide, including many of the top-selling drugs in the world. Among the top 10 best-selling US prescription small-molecule pharmaceuticals in 2009, six of these are single enantiomers, two are achiral, and only two racemates. The chiral drugs increased from 30-40% in the 1990s to around 60% or above since 2000. There is clear trend that the racemate drugs are decreasing from 1992 (about 21%) to 2008 (5%), with no racemic drug introduction at all in 2001 and 2003 (2).

The modern trend of chiral technology has been greatly shifted towards the single enantiomeric drugs due to the strict regulations imposed by drug approval authorities in order to obtain higher drug efficiency and to alleviate undesirable side effects (3). Enantiopure compounds can be accessed either by traditional organic synthesis or by resolution technologies, i.e. kinetic resolution, chromatographic resolution (4). Recently, chromatographic enantioseparation has become the preferred method for its cost effectiveness, ease of operation, and flexibility (4), as it covers variety of processing materials and methods supported by rich theoretical background (5–10).

Chromatographic separation process design schemes vary from single-column batch separation to fully automated simulated moving bed (SMB), which resembles a continuous process. Depending on the scale of operation, the chromatographic separation can also be divided into three broad groups: analytical, semi-preparative and preparative chromatography. The objectives of developing new processes can be increasing the productivity and reducing the total production cost. Observing the ever-growing stringent quality control regulations and safety can also be other motivations. There is no cure-all for all problems and a compromise might be necessary for any specific demand. For instance, batch operation is well suited for varying feeds and research activities while at large scale and for a fixed production, an SMB process is favorable and outruns the batch operation.

In recent years, most enantioseparation uses traditional elution chromatography approaches utilizing ‘touch band’ separations. Moving from the touching band situation to the sample overloading situation results in a complex peak, where peaks become merged to a degree (4). Higher productivity can be obtained through this method if appropriate place for fraction cutting within the complex chromatographic peak is chosen. In addition, the solvent requirements for such separations can be reduced which can improve the economics of a separation process at the appropriate scale. Continuous chromatography is a conventional technique for the separation of commodity chemicals since its origins in 1950s. A continuous chromatographic separation with proper initiative i.e., SMB can handle this situation better than traditional elution chromatography process. Therefore, continuous chromatographic process i.e., SMB has recently gained attention as a useful tool for industrial-scale chromatographic separation (7, 8, 11).

SMB is one of the most advanced continuous chromatographic separation methods

innovated so far. Despite boosting the productivity and reducing the operation costs, SMB is hard to design and control due to its hybrid nature (12). Also, it needs a considerable time to reach a cyclic steady state. SMB is relatively expensive and therefore it demands significant capital investment. Therefore, some efforts are investigated to find simpler processes, which can resemble SMB in characteristics (13–17). Most of these approaches are based on single-column arrangement.

In many cases, it would be advantageous to work with the limiting case of a single column because it reduces the number of columns, since less stationary phase is used, the set up is more economic, and the overall pressure drop can be reduced (4). Single column continuous chromatographic process with proper design for fraction collecting in different cutting times would be an efficient method for chiral separation. It is usually superior to conventional batch chromatographic processes and analogous to the multicolumn continuous separations i.e., SMB, where a same mathematical frame works is used for calculating the cyclic steady state (4, 5, 17–21).

In order to investigate the performance of different processes on a fair basis, they should be examined at their optimal operating points (22–26). In addition, parameters must be defined in a consistent manner, including decision variables, constants, constraints, and objective functions.

The proper optimization of the process plant can give the better productivity, desire purity and less solvent consumption to achieve better economic production in efficient way for the fixed method of separation. Meanwhile, most of the cases the industrial plant is running under sub-optimal point which is far beyond the optimal point of operation to avoid the uncertainties of the process near the optimal point (27). In past few years, the researchers in this field thought that the use of a proper optimizing controller could improve this situation (27–38). The performance of this optimizing controller is greatly affected by the reliability and quality of the feedback information from the process which leads to the necessity of fast and trustworthy online monitoring system. In previous publications, the optimizing controller was based on the combination of two online optical detectors, i.e. polarimeter and UV detector, to determine the product purity (12, 32). However, the accuracy of the polarimeter is greatly sensitive to the variations in process operating conditions, e.g. pressure, concentration, etc. As a consequence, recently much attention is given to modify the online monitoring system to improve the performance of the optimizing

controller. An automated online HPLC monitoring system is introduced to determine the average concentrations of the outlet streams to feedback the accurate and precise information to the controller (39, 40). There are certain drawbacks with this system in terms of feed injection and sample collection which add up unnecessary delay to analysis time. Moreover, a significant improvement in the solvent consumption can be obtained by lessening the time gaps between two consecutive injections. Therefore, certain modification of the conventional HPLC is essential.

1.1 Contribution of this work

In this work, a single column process integrated with a high performance liquid chromatography (HPLC) system has been introduced for the continuous separation of chiral compounds e.g., guaifenesin. Design modifications have been done to the conventional HPLC system to reduce the detrimental time delay. The combination of an injection loop and eight port two positions valve are used instead of costly autosampler. This arrangement helps to inject feed repeatedly and automatically through the preparative process column. The breakthrough curve is obtained from an UV detector after the process column. The outlet stream is cut into four portions by means of a five port, four position switching valve to obtain both enantiopure products, the mixture of the products, and pure solvents. These four cut times are very essential to achieve the desire purity and yield of the products. The cycle time of the feed injection and injection volume have the great impact on the output profile of the process column. After fraction collection, a portion of the enantiomerically enrich are analyzed using an online monitoring system to provide feedback information to the controller. Two analytical columns ensure simultaneous analysis both of the product streams to facilitate the frequent feedback information.

Multi-objective optimization of the ISCC process was accomplished. The aim of this optimization was to maximize the productivity and minimize the solvent consumption under product and process constraints. A virtual ISCC process model has been used in Matlab based Simulink resembling the real plant. Finite volume method has been utilized to solve the stiff set of partial differential equations (41). Solvent flow rate, cycle time, injection volume of the feed sample and four cut intervals are considered as the decision variables. Maximum allowable pressure drop along with purities of

the each products and overall recovery are considered as the process constraints. The solution appears as a set of Pareto optimal points, which are non-dominated with respect to one another. The optimization results provide a quantitative basis for the full potential benefits of a single column chromatographic process. At the same time, it allows comparison with other multi-column processes such as SMB chromatography.

Detector calibration is in general a prerequisite for isotherm determination. This posed as a challenge due to high nonlinearity of the response of the detector. This has been overcome by adopting a new method for simultaneous calibration of detector and determination of adsorption isotherm. The nonlinear direct inverse method developed in this study can readily be used for a mixture of enantiomers under base line separation or overlapping of elution profiles. This is a relatively fast and economical techniques compared to existing alternatives.

Finally, the cycle-to-cycle optimizing controller was developed for the ISCC process to separate the mixture of guaifenesin enantiomers. There were some key implementation issues such as: accuracy of the online measurement system, integration of this online monitoring system with controller and automation of the whole process. These issues were managed by designing and developing a human machine interface (HMI) that was able to communicate effectively among the three essential components of the control loop. The performance of the controller was tested for set point tracking and disturbance rejection. Results indicate that the controller was able to deliver product specifications, and at the same time, optimize the process performance.

The main contributions of this thesis are: (i) a customized and improved single-column chromatographic separation process was developed for preparative scale production, (ii) an optimizing controller was embedded in the process for the robust operation, (iii) an efficient online monitoring system was integrated with the controller, (iv) a human machine interface was designed in-house for complete automation of the process, and (v) finally, the performance of this ISCC process along with its optimizing controller was verified through experiments.

1.2 Outline

This thesis is organized into six chapters. A list of references is included at the end of the report and the symbols used in this thesis are explained at the end of every chapters. Chapter 1 describes the main contribution of this work. Chapter 2 provides the motivations and description of the ISCC process and its online monitoring system. The multi-objective optimization of the ISCC process is reported in Chapter 3. The development of nonlinear direct inverse method for simultaneous calibration and isotherm determination is presented in Chapter 4. Chapter 5 presents the experimental implementation of the ISCC process. Finally, concluding remarks and outlooks are given based on perspectives.

Chapter 2

Improved Single-Column Chromatographic Separation Process

In this chapter, we present the design of an improved single-column continuous chromatographic separation process. We define it as improved process as it involves improvements in the conventional HPLC system that works in a semi-continuous manner for preparative scale separation. The design contains both physical and conceptual improvements. It is found from a comprehensive literature review, that there are many scopes to develop a process, which can harness both the advantages of batch, and continuous chromatographic separation processes. Moreover, the separation performance and the online monitoring system can be improved by designing efficient feed injection and fraction collection mechanisms.

2.1 Motivation of the design

Different types of design schemes are available for chromatographic separation process ranging from single-column batch separation (also known as elution mode (42)) to completely automated simulated moving bed (SMB) (43–45). Application of continuous chromatographic separation processes are increasing in the fast growing field of chiral and pharmaceutical products where time to market is the decisive criterion compared to economics of the separation (46). In pharmaceutical industries,

early tests of the newly developed drugs and the future production phase of those are two opposing factors. They require short development time for being the first player in the market. On the other hand, they need low cost large-scale production method with high productivity to increase their profit. Currently, continuous chromatographic separation processes are getting more attention as they are useful in both phases especially for the purification of low selectivity species such as chiral molecules for single enantiomeric drug development (46). However, batch operation is simple to design and require less capital cost compared to continuous processes and continues to be attractive for changing feeds and small-scale operation.

2.1.1 Essence of improved single-column design

Reviewing the merits and demerits of batch and continuous process, it is evident that a process that encompass the advantages of both will be attractive and useful. Many researchers have attempted to imitate the continuous process with some modification in the batch mode with innovative ideas (13, 47, 48). Single-column process where a recycle stream is used to reprocess a portion of product that does not fulfill the purity requirements is one example. The injection and fractionation procedure of this process is similar to elution mode from dynamic point of view, its behavior is similar to continuous process. This process is called steady state recycling (SSR). The design of SSR process is simpler than continuous process, i.e SMB. However, its operation is not as straight forward as elution mode (49). Performance of this process is better than elution mode, but the productivity is low and solvent consumption is high compared to a similar SMB unit at large scale operation (14, 50).

Abunasser et al. (16) attempted to replicate SMB employing a single-column setup in combination with an array of tanks. Later, a two-column set up was used (18). The performance of their process was better than an elution mode single-column chromatographic process. They showed that a sophisticated design of plug-flow recycle path comprising a variable length tube and a moving piston could obtain the identical product purity at constant productivity. This process was simpler and less expensive than an equivalent SMB.

Nowadays, SMB is considered to be the most efficient continuous chromatographic separation process for the pharmaceuticals and fine chemicals industries. Although

SMB process significantly improves the productivity and reduces solvent consumption compared to batch chromatography, design and robust optimum operation of a SMB process, especially long-term operation, is a challenge due to reasons like aging of the stationary phase and change in ambient conditions. SMB technology also requires high capital investment and expert operators.

Considering the above facts, we have introduced an improved single-column chromatographic (ISCC) separation process, which works in a semi-continuous mode. We have modified the feed injection and fraction collection mechanism. This modified injection mechanism can deliver variable amount of feed during different cycle which is necessary for online optimizing control of the process. The improved fraction collection system reduces delays in sample analysis outperforming available system.

2.1.2 Essence of improved online-monitoring system

An accurate online monitoring system is vital for the control scheme. It continuously gives the measurement of the product purity values to the controller. Any time delay in online monitoring system will affect the performance of the controller adversely. Moreover, the online monitoring system should be able to withstand the variation in the process operating parameters such as pressure, concentration, etc. (12). Actually, for chiral separation, accurate online monitoring system remains to be challenge. A number of research groups attempted to build an accurate and fast online monitoring system for the chiral separation as summarized below:

Conventionally, a combination of UV detector and polarimeter is used for measuring the products' concentration profile. UV detector gives the absorbance of the mixture, which is proportional to the sum of the concentrations of the two enantiomers. Whereas, polarimeter provides a measurement that is proportional to the difference of two concentrations. With appropriate calibration and signal processing, the absolute concentration of the two enantiomers can be calculated (51). This method is widely used in the field of continuous chromatography including SMB. However, frequent necessity of polarimeter calibration and its sensitiveness to pressure fluctuations in the presence of impurities in the mixture drives the researchers to develop alternative online monitoring system for chiral separation (12, 51, 52).

Reetz et al. (53) developed an online monitoring system based on the application of

circular dichroism (CD) followed by a UV detector. This chiral detection method was not very successful in the industrial applications (54). Another concept of online monitoring system was developed using an efficient multi-wavelength detector i.e., diode array detectors (DAD). This online monitoring system was based on the fact that any specific substance has an optimum detection wavelength in spectrometry. However, the practicability of this process becomes questionable as enantiomers have equal absorbance at different wavelengths. Several researchers also tried the curve-fitting method based on mathematical formulation (55, 56) and found many difficulties due to noise level and other external factors in the process and monitoring system.

Araujo et al. (39) developed a novel online monitoring system for SMB, which offered a good sampling rate and reasonable level of accuracy. This method consists of two UV detectors, one was positioned inside the SMB loop giving the total concentration and other was the part of a custom-made analytical HPLC coupled with an SMB. The unique valves arrangement of that proposed system allowed uninterrupted sampling and facilitated measuring the individual concentrations precisely but over a short period of time.

Langel et al. (40) proposed a different online monitoring system where they used a modified HPLC unit working on a cyclic basis. Their system contains the components of a typical analytical HPLC such as injection arm, chromatographic column, detectors and some custom made part like glass-made tank as intermediate vessels, automatic valves. Their target was to collect the extract and raffinate in cyclic basis like an SMB without any interruption. They used two glass-made tanks for the products collection and simultaneously other two tanks were washed with pure solvent to prevent cross-contamination for the next cycle. A robotic injection arm was used to put the sample in to the analytical column. This process has some advantages over the previous processes in terms of higher sampling frequency and reliability. Nevertheless, its design can be modified to make it more effective and fast. First, the injection arm can be replaced to remove detrimental time delay during the analysis. The design of the customize glass-made tanks may be improved to relax the airtight condition. Solvent consumption of this system is significant. Moreover, the cost of the downstream processing is high due to the removal step of the solvent from the products. Analysis time between two consecutive sample is the bottleneck of this system. This problem can be resolved by special arrangements of the valves and HPLC components. Finally,

no mixing was provided to ensure the average concentration in each cycle.

From the above facts, it is evident that there is a clear scope to design a well-organized online monitoring system for closed-loop operation of the enantiomeric separation and for quality assurance of the products. We designed an online monitoring system comprising HPLC units along with two analytical columns. This proposed system has some parts to share with previous implementation, but it also includes some unique features. In the design, valves and fraction collector are arranged in a way that two analytical columns can work simultaneously to reduce the analysis time of one cycle. In our online monitoring system, conventional needle-arm injecting mechanism is replaced by a less expensive but faster mechanism. We have used two custom-made intermediate vials that assure accurate average concentration of each fraction of the products by proper mixing. Mixing was guaranteed with an external shaker. It provides orbital movement to the vial along with its accompanying switching valves. Most importantly, our online monitoring system can be coupled with the improved single-column chromatographic separation process easily. The details design of this system is given in a later section.

2.2 Description of ISCC process

Detail design and working flow of an improved single-column chromatographic separation process is discussed here. Total cost of this process is less compared to an SMB unit and its performance is much better than the conventional stacked injections. Some parts of a HPLC system are redesigned to suit the main objective of preparative binary separation. In this design, less retained compound is referred to as B and more retained compound as A. The tag numbers refer to the process flow diagram as shown in Fig. 2.1.

2.2.1 Injection mechanism

To deliver accurate mass throughput to the system, we inject feed with the arrangement of an HPLC pump (P1) and an 8 port, 2 position switching valve (V1). It assures feed delivery at a specific concentration and flow rate for a certain period. The arrangement replaces conventional auto-sampler, reduces sample injection time and

Figure 2.1: Schematic process flow diagram along with the online monitoring system.

delivers the feed as a train of pulses continuously. It allows changing of the injection volume in a gradual manner by partial loop filling which helps to search the optimal point in the entire range of injection volume. A second HPLC pump (P2) is used to deliver the desorbent. The desorbent flow rate is determined based on maximum allowable pressure drop that the stationary phase can withstand.

2.2.2 Process column

A semi-preparative column (C1) is used as the core of this separation process. This process column is followed by a UV detector (D1) which measures the concentration of the outlet stream, i.e records a chromatogram, as shown in Fig. 2.2(a) under steady state operation. The chromatogram obtained over one cycle may be divided into four fractions based on the target products as shown in Fig. 2.2(b). The start of the first cycle is detected by the rising shoulder of the first peak elute. The consecutive starting point of the next cycles are calculated in same way. Furthermore, there is no restriction that the elution profile must be completed before the next cycle, as there is no limitation for baseline separation in our scheme.

2.2.3 Fraction collection

In this design, the conventional fraction collection is revised both conceptually and physically. A 5 port, 4 position valve (V6) is used as fraction collector as shown in Fig. 2.1. Our fraction collector incises the elution profile into four fractions: the first portion is rich in B, the second portion is a mixture of A and B, the third fraction is rich in A and the last portion is again a mixture of A and B (Fig. 2.2(b)). It is worthy of attention that the concentration of second and fourth mixture is not same. For a Langmuir type isotherm, the fourth fraction is usually diluted and its total concentration is by far less than the second fraction. For this reason, we are collecting these two mixtures separately so that in future when we will consider the recycle stream in our design it may play a significant role. Moreover, the fourth fraction has an important effect on the product purity. This fraction collection scheme starts immediately after the first peak is detected and offers three cut intervals as three degree of freedom to the designer.

2.2.4 Intermediate product collection

After the fraction collector, the product streams are sent to two intermediate vials (VI1/VI2) where average concentration of entire respective fractions is assured by perfect mixing prior to analysis. Natural circulation of mobile phase is not enough to provide the perfect mixing. We have to design our intermediate vials to achieve desirable results to assure the homogeneity for every cycle. Schematic drawing of one of the vials is given in Fig. 2.3. The main body of this intermediate vial is a commercial sampling cylinder. The outlet port of the vial was reconciled by using an insert for reducing the internal diameter to minimize the dead volume as shown in Fig. 2.3. A deep-jet nozzle was created by using a piece of tubing. The length of the tubing was selected in such a way that it reaches underneath the liquid level for causing additional mixing. Moreover, the tip of the nozzle was slightly tilted to act as a baffle. Purging gas (helium) enters the vial from lower port to pressurize the vial and regulate the purging speed. The rising flow of gas blocks the flow of liquid downward and hence cut off dead volumes under the outlet nozzles. Bubbles creating from the purging gas also help for enhancing mixing when it passes through the liquid hold up in the vials. Lastly, the vial and its accompanying switching valve

(a)

(b)

Figure 2.2: Typical elution profiles: (a) train of consecutive eluted peaks; (b) allocation of cut intervals and fractions. t_{sc} is the start of cycle and dt_{c1} to dt_{c4} are the assigned cut intervals comprising one cycle time.

are mounted on a variable-speed external shaker, which provides orbital movement for better mixing.

Figure 2.3: Cross-section of the customized intermediate vial.

2.2.5 Online monitoring system

After sufficient mixing, the two fractions of products of intermediate vials are purged to the product bottles. During purging a small portion of the products from each vial are sent to our online monitoring system for product analysis. The online monitoring system comprises two analytical columns followed by two UV detectors. Some modifications are done especially in sampling mechanism in typical a HPLC system to embed this monitoring system to our ISCC process. The concept of using HPLC system for online monitoring system is similar to what suggested by Cavazzini et al, Langel et al, Araujo et al, but the way the products are collected and directed to the online monitoring system, is a novel approach. Moreover, compare to conventional low-frequency online HPLC detection, this system works as moderate-

frequency detector. The schematic diagram of our designed online monitoring system is given in Fig. 2.1 along with the process flow diagram.

Fraction collector sends two product streams to intermediate vials (VI1/VI2). Necessary arrangement is made for proper mixing to guarantee the average concentration for a specific cycle. Later, the outlet valve (V2/V3) is opened to purge the intermediate product to the final product bottle. At the time of purging, the sampling valve (V4/V5) is switched to load a small sample of the stream in an injection loop (IL2/IL3) without any interruption in the flow of product. Shortly, the sampling valve is switched back to normal position (inject position) for injecting the product sample into a stream of solvent. Subsequently, this sample passes through the analytical column (C2/C3). UV detectors (D2/D3) analyze the peaks of the samples following the analytical columns. As soon as the next fraction collection is started the same procedure is repeated. Two fractions can be analyzed simultaneously for saving the extra time delay for the analysis of two products in one cycle. Finally, the purging gas (helium) passes through the vials and tubing to reduce the cross-contamination from the previous cycle and the system is always filled with pressurized inert gas to remove the adverse effects of air penetration and solvent evaporation.

Our online monitoring system is designed for binary separation but it can be used for multi-component separation with suitable modifications. In any case, this novel online monitoring system is faster and less expensive compared to similar commercial devices.

2.2.6 Human machine interface

A Human Machine Interface (HMI) is necessary to communicate with the process devices and to interface with the users. In this work, the backbone of the interface was National Instrument software and hardware products. LabVIEW development software package was employed as programming environment and various hardware products were used as input/output devices.

Every part of the process equipment was programmed separately as a module and later each module was merged together in a straightforward manner. It helped us to reduce the development time of the interface. HPLC pump and UV detector modules contain initialization state, manual mode, method mode, and shutdown state. Switching and

Figure 2.4: A snapshot of the ‘main menu’ of the process HMI in the automatic mode of operation.

solenoid valves contain all the steps of pumps and detectors, except the method mode. In method mode, all raw data are collected in a log files. Each module is designed with disable/enable options so that in emergency case we can remove the specific module from the main interface. Although the interface was build up in a modular way, a main menu was designed for control and monitoring of the entire process components from single page as shown in Fig. 2.4. Our interface can work both in manual and automatic mode. In manual mode operator can set all parameters’ values including pumps’ flow rates, detectors’ wavelength etc. Manual mode is the default mode and is designed to override the automatic mode to interrupt the process flow and make necessary changes in emergency case. In automatic mode, feed injection and fraction collection schemes are executed at steady state by proper valve sequencing and time planning (see Figs. 2.5 and 2.6). The fraction collection task is a constrained time scheduling problem with overlapped steps, it needs special attention to implement. This scheme was written in a MathScript node in LabVIEW. A shutdown button is designed in the interface for normal or emergency interruption of the process. When shutdown button is pressed, it sends stop command to all devices’ module. It also put the devices in their default settings, close the data log files, and terminate the communications. This Human Machine Interface is easy to understand and gives clear options to end users, which will produce fewer errors, as well as a more pleasant user experience.

Figure 2.5: Implementation of the fraction collection scheme.

Figure 2.6: Implementation of time constraints arising in the fraction collection scheme.

2.3 Concluding remarks

In this chapter, we first discuss about the motivation of our design, essence of our ISCC process and online monitoring system. We described the ISCC process in technical terms and showed how the proposed online monitoring system works. Design of intermediate vials for proper mixing is presented here. A novel fraction collection scheme and its working principle are also described here. The proposed design of the process has been assembled in a laboratory and integrated with a dedicated human-machine interface (HMI) software package developed in-house. The reliability of the process, the online monitoring system and the HMI was confirmed in practice for steady state runs. Experimental evaluation of this process is presented in chapter 5.

Nomenclature

c_T^F total feed concentration [g/L]

t_{cy} cycle time [s]

t_{sc} start of cycle [s]

Subscripts and superscripts

A more retained component (S)-(+)-guaifenesin

B less retained component (R)-(-)-guaifenesin

Chapter 3

Optimization of ISCC Process

In Chapter 2, a detailed process design of improved single column-chromatographic (ISCC) separation process was developed. For robust operation of this process, development of an online optimizing controller is necessary. This controller should be compatible with the designed online monitoring system. The backbone of this optimizing controller will be a strong offline-optimization. This offline-optimization will be used as the reference for online optimization of the designed controller. This chapter addresses the optimization of this ISCC process. The objectives are to maximize the productivity and minimize the desorbent requirement. Appropriate formulation for the optimization is the trickiest part. A detailed model is used for process modeling accounting for all the non-ideal effects such as mass transfer resistance and dispersion effects. The optimization is carried out using a evolutionary optimization algorithm named NSGA-II (non-dominated sorting genetic algorithms) (57). The optimization problem is formulated as a multi-objective optimization problem. The motivations of multi-objective genetic algorithm are twofold: First, based on a preliminary analysis, classical gradient-based optimization techniques are inefficient for our problem due to its nonlinear behavior and presence of scores of local optimum points, second, performance indicators (i.e., productivity and desorbent requirement) may not be simultaneously maximized/minimized. There exists a trade-off between these two objectives while constraints arise from the product quality requirements and the technical limitations of the operation. These facts necessitate using evolutionary algorithm (EA) as solution methods, which can offer chance of finding possible global optimum point or at least a set of points of optimal solutions which are non-dominated with respect to one another (Pareto sets) (58–62).

3.1 Multi-objective optimization using genetic algorithm

Genetic algorithm (GA) is a nature-inspired stochastic global search method which was first introduced by Holland (63). GA is different from other classical deterministic search and optimization methods; it has no limitation to find global optima and less possibility to trap in the local optima. GA is a multi-point search method that can guarantee global optimality (63). GA begins with defining decision variables and cost functions (objective functions) and ends with testing convergence. However, it uses only objective function values, not derivatives, in the search procedure.

In GA terminology, the solution vector of each decision variable is called an individual or a chromosome. Discrete units of these chromosomes, also known as genes, control the characteristics of each individual. Collection of these individuals or chromosomes is termed as population. GA works with a population of solution instead of single solution. After evaluation of each solution, a relative merit is assigned to it, which is named fitness, using objective function values. The ultimate objective is to maximize the fitness of that population by evolution over generations under specified selection rules (22).

GA employs three different operators named selection, crossover, and mutation in optimization. In selection process, the chromosomes in a population are selected based on their fitness values for the next generation. Individuals with higher fitness values have more chance of being selected for mating and subsequent genetic action. This ensures survival of more fit individuals and extinction of less fit ones (22). After selection, crossover operation is performed. In crossover, a new chromosome is formed by combination of two parent chromosomes. This newly formed chromosome is called offspring, which contains information from both parents. On the other hand, in mutation operation, random changes occur in the genes level. Mutation reintroduces genetic diversity back into the population and assists the search to escape from local optima (22).

Most multi-objective optimization algorithms use the concept of domination (22). A solution $x^{(1)}$ is said to dominate the other solution $x^{(2)}$, if $x^{(1)}$ is no worse than $x^{(2)}$ in all objectives and $x^{(1)}$ is strictly better than $x^{(2)}$ in at least one objective

function (22). This non-dominated set of entire search space is called Pareto-optimal set (22). The corresponding objective function values for a given Pareto optimal set are called Pareto front (22). Any effort to improve Pareto solution with respect to any objective will lead to deterioration of at least another objective (22).

We have chosen MATLAB for optimization programming, which employs one of the most powerful and robust multi-objective optimization algorithms, namely NSGA-II (non-dominated sorting genetic algorithm) (22). In this algorithm, solutions are categorized based on sorting non-dominated solutions into layers spearheaded by Pareto set. The convergence is measured by change in relative distance or spread of Pareto set members (22).

3.2 Process description

The ISCC process is presented in Chapter 2. A train of pulses is injected to the column which is similar to the conventional stacked injection (64). In ISCC process, there is provision for partial loop filling for variable injection volumes for better optimization studies. The maximum flow rate is determined by the maximum allowable pressure that the stationary phase can withstand. The elution profile is not limited to baseline separation since the newly developed fraction collection scheme is able to handle both intra and inter profile overlapping which is an important feature of this scheme.

3.3 Modeling

Simulation of the improved single-column chromatographic process has been carried out using a detailed one-dimensional model, which considers the convection and axial dispersion in the fluid phase. Linear driving force model is used for the mass transfer dynamics. The material balance, mass transfer, and adsorption equilibrium are expressed by the following equations (42),

$$\frac{\partial c_i}{\partial t} + \frac{1 - \varepsilon}{\varepsilon} \frac{\partial n_i}{\partial t} + v_0 \frac{\partial c_i}{\partial z} = D_{ax} \frac{\partial^2 c_i}{\partial z^2} \quad (3.1)$$

$$\frac{\partial n_i}{\partial t} = k_i (c_i - c_i^*) \quad (3.2)$$

$$n_i = f_i(c) \quad (3.3)$$

here t and z are the time and space coordinates, respectively. ε is the overall void fraction of column and v_0 is the interstitial velocity. D_{ax} is axial dispersion coefficient and k_i is overall mass transfer coefficient of species i . The function f_i in Eq.(3.3) is the adsorption isotherm of component i .

The axial dispersion coefficient D_{ax} is calculated using the following correlation (65).

$$\varepsilon Pe = 0.2 + 0.011 Re^{0.48} \quad (3.4)$$

$$Pe = \frac{v_0 d_p}{D_{ax}} \quad (3.5)$$

The pressure drop in the column is calculated using Darcy's law (4):

$$\Delta P = \frac{\phi \times v \times L \times \mu}{d_p^2} \quad (3.6)$$

where ϕ is an empirical constant, which is known as the resistance parameter. v is superficial velocity, L is column length, d_p is particle diameter, and μ is viscosity.

3.3.1 Separation model

Guaifenesin has been taken as the model chiral compound to separate, where (S)-(+)-guaifenesin is the more retained enantiomer denoted by A and (R)-(-)-guaifenesin is the less retained enantiomer denoted by B throughout this paper. In optimization, upper limit of feed concentration has been taken as 35 g/L. Experimentally, we have checked the solubility of guaifenesin in heptane-ethanol (65:35, v/v) mixture at room temperature (23°C) to justify the upper limit of feed concentration. This value is in close proximity of the value used by Francotte et al. (66). At room temperature (23°C), the liquid density of heptane-ethanol (65:35, v/v) mixture is 785.8 kg/m³ and the viscosity of the mixture is 6.075 × 10⁻⁴ Pa.s. These data were calculated from Perry's chemical handbook and DIPPR physical and thermodynamic properties database respectively.

3.3.2 Isotherm

The competitive binary Langmuir isotherm of guaifenesin enantiomers (Eq. 3.7) in heptane-ethanol (65:35, v/v) mobile phase and on Chiralcel OD stationary phase has

been found adequate to describe the separation behaviour (66).

$$n_i = \frac{H_i c_i}{N_c} (i = A, B) \quad (3.7)$$

$$1 + \sum_{i=1} K_i c_i$$

Where, H_i is the Henry constant and K_i is the equilibrium constant of the component i . The values of parameters are reported in Table 3.1.

Table 3.1: Physical parameters.

Parameter	Value	Unit	Reference
D	1	cm	-
L	10	cm	-
ε	0.704	-	(66)
H_A	3.49	-	(66)
H_B	1.41	-	(66)
K_A	0.0550	L/g	(66)
K_B	0.0135	L/g	(66)
d_p	20	μm	-
k_i	18.3	1/s	(67)
ϕ	500	-	(4)
μ	6.08×10^{-4}	Pa.s	-
m_{ad}	4.7	g	-

3.4 Optimization

3.4.1 Problem statement

Optimization of the ISCC process has been formulated as a multi-objective optimization problem to maximize productivity (Pr) and minimize desorbent requirement (Dr), while fulfilling process and product constraints.

The solution domain is defined by decision variables, namely operating parameters to be changed in order to optimize the process. They are injection volume (V_{inj}), cycle time (t_{cy}), desorbent flow rate (Q^D), total feed concentration (c_T^F), and three cut intervals (dt_{c1} , dt_{c2} , and dt_{c3}).

Table 3.2: Range of decision variables.

Decision variable	Range
V_{inj}	300-5000 μL
t_{cy}	10-90 s
Q^D	5-70 mL/min
c_T^F	10-35 g/L
dt_{c1}	1-90 s
dt_{c2}	0.2-90 s
dt_{c3}	1-90 s

Productivity is defined as

$$Pr = \frac{\int_0^{t_{cy}} (c_A^E + c_B^E) Q^E dt + \int_0^{t_{cy}} (c_A^R + c_B^R) Q^R dt}{m_{ad} t_{cy}} \quad (3.8)$$

where m_{ad} is the mass of adsorbent in the column.

Desorbent requirement is defined as

$$Dr = \frac{t_{cy} Q^D + V_{inj}}{c_T^F V_{inj}} \quad (3.9)$$

The flow rate of raffinate stream is defined as

$$Q^R = \begin{cases} Q^D & \text{if } 0 \leq t - t_{sc} < dt_{c1} \\ 0 & \text{else} \end{cases} \quad (3.10)$$

Similarly, the flow rate of extract stream is defined as

$$Q^E = \begin{cases} Q^D & \text{if } 0 \leq t - t_{sc} - (dt_{c1} + dt_{c2}) < dt_{c3} \\ 0 & \text{else} \end{cases} \quad (3.11)$$

Purities are defined as

$$P_B = \frac{\int_0^{t_{cy}} c_B^R Q^R dt}{\int_0^{t_{cy}} (c_A^R + c_B^R) Q^R dt} \quad (3.12)$$

$$P_A = \frac{\int_0^{t_{cy}} c_A^E Q^E dt}{\int_0^{t_{cy}} (c_A^E + c_B^E) Q^E dt} \quad (3.13)$$

and recoveries are defined as

$$Y_B = \frac{\int_0^{t_{cy}} c_B^R Q^R dt}{c_B^F V_{inj}} \quad (3.14)$$

$$Y_A = \frac{\int_0^{t_{cy}} c_A^E Q^E dt}{c_A^F V_{inj}} \quad (3.15)$$

Constraints dictated by product specifications are purity and recovery and those dictated by hardware limitations are maximum allowable pressure drop across the column and maximum pump flow rate

$$P_i \geq P_i^{min} \quad (i = A, B) \quad (3.16)$$

$$Y_i \geq Y_i^{min} \quad (i = A, B) \quad (3.17)$$

$$\Delta P \leq \Delta P_{max} \quad (3.18)$$

$$Q^D \leq Q_{max}^D \quad (3.19)$$

The range of values for decision variables are given in Table 3.2. They were obtained from the analysis of physical limitations such as solubility limit, valve response time, etc. The maximum allowable pressure drop is taken as 40 bar. There are also a few logical constraints bounding the decision variables: injection time (V_{inj}/Q^D) cannot be greater than cycle time t_{cy} . Therefore,

$$\frac{V_{inj}}{Q^D} < t_{cy} \quad (3.20)$$

and the sum of three assigned cut intervals must be smaller than cycle time t_{cy}

$$\sum_{i=1}^3 dt_{ci} < t_{cy} \quad (3.21)$$

The performance indicators are considered as Dr and $1/Pr$ to suit a minimization problem. The nonlinear inequality constraints on product purity and recovery (Eqs. 3.16 and 3.17) are incorporated in the objective functions as penalty functions

$$J_1 = \frac{1}{(\alpha + Pr)} + \lambda_{pt} f_{pt} \quad (3.22)$$

$$J_2 = Dr + \lambda_{pt} f_{pt} \quad (3.23)$$

where f_{pt} is defined as

$$f_{pt} = \sum_{i=1}^2 \max \left(0, \frac{(P_i^{min} - P_i)}{P_i^{min}} \right) + \sum_{i=1}^2 \max \left(0, \frac{(Y_i^{min} - Y_i)}{Y_i^{min}} \right) \quad (i = A, B) \quad (3.24)$$

α is a very small positive number added to avoid division by zero and λ_{pt} is a penalty factor, regulating the relative weight of the penalty function.

3.5 Numerical solution techniques

The model equations comprise partial differential equations (PDEs), which are discretized in space using third-order weighted essentially non-oscillatory (WENO) scheme (68), which is more convenient (e.g., van Leer flux limiter (41)) when axial dispersion is significant and as a result, sharp fronts are smoothed. The resulting set of ordinary differential equations (ODEs) are solved by the method of lines. Among different ODE solvers that we have tested, Adams-Bashforth-Moulton PECE solver (69) seemed to be the most satisfactory in terms of handling computationally intensive problems. The simulation parameters are given in Table 4.2.

Table 3.3: Simulation parameters

Parameter	Value
ODE solver	Adams-Bashforth-Moulton (69)
Absolute integration tolerance	10^{-6}
Relative integration tolerance	10^{-4}
Initial time step	0.001 s
Number of grid points	400
Population size	80
Crossover fraction	0.3
Pareto fraction	0.5

The discretized equations have been compiled in C programming language, but embedded in MATLAB environment. In this way, the computational speed could be boosted drastically. Moreover, mass balance equations must be solved for intermediate vials. As a result, purity, recovery, productivity, and desorbent requirement are calculated in each cycle as average values. Calculations are restarted when a new cycle emerges.

The optimizer calls the model with a set of decision variables as individuals and receives the process performance indicators in return at the end of each run. In the simulation studies, the cyclic steady state can be achieved quickly, but for more assurance, several cycles of operations are considered and these are shown in Fig. 2.2(a).

We have chosen NSGA-II (non-dominated sorting genetic algorithm) (22) in MATLAB

for optimization programming, which is one of the most powerful and robust multi-objective optimization algorithms. In this algorithm, solutions are categorized based on sorting their ranks into layers spearheaded by Pareto front. The optimization algorithm converges when change in average Pareto spread falls below a certain limit over several generations.

3.6 Results and discussion

3.6.1 Improved single-column chromatography

Purity and recovery constraints values were chosen over a wide range starting from less stringent conditions and gradually moving to more stringent conditions. We have aimed at two industrial cases: (1) separation of pharmaceuticals whose purity cannot be compromised, (2) other materials such as sugars, which can be processed as lower purity. Other case studies were added to analyze the transition between the two cases given above. In this case, A is the least stringent condition (purity 90%, recovery 85%) and D is the most stringent condition (purity 99.9%, recovery 98%). The idea is to show that the optimization algorithm is able to find the optimal solution under a wide range of process constraints.

The results of four case studies with different purity and recovery constraints are furnished here as summarized in Table 3.4. The optimization results are presented in terms of Pareto fronts. Furthermore, the effects of decision variables on the performance indicators are analyzed and presented.

Table 3.4: Purity and recovery requirement constraints for optimization case studies.

Case	Purity (P)	Recovery (Y)
A	90 %	85 %
B	95 %	90 %
C	98 %	95 %
D	99.9 %	98 %

3.6.2 Pareto fronts

The optimal operating points obtained as Pareto fronts are shown in Fig. 3.1 where the horizontal axis and vertical axis correspond to productivity and desorbent requirement, respectively. Any operating point that falls in the left and above part of a Pareto front is suboptimal. On the other hand, any point to the right and below of any Pareto front is inaccessible. It is observed from Fig. 3.1 that as we move from less stringent constraints (case A, $P=90\%$, $Y=85\%$) to more stringent constraints (case D, $P=99.9\%$, $Y=98\%$), the Pareto curves move up and left indicating higher desorbent requirement and lower productivity. Apart from this shift, the Pareto fronts become steeper, indicating that at higher purity and recovery, any increase in productivity requires a greater increase in desorbent requirement compared to less stringent cases.

Figure 3.1: Pareto fronts as productivity and desorbent requirement under different purity and recovery constraints. Case A: $P=90\%$, $Y=85\%$, case B: $P=95\%$, $Y=90\%$, case C: $P=98\%$, $Y=95\%$, and case D: $P=99.9\%$, $Y=98\%$.

Across these case studies, a 10% decrease in purity constraint can boost productivity by about a factor of six, while it can only reduce desorbent requirement by about a factor of two. Therefore, while there is a large degree of freedom on productivity, in comparison, desorbent requirement is limited to a narrow range of values.

There are discontinuous sections observed in some of the Pareto fronts. This can be explained by looking at the entire feasible population. In the discontinuous regions, the population passes through a maximum when Dr is plotted vs. Pr . The maximum point and its neighboring points are dominated by the right hand section of Pareto front and therefore they do not appear as a part of optimal points. This phenomenon may result in a wide gap in final Pareto front. This reiterates the necessity of observing good level of diversity during optimization to ensure that all discontinuous sections were explored.

3.6.3 Elution profiles

In Figs. 3.2 and 3.3, the simulated chromatograms are given for the two extreme points of Pareto fronts of case A and case D, respectively. It was observed that for case study A, there is significant amount of overlapping between peaks of two consecutive cycles. For case study D however, overlapping diminishes and we have almost base-line separation. This implies that an overlapping scheme is favorable for reduced-purity and recovery conditions as the optimizing algorithm adopts majority of solution points from this region of operation.

3.6.4 Effects of decision variables

In Figs. 3.4(a)-3.4(f), the effects of decision variables on productivity and desorbent requirement for cases A and D are shown. The results of cases B and C show similar pattern. Since it has a clear relation with productivity and desorbent requirement, we have also reported the effect of throughput (Eq. 3.25), which is a function of three independent decision variables namely, feed concentration (c_T^F), cycle time (t_{cy}), and injection volume (V_{inj}):

$$T_F = \frac{c_T^F V_{inj}}{t_{cy}} \quad (3.25)$$

For a better insight, the Pareto results of case study D given in previous figures are summarized in Table 3.5. These points are all the subset of feasible solutions yielding the best values of objective functions.

Fig. 3.4(a) shows that feed concentration has a significant effect on the performance indicators. Most of the optimal points are located in a narrow range near the solubility

(a)

(b)

Figure 3.2: Chromatograms of case A ($P=90\%$, $Y=85\%$): (a) Left most point of the Pareto front; (b) Right most point of the Pareto front.

(a)

(b)

Figure 3.3: Chromatograms of case D ($P=99.9\%$, $Y=98\%$): (a) Left most point of the Pareto front; (b) Right most point of the Pareto front.

Figure 3.4: Effects of decision variables on productivity and desorbent requirement: (a) feed concentration; (b) injection volume; (c) cycle time; (d) throughput; (e) desorbent flow rate; (f) second cut interval (case A: $P=90\%$, $Y=85\%$, case D: $P=99.9\%$, $Y=98\%$).

Table 3.5: Decision variables and objective functions of the Pareto front for case D.

Pr (g/(min g))	Dr (L/g)	V_{inj} (μ L)	t_{cy} (s)	Q^D (mL/min)	c_T^F (g/L)	dt_{c1} (s)	dt_{c2} (s)	dt_{c3} (s)
0.0070	0.228	1341	83.6	6.7	35.0	18.5	2.9	61.8
0.0070	0.228	1341	83.6	6.7	35.0	18.5	2.9	61.8
0.0074	0.232	1338	79.2	7.2	34.9	17.4	2.6	58.2
0.0075	0.235	1326	77.4	7.4	34.9	17.0	2.5	56.2
0.0077	0.238	1311	75.0	7.7	34.9	16.4	2.4	53.5
0.0079	0.241	1299	72.1	8.0	35.0	15.8	2.3	53.3
0.0083	0.244	1290	67.8	8.6	34.9	14.8	2.2	49.2
0.0087	0.258	1293	62.9	9.5	33.7	13.6	2.2	46.8
0.0091	0.270	1290	58.8	10.4	33.1	12.5	2.0	42.2
0.0091	0.270	1290	58.8	10.4	33.1	12.5	2.0	42.2
0.0107	0.297	1151	47.1	13.8	35.0	9.4	1.9	35.4
0.0138	0.302	1057	33.3	18.2	34.9	7.4	1.5	23.8

limit. This is because when the feed concentration increases, the productivity increases and the desorbent requirement decreases. In fact, feed concentration acts mostly as a scaling factor; it increases the loading, but has a less significant effect on peak width.

The effect of injection volume is shown in Fig. 3.4(b). In the nonlinear range of operation and in the presence of nonideal effects, injection volume may not be fixed, although it has a relatively narrow range of variation. Besides, as purity and recovery requirements rise, lower injection volumes are favored.

Fig. 3.4(c) shows that the productivity and the desorbent requirement monotonically fall as cycle time increases. The effect on productivity can be readily explained by Eq. 3.8. However, the effect of cycle time on desorbent requirement can be explained when variations in the desorbent flow rate and cycle time are observed together. In fact, cycle time and desorbent flow rate compensate the effect of each other as the term $Q^D t_{cy}$ which appears in the definition of desorbent requirement (Eq. 3.9), has a narrow range of variation with a small negative slope once plotted vs. cycle time.

Fig. 3.4(d) shows that throughput, which is a combination of three decision variables

as described in Eq. 3.25, has a linear relation with Pr . However, because all the three combined variables are constrained, they have to be taken as independent decision variables for optimization.

Eq. 3.9 can be written in terms of throughput

$$Dr = \frac{Q^D}{T_F} + \frac{1}{c_T^F} \quad (3.26)$$

The pattern observed in Fig. 3.4(d) shows that unlike what is inferred from Eq. 3.26, desorbent requirement increases as throughput increases because the effect of desorbent flow rate completely dominates the effect of throughput. Therefore, these effects must be understood in a holistic way.

The increase in desorbent requirement with increasing desorbent flow rate may look intuitive as it can be inferred from Eq. 3.9 and seen in Fig. 3.4(e). However, apart from what Eq. 3.9 implies, the adverse effect of flow rate on the column efficiency must also be accounted for. This means that at higher flow rates, a larger elution volume is required for a fixed resolution.

On the other hand, an increase in Pr with increasing Q^D is due to the fact that for a certain purity and recovery requirement, the larger desorbent flow rate allows for shorter cycle time and as a result, higher productivity.

The primary role of the cut intervals is to guarantee purity and recovery with the ultimate objectives of increasing productivity and decreasing desorbent requirement. For a specific purity and recovery requirements, the first and third cut intervals vary in a similar fashion as of the cycle time (results are not shown). Although due to the tailing effect of the Langmuir-type isotherm, the third cut interval constitutes a relatively larger portion of the cycle time. As a result, the more retained product fraction (rich in component A) is less concentrated than the less retained one (rich in component B).

In contrast to first and third intervals, second cut interval is determined such that specifications of product fraction A are satisfied at minimal cycle time and desorbent flow rate. Actually, second fraction is primarily the overlapped part of the concentration profiles of products B and A. A low value of second cut interval is therefore beneficial for reducing the loss of product A as it increases recovery. It is also beneficial for increasing productivity as it decreases the cycle time, which is observed in Fig. 3.4(f) where it is clustered towards its lower limit. A higher value

of second cut interval is observed for case study D compared to case study A. This is expected since the product purity requirement is more stringent in the former case.

3.6.5 Simulated moving bed

For comparison, we have also presented the results of a closed-loop SMB process equivalent to the ISCC process. The overall length and diameter of the SMB unit is the same as of the ISCC. A 1:2:2:1 configuration is assumed for this unit. Objective functions are defined in a similar fashion as of the ISCC

$$Pr = \frac{c_T^F Q^F}{m_{ad}} \quad (3.27)$$

$$Dr = \frac{Q^F + Q^D}{c_T^F Q^F} \quad (3.28)$$

and the decision variables are m_1, m_2, m_3, m_4, t^* , and c_T^F (44).

Process constraints and ranges of decision variables are also the same as the reports of ISCC as found in Table 3.2. The optimization of the SMB unit was done only under the highest purity and recovery requirements (i.e., $P \geq 99.9\%$). The Pareto front of the SMB process shown in Fig. 3.5, along with that of ISCC under comparable conditions (i.e., $P = 99.9\%$, $Y = 99.5\%$), illustrates that the SMB process significantly outperforms the ISCC process.

3.7 Concluding remarks

We have presented an improved single-column chromatographic (ISCC) process for the separation of mixture of enantiomers with an online monitoring system that has provisions for future use of an online optimizing controller. This provides the basis for reaping the full potential of a single-column process that adopts cyclic injection.

The ISCC process was optimized over a wide range of operating parameters namely, injection volume, cycle time, desorbent flow rate, feed concentration, and three cut intervals with the objectives of maximizing productivity and minimizing desorbent requirement for different product purity and recovery specifications. It is apparent that traditional experimental optimization techniques could not handle the complexity of this problem. Therefore, the resulting solutions were obtained through genetic

Figure 3.5: Pareto fronts of ISCC and SMB.

algorithm and presented as a set of Pareto-optimal points providing a way for quantification of the best achievable sets of productivity and desorbent requirement values. Depending on economic and/or environmental considerations, the end user is able to make an informed choice of a suitable operating point from Pareto set. Calculation of gain in productivity and saving in desorbent consumption under less stringent product specification was also facilitated through this work.

The relative contribution of the decision variables were ascertained through the study of their effects on the performance indicators. Productivity was found to be a linear function of throughput, which comprises three independent decision variables namely, feed concentration, injection volume, and cycle time. However, desorbent requirement expresses a complex relation with throughput. The importance of the second cut interval of fraction collection which primarily regulates purity and recovery values, was also demonstrated.

The results demonstrated that overlapped peaks (either from the same cycle or from adjacent cycles) can be admitted advantageously to enhance productivity and decrease desorbent requirement. The operability at such a point must be guaranteed by using an online optimizing controller, which is discussed in Chapter 5.

Finally, the optimized ISCC process was compared with an optimized SMB process under pure and almost fully recovered products. Results confirmed the advantages of continuous SMB process.

Nomenclature

c	fluid phase concentration of solute [g/L]
D	column diameter [cm]
D_{ax}	axial dispersion coefficient [cm^2/s]
Dr	desorbent requirement [L/g]
d_P	particles diameter [μm]
dt_{ci}	cut intervals [s]
H_i	Henry constant of species i [-]
K_i	equilibrium constant in Langmuir isotherm of species i [L/g]
k_i	overall mass transfer coefficient [1/s]
L	column length [cm]
m_{ad}	mass of adsorbent [g]
m_j	Dimensionless flow-rate ratio [-]
n	solid phase concentration of solute [g/L]
P	purity [%]
Pe	Peclet number [-]
Pr	productivity [g/(min g)]
ΔP	pressure drop [bar]
Q	volumetric flow rate [mL/min]
Re	Reynolds number [-]
t^*	switching time [s]
t_{cy}	cycle time [s]
t_{sc}	start of cycle [s]
T_F	throughput [g/min]
u	superficial velocity [cm/s]
v	interstitial velocity [cm/s]
V_{inj}	injection volume [μL]
Y	recovery [%]

Greek letters

ε	overall void fraction of column [-]
ϕ	resistance parameter [-]
λ_{pt}	penalty factor [-]
μ	viscosity [Pa.s]

Subscripts and superscripts

ad	adsorbent
ax	axial
A	more retained component (S)-(+)-guaifenesin
B	less retained component (R)-(-)-guaifenesin
D	desorbent
E	extract
F	feed
i	component index
inj	injection
min	minimum
max	maximum
R	raffinate

Chapter 4

Nonlinear direct inverse method: a shortcut method for simultaneous calibration and isotherm determination

4.1 Introduction

Adsorption isotherms describe the equilibrium with which the solute molecules are divided between fluid phase and adsorbent. In chromatographic separation technology, adsorption isotherm plays a significant role in process design and optimization. Although several experimental methods with varying levels of accuracy are available for isotherm determination (42, 70, 71), it is still a tedious and laborious task. Therefore, accurate determination of adsorption isotherm parameters continues to be a challenging task for designers and practitioners.

In preparative chromatography, it is not straightforward to estimate the isotherm parameters through correlations considering the system complexity (42), and therefore experimental efforts are always necessary, which can be carried out in various ways. In this regard, there is a compromise necessary between the accuracy and cost (time, labor, and materials) of experiments (72).

Static methods such as gravimetry (73), volumetry, and infrared absorption (74) or dynamic methods such as frontal analysis (FA) (75), perturbation method (PM) (76),

elution by characteristic points (ECP), and inverse method (IM) (77) have been used for isotherm determination. Static methods are typically slow and mostly used for gas adsorption (72), whereas dynamic methods which involve the flow of a fluid through a column packed with stationary phase, are well suited for liquid chromatography.

The conventional methods such as FA can estimate both single and multi-component isotherms, but they require a significant number of experiments and amount of materials. The inverse method alleviates these requirements to some extent. Hence, it has been extensively applied in various fields (45, 78–80). However, IM requires calibration of the detector signals to convert into concentration values. This is generally a time-consuming step and is an important source of error in isotherm determination tasks. Moreover, in the case of achiral compounds, where the elution profiles overlap, the problem becomes aggravated (80). Considering these factors, Cornel et al. (80) have proposed a modified version of inverse method called direct inverse method (DIM) to circumvent calibration. This method directly utilizes the detector signal without any need for a separate calibration. It was shown that this approach was equally applicable in the case of strongly overlapping profiles. Nevertheless, the main limitation of DIM has been the requirement of the linearity of the calibration equation emanating from the solution approach (81). In chromatographic processes however, nonlinearity of the detector signals due to overloaded solute concentration is very common. Moreover, this method necessitates the use of a diode-array detector and collection of large amount of data produced during every experimental run. Therefore, an extension of the DIM to encompass nonlinear calibration is necessary and useful for a wider range of separation and higher degree of accuracy.

In this chapter, we propose a nonlinear direct inverse method (NDIM) whose application is not limited to linear calibration equations. This method is in fact different from what developed by Cornel et al. (80) as the calibration procedure is carried out at the same time with isotherm determination (in contrast to the classical inverse method, (42)), by comparing simulated and experimental concentration profiles in order to obtain the best-fit parameters. The detector calibration parameters, isotherm parameters, and transport parameters (mass transfer and axial dispersion coefficients) are incorporated as the decision variables of an optimization problem.

Due to a large number of decision variables and nonlinearity of the detector response and adsorption isotherm that describes the separation behavior, the optimization problem is challenging. Therefore, genetic algorithm (GA) (82) is used here to search for the optimum values in combination with sequential quadratic programming (SQP) (83), to pinpoint the final solution.

4.2 Problem formulation

4.2.1 Modeling

Various models with different levels of details are available in the literature for simulating chromatographic systems (42). A one-dimensional model, which considers the convection and axial dispersion in the fluid phase, is employed here. In addition, the linear driving force model is used for approximating the mass transfer kinetics. The material balance and mass transfer kinetics are expressed by the following equations, respectively:

$$\frac{\partial c_i}{\partial t} + \frac{1 - \varepsilon}{\varepsilon} \frac{\partial n_i}{\partial t} + v \frac{\partial c_i}{\partial z} = D_{ax,i} \frac{\partial^2 c_i}{\partial z^2} \quad (4.1)$$

$$\frac{\partial n_i}{\partial t} = k_i (n_i^* - n_i) \quad (4.2)$$

here t and z are the time and space coordinates, respectively. ε is the overall void fraction of column and v is the interstitial velocity. n_i^* is the solid phase concentration in equilibrium with fluid phase concentration c_i . $D_{ax,i}$ is axial dispersion coefficient and k_i is overall mass transfer coefficient of species i .

The initial conditions for these equations are as follows:

$$c_i(0, z) = 0, \quad n_i(0, z) = 0 \quad (4.3)$$

For Eq. 4.1, the Danckwerts' boundary conditions are applied at inlet and outlet:

$$D_{ax,i} \frac{\partial c_i(t, 0^+)}{\partial z} = v(c_i(t, 0^+) - c_i^{in}(t)), \quad \frac{\partial c_i(t, L)}{\partial z} = 0 \quad (4.4)$$

where $c_i^{in}(t)$ is defined as:

$$c_i^{in}(t) = \begin{cases} c_i^F & \text{if } 0 \leq t < t_p \\ 0 & \text{else} \end{cases} \quad (4.5)$$

This definition implies that the feed is ideally injected as a pulse with width t_p . In reality however, this is a simplistic assumption because axial dispersion in injection mechanism may distort the injection pulse in an asymmetric way (84), causing tailing in extreme cases even when no column is installed in the flow path. These effects will be discussed in the results section.

In the classical inverse method (referred to as CIM here), often mass transfer and axial dispersion effects are lumped together (79). However, Dunnebie and Klatt (85) argue that this is theoretically correct only in the case of linear isotherms, and it is a good approximation for Langmuir isotherm as originally investigated by Golshanshirazi and Guiochon (86). As we are using bi-Langmuir isotherm, it is prudent to separate these effects in the modeling and parameter estimation.

It should be noted that the mass transfer resistance has two separate effects; on one hand, it affects band broadening, and on the other hand, it affects retention time and thus changes Henry constants. Therefore, when a significant level of mass transfer resistance prevails (i.e., k_i is small), the Henry constants measured via analytical injections must not be used in the model equation that explicitly includes mass transfer limitations. This may explain the difference occasionally observed between the Henry constants measured by direct retention time measurement and those by the classical inverse method (79). The effects of change in mass transfer coefficients are investigated via simulation (Section 4.5).

4.2.2 Isotherms

A competitive Langmuir isotherm accounting for competition and a finite number of sites is given as:

$$n_i = \frac{q_{s,i} K_i c_i}{1 + \sum_{i=1}^{N_c} p_i K_i c_i} \quad (4.6)$$

Where, $q_{s,i}$ is the saturation capacity of the adsorbent and K_i is the equilibrium constant of adsorption for component i . p_i is the parameter that shows the type of competition, and can only take 1 and -1 values. For a binary system, four types of Langmuir isotherms can be obtained (31). The classical competitive Langmuir isotherm is obtained for $p_1 = 1$ and $p_2 = 1$. For simplicity, we drop these parameters

from our formulations.

In practical applications, it is more convenient to write the above equation in terms of Henry constants:

$$n_i = \frac{H_i c_i}{1 + \sum_{i=1}^{N_c} K_i c_i} \quad (4.7)$$

where

$$H_i = q_{s,i} K_i \quad (4.8)$$

Some separations, especially in chiral chromatography equilibrium is described by a bi-Langmuir isotherm, which accounts for both selective and non-selective adsorption (59):

$$n_i = \frac{H_i c_i}{1 + \sum_{i=1}^{N_c} K_i c_i} + \frac{H_{ns} c_i}{1 + \sum_{i=1}^{N_c} K_{ns} c_i} \quad (4.9)$$

H_{ns} and K_{ns} are non-selective parameters, but carry the same definition as given for selective parameters above. Furthermore, we must point out here that we do not assume equal saturation capacities for the isotherms employed here.

4.2.3 Calibration equations

While satisfying material balance, a calibration equation takes into account absorbance intensity and signal value at baseline. Therefore, for linear operating range:

$$c(t) = ay(t) + b \quad (4.10)$$

where, $y(t)$ is the detector signal in an appropriate unit (e.g., mAU) collected as a function of time. The parameter a is a constant which is inversely proportional to absorbance intensity, and the term $-b/a$ is the signal value at baseline. This direct formulation of concentration vs. detector signal is sometimes called absolute calibration (84).

Since nonlinearity of the detector signal is expected, we propose the following rational and exponential equations:

$$c(t) = \frac{ay(t) + b}{(cy(t) + 1)^2} \quad (4.11)$$

$$c(t) = ay(t)e^{-cy(t)} + b \quad (4.12)$$

It may be noted that both of the nonlinear equations reduce to the linear equation at low $y(t)$ values. Therefore, the term $-b/a$ is the signal value at baseline for these equations. This information is used to enhance the convergence of the parameter estimation technique as can be described in Section 4.3.1.

The two nonlinear equations above contain three degrees of freedom each. Using higher degrees of freedom is not recommended because of the risk of over fitting when the experimental data is scarce.

4.3 Parameter estimation

4.3.1 Calibration

In analytical chromatography, it is customary to calibrate the detector by relating the peak area S to the amount injected, which is called analytical calibration (87) (typically at constant injection volume). In fact the same procedure can be employed for absolute calibration as long as we are in the linear range of absorbance. Under such condition:

$$S = \alpha c_T^F + \beta \quad (4.13)$$

Since we focus on enantiomers which have identical absorbance characteristics in pure form or as a mixture, total feed concentration c_T^F is used. Assuming that the peak or peaks are completely eluted, we can use a material balance to relate Eq. 4.13 and Eq. 4.10. Therefore, from material balance we have:

$$Q \int_0^{t_e} c(t) dt = V_{inj} c_T^F \quad (4.14)$$

where Q and V_{inj} are mobile phase flow rate and sample injection volume, respectively. t_e is the end time of experimental run. We can then replace concentration from Eq. 4.10 and rearrange this equation:

$$a \int_0^{t_e} y(t) dt + bt_e = \frac{V_{inj} c_T^F}{Q} \quad (4.15)$$

or

$$aS + bt_e = \frac{V_{inj} c_T^F}{Q} \quad (4.16)$$

Without further experimental efforts, the parameters a and b can be obtained directly as functions of α and β via comparing Eq. 4.16 with Eq. 4.10:

$$a = \frac{V_{inj}}{\alpha Q} \quad (4.17)$$

and

$$b = -\frac{\beta V_{inj}}{\alpha Q t_e} \quad (4.18)$$

Therefore, as long as we are in the linear range, an analytical calibration yields absolute calibration provided that some extra information about the experimental conditions, namely flow rate, injection volume, and run time are accurately available.

On the other hand, this approach cannot be extended to nonlinear calibration (84, 87). In fact the experimental procedure is the same for nonlinear calibration, but it is the solution method that must be revised. One of the effective and economical solutions is based on material balance (79, 87). In this approach, a predefined form for the calibration equation is assumed, and then the material balance equation is numerically solved as an error minimization problem to obtain the best-fit parameters. In this work, we have defined a slightly modified objective function to improve the accuracy and facilitate convergence:

$$E_C = \sum_{j=1}^{N_{cy}} \left| \frac{Q_j \int_0^{t_e} c_{exp,j}(t) dt - V_{inj,j} c_{T,j}^F}{N_{cy} V_{inj,j} c_{T,j}^F} \right| + \lambda_C \sum_{j=1}^{N_{cy}} \left| \frac{b + a \bar{y}_{j,0}}{N_{cy} \bar{y}_{j,0}} \right| \quad (4.19)$$

where N_{cy} is the number of experiment cycles. $c_{exp}(t)$ is calculated from any of the equations given earlier (Eq. 4.10-4.12). $\bar{y}_{j,0}$ is the average baseline signal value for the j th experiment. The role of the second summation in this equation is to enforce zero concentration at baselines for all experiments. As a result, this equation has only three unknowns, namely a , b , and c , which must be obtained implicitly via a numerical optimization procedure.

It must be emphasized that in any of the equations involving integration over time, the integration limits can be reduced to any area around peak or peaks in order to reduce the effects of noise and baseline drift. This approach requires application of peak detection techniques, which is beyond the scope of this work and besides, in our experiments, the improvement was minor. Therefore, the integration range was selected as the entire time interval.

4.3.2 Isotherm determination

In the classical inverse method, after identifying a proper calibration equation and converting the detector signal to experimental concentration profile, it must be compared with the simulated concentration profile obtained through solving the set of Eqs. 4.1 and 4.2 as follows:

$$\min E_{I1} = \sum_{j=1}^{N_{cy}} \sum_{k=1}^{N_{t,j}} \frac{|c_{exp,j}(k) - c_{sim,j}(k)|}{N_{cy} N_{t,j} c_{T,j}^F} \quad (4.20)$$

where $N_{t,j}$ is the number of discretized data points collected over time for the j th experiment.

In our approach which is referred to as NDIM throughout this paper, isotherm determination is an extension to the calibration procedure. We just need to combine Eqs. 4.19 and 4.20 with proper weight factors to formulate the single objective function of the optimization problem:

$$\min E_{I2} = E_{I1} + \lambda_{I1} \sum_{j=1}^{N_{cy}} \frac{\left| Q_j \int_0^{t_e} c_{exp,j}(t) dt - V_{inj,j} c_{T,j}^F \right|}{N_{cy} V_{inj,j} c_{T,j}^F} + \lambda_{I2} \sum_{j=1}^{N_{cy}} \left| \frac{b + a \bar{y}_{j,0}}{N_{cy} \bar{y}_{j,0}} \right| \quad (4.21)$$

Integration of this equations above should be carried out numerically. The time delay caused by the dead volume of the experimental setup should be accounted for prior to parameter estimation.

In summary, the decision variables for this optimization problem are isotherm, calibration, and transport parameters. In order to facilitate the convergence, we have carefully constrained the multi-dimensional search space with lower and upper bounds on decision variables. Negative values are not allowed for K_i due to the shape of the experimental concentration profile. The range of decision variables are given in Table 4.1.

4.3.3 Optimization algorithms and numerical solution techniques

Literature related to inverse method indicates that solving this problem is of challenging nature. The large number of decision variables and extreme nonlinearities need proper care in this problem. Investigating the calibration problem alone reveals that there are many local minima present in the solution space, adding an extra level

Table 4.1: Constraints imposed on the optimization problem.

Parameter	Unit	Lower bound	Upper bound
H_A	-	0.1	4.5
K_A	L/g	0	0.05
H_B	-	0.01	2.0
K_B	L/g	0	0.05
H_{ns}	-	0	2
K_{ns}	L/g	0	0.1
k_A	1/s	10^{-10}	20
k_B	1/s	10^{-10}	20
$D_{ax,A}$	m ² /s	10^{-10}	10^{-5}
$D_{ax,B}$	m ² /s	10^{-10}	10^{-5}
a	g/L/mAU	0	0.01
b	g/L	-0.05	0.05
c	1/mAU	-0.01	0

of complexity to the overall problem. This is illustrated in Fig. 4.1 where the objective function E_C is plotted against a and c around an optimal point. Therefore, a global search approach is more appropriate for this kind of problem. Here we employ GA in single-objective formulation for global search (59), (88), (82). In every iteration (generation), an entire population is evaluated in a parallel fashion. Although this was a drawback of evolutionary algorithms in the past, thanks to the now-available parallel computing capabilities of commercial computers, it is possible to carry out this task quickly and efficiently.

Another drawback of GA is its inefficiency in pinpointing the final solution. GA is of stochastic nature, and works with a population of candidate solutions. In contrast, classical gradient-based methods such as sequential quadratic programming (SQP) utilize deterministic computations (83). The goal is to pinpoint the final solution with a better accuracy. Therefore, we feed the final solution obtained from GA to SQP as an initial guess. The time and computational efforts taken by the latter step is insignificant compared to the former one, but it has the advantage of a precise search around the final GA solution without the risk of falling into a local minimum. We have used this approach for both combined and separate determination of calibration

Figure 4.1: Response curve of E_C for changes in the calibration parameters a and c around the optimal point obtained from NDIM using exponential calibration ($b = 4.60 \times 10^{-5}$ g/L, see Table 4.5).

and isotherm parameters.

The model equations comprise partial differential equations (PDEs), which are discretized in space using third-order weighted essentially non-oscillatory (WENO) scheme (68). This class of finite-volume based schemes is competitive to van Leer flux limiter, which was investigated in our previous work (41), especially when facing large axial dispersion. The resulting set of ordinary differential equations (ODEs) is solved by the method of lines. Among different ODE solvers that we have tested, Adams-Bashforth-Moulton PECE solver (ode113) (69) seemed to be the most satisfactory in terms of handling computationally intensive problems. The simulation parameters are given in Table 4.2. The number of grid points is chosen in such a way that numerical diffusion becomes negligible compared to axial dispersion. The weight factors introduced in Eqs. 4.19 and 4.21 are also given in Table 4.2.

The discretized equations were compiled in C programming language, but embedded in MATLAB environment. Parallel computing facilities of MATLAB were also utilized. In this way, the computational speed could be boosted drastically. Moreover, material balance and peak area integrations were carried out using trapezoidal rule.

4.4 Experimental

Guaifenesin has been taken as the model chiral compound to be separated, where (S)-(+)-guaifenesin is the more retained enantiomer denoted by A and (R)-(-)-guaifenesin is the less retained enantiomer denoted by B. Heptane and ethanol solvents were used

Table 4.2: Simulation parameters and weight factors.

Parameter	Value
ODE solver	ode113 (69)
Absolute integration tolerance	10^{-6}
Relative integration tolerance	10^{-4}
Number of grid points	400
Weight factor λ_C	0.1
Weight factor λ_{I1}	0.3
Weight factor λ_{I2}	0.1

as mobile phase. The composition of the mobile phase (heptane-ethanol) for both preparative work and analysis was 65:35 (v/v). Chiralcel OD, cellulose based chiral stationary phase (cellulose tris (3,5-dimethylphenylcarbamate) coated on silica) has been considered as the preparative column (10 cm $\times$ 1 cm I.D., particle size 20 μ m). The overall bed void fraction (ε) was calculated using 1, 3, 5-tri-tert-butylbenzene as tracer. The extra-column dead volume was also measured using the tracer injection experiments with and without the chromatographic column. Experimentally the solubility of guaifenesin in heptane-ethanol (65:35,v/v) mixture in room temperature (23°C) was checked and it was found near 35 g/L, which is within the range of values reported by other investigators (66).

All raw data for isotherm determination were collected using certain parts of an existing improved single-column chromatographic (ISCC) separation process in our lab (88). A Flexar isocratic LC pump, a six port valve, and injection loop arrangement were used for feed injection. A similar binary pump was used for pumping the mobile phase. The HPLC modules, that is, pumps, UV detectors, column oven, and degassers were purchased from local vendor (Singapore).

Attention must be given in the proper selection of injection loop; it should have small internal diameter to suppress axial dispersion as also noted by Felinger et al. (77). The pressure drop is higher and this may limit the minimum tubing size for practical purpose. In this work we used the largest available piece of tubing with 1/30 inch internal diameter to minimize dispersion. The loop volume was obtained by measuring the mass of injection loop when filled with pure heptane and comparing

it with the mass of empty loop at room temperature. These provided close match between experimental and simulated concentration profiles.

Time delay (t_d) caused by extra-column dead volume was measured and accounted for in all the reported data. Five different concentrations (10, 13, 15, 18 and 20 g/L) of guaifenesin mixture were used for the determination of isotherm parameters. In-house customized data-logging and control software developed in our laboratory were used for preparative work. The software was developed using LabVIEW (National Instruments, Singapore). The experimental conditions are summarized in Table 4.3.

Table 4.3: Experimental operating conditions.

Parameter	Unit	Value
D	cm	1
L	cm	10
ε	-	0.717
d_p	μm	20
V_{inj}	μL	1192
Q_D	ml/min	2.0
t_d	s	29.0
λ	nm	295

4.5 Results and discussion

Results of simultaneous determination of detector calibration and isotherm parameters using the nonlinear direct inverse method (NDIM) are presented and compared with the classical inverse method (CIM). Nonlinear equations (Eqs. 4.11 and 4.12) and the ubiquitous linear equation (Eq. 4.10) have been used for calibration. The performance is evaluated in terms of material balance error and sum of residuals as given by the first term on the RHS of Eq. 4.19 and Eq. 4.20, respectively. Chromatograms of all five injections have been used together for parameter estimation.

4.5.1 Sensitivity analysis

The results of sensitivity analysis around the optimal operating point which was obtained by nonlinear direct inverse method and exponential calibration are given in Table 4.4 for $\pm 10\%$ change in every decision variable. The procedure is as follows: in each run only one decision variable is changed and the others remain constant at their respective optimal value. The change in the objective function is evaluated as reported in the rows of Table 4.4. The results imply that all decision variables contribute to the variations of the objective function E_{I2} though at different extents. We must emphasize that the higher the sensitivity is, the higher is the reliability of the value obtained for each decision variable.

This method of sensitivity analysis clarifies the role of individual decision variables independently. In particular, as equilibrium constants K_A , K_B , and K_{ns} have more or less important effects on the objective function, we ensure that the experiments are overloaded enough to capture the nonlinear curvature of the bi-Langmuir isotherm up to the maximum concentration seen in the elution profiles.

4.5.2 Parameter estimation

The results of parameter estimation are given in Table 4.5. The results obtained through NDIM and CIM are nearly the same. Besides, the material balance and sum of residuals of these methods are also very similar showing that NDIM approach is as good as the classical one (see Table 4.6) while the former one is computationally more efficient and allows simultaneous determination of calibration and isotherm parameters.

From Table 4.5, the values of non-selective parameters of bi-Langmuir isotherm are comparable to selective ones indicating that there are at least two types of sites available for adsorption. Therefore, simpler isotherms such as ordinary Langmuir is inadequate for describing the separation behavior though the cumulative Henry constants (i.e., $H_i + H_{ns}$) obtained here are close to what reported by Francotte et al. (66) using a Langmuir isotherm. On the other hand, this observed amount of non-selective adsorption suggests a better experimental operating condition must be sought for preparative work.

Table 4.4: Sensitivity analysis: change in the objective function E_{I_2} for $\pm 10\%$ change in the decision variables one at a time. Values are in percent with respect to the base case value of $E_{I_2}=0.0136$ and the values of decision variables given in Table 4.5 for exponential calibration using NDIM.

	+10 %	-10 %
H_A	85.4	75.7
K_A	0.19	2.1
H_B	3.9	2.9
K_B	0.18	0.48
H_{ns}	66.1	65.3
K_{ns}	4.6	2.6
k_A	0.08	0.33
k_B	0.36	-0.15
$D_{ax,A}$	0.37	0.14
$D_{ax,B}$	-0.11	0.61
a	179.5	193.3
b	0.07	0.07
c	42.6	50.4

The estimated axial dispersion coefficients are in the range of correlations given by Butt (65) and Guiochon et al. (42). However, the mass transfer coefficients are smaller than the results as reported by Zabka et al. (67) and Phillips et al. (89). This could be due to the distortion in the boundary condition caused by imperfect injection mechanism.

Table 4.5: Results of parameter estimation using the proposed approach (NDIM) and the classical inverse method (CIM) for various calibration equations.

		CIM			NDIM		
Parameter	Unit	Rational	Exponential	Linear	Rational	Exponential	Linear
H_A	-	2.89	2.91	2.99	2.87	2.91	2.99
K_A	L/g	0.0188	0.0187	0.0221	0.0188	0.0193	0.0221
H_B	-	0.26	0.26	0.32	0.26	0.26	0.32
K_B	L/g	0.0307	0.0352	0.0483	0.0307	0.0352	0.0483
H_{ns}	-	1.21	1.17	1.16	1.21	1.17	1.16
K_{ns}	L/g	0.0414	0.0358	0.0404	0.0402	0.0350	0.0404
k_A	1/s	1.81	1.78	3.60	1.81	1.78	3.59
k_B	1/s	2.39	2.04	3.37	2.45	2.04	3.37
$D_{ax,A} \times 10^8$	m ² /s	5.07	5.43	7.69	5.07	5.50	7.72
$D_{ax,B} \times 10^8$	m ² /s	4.62	4.80	13.35	4.66	4.86	13.35
$a \times 10^3$	g/L/mAU	5.46	5.20	7.84	5.46	5.20	7.84
$b \times 10^5$	g/L	5.22	4.58	6.92	5.30	4.60	6.89
$c \times 10^3$	1/mAU	-0.405	-1.02	-	-0.405	-1.02	-

The comparison of experimental and simulated elution profiles using NDIM is shown in Figs. 4.2 and 4.3 for exponential and linear calibrations, respectively. It is clear from these figures that the matches are much better for experimental calibration compared to the linear one. The results also show that nonlinear calibration with bi-Langmuir isotherm satisfactorily describes the separation behavior of guaifenesin enantiomers on Chiralcel OD stationary phase using heptane-ethanol (65 : 35, v/v) mobile phase. The results of the rational calibration are similar to the exponential one.

The material balance and sum of residuals obtained using CIM and NDIM methods are given in Table 4.6. The material balance error is less than 5% for the rational and exponential calibrations, which is acceptable for this type of separation problem, but

it is large for linear calibration indicating inadequacy of the linear calibration.

It is important to note that the sums of residuals are all small and acceptable (see Table 4.6). However, these results can be misleading if the material balance error is not accounted for at the same time. Table 4.5 shows that rational and exponential calibration equations have resulted in similar estimated parameters, but the results obtained through linear calibration are significantly different. This difference is manifested in the material balance error and not in the sum of residuals. This finding suggests that an inaccurate calibration may bring about results that offer good fit to the experimental elution profiles, but will seriously violate the material balance. Therefore, in any parameter estimation problem, the material balance error, which is primarily regulated by the calibration equation, should be included as a part of the objective function. This is in fact a major advantage of the proposed method, which simultaneously takes into account material balance and sum of residuals.

Table 4.6: Individual material balance and sum of residuals. The material balance errors were calculated by the first term on RHS of Eq. 4.19, and the sum of residuals were calculated by Eq. 4.20 (values are in percent).

		Material balance (%)					Sum of residuals (%)				
Run		1	2	3	4	5	1	2	3	4	5
CIM	Rational	-0.5	2.6	0.004	3.9	-5.0	0.6	0.6	0.6	0.8	1.0
	Exponential	-0.01	2.7	-0.005	3.9	-4.8	0.5	0.5	0.5	0.7	1.0
	Linear	-11.2	-1.5	0.006	7.4	3.5	0.9	0.6	0.6	0.8	0.9
NDIM	Rational	-0.5	2.6	0.004	3.9	-5.0	0.7	0.6	0.6	0.8	1.0
	Exponential	-0.01	2.7	-0.005	3.9	-4.8	0.5	0.5	0.5	0.7	0.9
	Linear	-11.2	-1.5	0.006	7.4	3.5	0.9	0.6	0.6	0.8	0.9

4.5.3 Calibration curves

The calibration curves are plotted in Fig. 4.4 using the estimated parameters obtained by NDIM given in Table 4.5. For comparison, we have also added the line obtained by analytical calibration, i.e. calculating the peak areas and using Eqs. 4.17 and 4.18. For detector calibration, this method gives inferior fit and seriously violates the material balance. Both of the nonlinear calibration equations, i.e. rational and exponential,

Figure 4.2: Comparison of experimental and simulated elution profiles obtained by NDIM: bi-Langmuir isotherm, exponential calibration; Feed concentrations: (a) 10 g/L, (b) 13 g/L, (c) 15 g/L, (d) 18 g/L, (e) 20 g/L.

Figure 4.3: Comparison of experimental and simulated elution profiles obtained by NDIM: bi-Langmuir isotherm, linear calibration; Feed concentrations: (a) 10 g/L, (b) 13 g/L, (c) 15 g/L, (d) 18 g/L, (e) 20 g/L.

provide similar results. In fact, they are practically identical at lower absorbance values and differ slightly at higher values as seen in Fig. 4.4. On the other hand, the method presented for linear calibration in this chapter is more accurate than the analytical approach.

Figure 4.4: Calibration curves obtained using NDIM as given in Table 4.5. The line obtained by the analytical method (Eqs. 4.17 and 4.18) is also given for comparison. Note that the calibration equations are just valid up to the maximum concentration observed on the elution profiles (ca 10 g/L).

4.5.4 Effects of transport parameters

To investigate the distinct contributions of mass transfer and dispersion effects, simulations are carried out by changing mass transfer coefficients, k_i , both at low and overloaded conditions near optimal points using NDIM as shown in Fig. 4.5. It is found that, as expected, the band broadening is a function of mass transfer coefficient, but the retention time is not affected by this parameter in the linear range of operation, except for very small k_i values. On the other hand, in the overloaded range of operation, the peak position is clearly shifted with varying k_i values. This asymmetric change cannot be explained by axial dispersion as its effect is merely symmetrical in usual operating conditions (except under very large dispersion, (90)). Therefore, a mathematical model that accounts for mass transfer resistance separately (i.e., differentiating it from axial dispersion), is more appropriate when dealing with

complex isotherms such as bi-Langmuir.

4.6 Concluding remarks

Detector calibration is in general a prerequisite step for isotherm determination. We have presented a method for simultaneous calibration of detector and determination of adsorption isotherm. It can readily be used for a mixture of enantiomers under base line separation or overlapping of elution profiles. For achiral compounds however, the chromatogram must be baseline separated to be processed by this method. This method is faster and more economical than other alternatives provided that efficient computational facilities are available.

We have shown that this method can reduce the risk of converging to a wrong calibration equation that violates material balance and subsequently a wrong set of isotherm parameters. This is achieved through simultaneous calibration and isotherm determination in a single step. This is indeed an advantage of our approach compared to the classical inverse method.

We have used a hybrid optimization method for parameter estimation as this problem suffers from several local minima. Genetic algorithm (GA) in conjunction with sequential quadratic programming (SQP) algorithm have been used to globally search for the optimum set of parameters and pinpoint the final solution, respectively. Faster convergence was achieved through improved formulation of the objective function.

We also proposed alternative nonlinear calibration equations. This is a major difference compared to the direct inverse method, which is limited to linear calibration because of its solution approach. Preparative chromatography necessitates nonlinear calibration to ensure detector sensitivity over a wide range of feed concentration and the proposed method is expected to be useful for the determination of calibration and isotherm parameters in a single step.

It appears that there is a gap in research regarding detector calibration under overloaded chromatographic conditions for generic compounds, not just enantiomers, which can be a useful subject of future work in this area.

(a)

(b)

Figure 4.5: Effects of change in mass transfer coefficients; (a) analytical injections ($V_{inj} = 100 \mu\text{L}$, $c_T^F = 1 \text{ g/L}$) (b) overloaded injections ($V_{inj} = 1192 \mu\text{L}$, $c_T^F = 15 \text{ g/L}$). The legends are mass transfer coefficients for both components in $1/\text{s}$. The vertical lines designate the peak position for $k_i = 10 \text{ 1/s}$. The simulated chromatograms were produced near optimal points obtained using NDIM.

Nomenclature

a	slope of absolute calibration equation [g/L/mAU]
b	intercept of absolute calibration equation [g/L]
c	nonlinear parameter of absolute calibration equation [1/mAU]
$c(t)$	fluid phase concentration of solute [g/L]
c_T^F	total feed concentration [g/L]
D	column diameter [cm]
D_{ax}	axial dispersion coefficient [m ² /s]
d_p	particles diameter [μ m]
E	estimation error [-]
H_i	Henry constant of species i [-]
K_i	equilibrium constant in Langmuir isotherm of species i [L/g]
k_i	overall mass transfer coefficient [1/s]
L	column length [cm]
N_{cy}	number of experimental cycles [-]
$N_{t,j}$	number of discretized data points collected over time for the j th experiment [-]
n	solid phase concentration of solute [g/L]
n^*	equilibrium solid phase concentration of solute [g/L]
S	peak area [mAU.s]
Q	volumetric flow rate [mL/min]
$q_{s,i}$	saturation capacity of species i [g/L]
t	time [s]
t_e	end time of experimental run [s]
t_p	feed pulse width [s]
v	interstitial velocity [cm/s]
V_d	extra column dead volume [μ L]
V_{inj}	injection volume [μ L]
y	absorbance [mAU]
z	axial coordinate [cm]

Greek letters

α slope of analytical calibration line [mAU.s.L/g]

β intercept of analytical calibration line [mAU.s]

ε overall void fraction of column [-]

λ penalty factor [-]

Subscripts and superscripts

A more retained component

ax axial

B less retained component

exp experimental

F feed

i component index

inj injection

ns non-selective

sim simulation

Chapter 5

Experimental Implementation of ISCC Process

This chapter presents the experimental implementation of the ISCC process. A mixture of guaifenesin enantiomers has been used to evaluate (i) the performance of the ISCC process, (ii) the online monitoring system, and (iii) the model predictive controller.

5.1 Model chiral compound

Guaifenesin as shown in Fig. 5.1 has been chosen as the model compound. It has been widely used in racemic form as an expectorant in cough remedy formulations (91–93). Recent studies showed that in racemic mixture of guaifenesin one enantiomer has greater physiological activity and fewer undesired side effects than the other enantiomer (94). Several reports suggest that there are different techniques other than chiral separation to separate the enantiomers of guaifenesin (95, 96). However, those processes are costly and the optical purity of the product obtained is only 63% (94). In comparison, other chiral compound such as β -amino acid, diacylglycerol enantiomers, methamphetamine, abscisic acid has been reported to obtain high purity separation using chiral separation technique (97–100). Therefore, chiral separation has been adopted as an alternative technique for obtaining highly enantiomerically enriched guaifenesin (12, 66, 101). In fact pure guaifenesin is expensive therefore; a properly optimized chiral separation technique will be useful. Availability of adsorption data

Figure 5.1: Guaifenesin enantiomers.

in the open literature provides added advantages when using this molecule as a model chiral compound to evaluate the performance of the optimizing controller.

5.2 Experimental

5.2.1 Materials

Racemic guaifenesin was used as solute and a mixture of heptane and ethanol was used as the mobile phase. Chiralcel OD, a cellulose based chiral stationary phase (cellulose tris (3,5-dimethylphenylcarbamate) coated on silica) was used as the stationary phase in the preparative column (10 cm $\times$ 1 cm I.D., particle size 20 μ m). Two Chiralcel OD-H columns were used as analytical column (15 cm $\times$.46 cm I.D., particle size 5 μ m) for the analysis of the product streams integrated in the online monitoring system.

5.2.2 Experimental set-up

ISCC process comprises different building blocks of HPLC modules such as pumps, UV detectors, oven, switching valves and degassers. A detailed process flow diagram of ISCC process is given in Fig. 5.2. Detailed description of this process can be found in Chapter 2. The setup was fabricated in a laboratory and commissioned. A photograph of final process setup is shown in Fig. 5.3.

Figure 5.2: Process Flow Diagram (PFD)

Figure 5.3: Process setup along with the instrument rack and monitoring computer.

5.3 Characterization

5.3.1 Overall bed void fraction (ε_t)

As the first step of the system characterization, the overall bed void fraction (ε_t) of the chiral columns was determined by measuring the retention time of a pulse of a non-retained compound. 1, 3, 5-tri-tert-butylbenzene was used as a tracer. This tracer was compatible with the column stationary phase and the mobile phase. From the residence time of the tracer (t_0) measurement of overall bed void fraction was calculated using (102):

$$t_0 = t_D + \frac{V\varepsilon_t}{Q} \quad (5.1)$$

Where, t_D is the extra-column dead time, V is the column volume and Q is the volumetric flow rate. The value of t_D of the system was obtained by injecting the tracer with a zero dead volume column instead of real column.

The overall bed void fraction values thus obtained are reported in Table 5.1.

These values are well within the range of values as reported by other investigators (66). Chiralcel OD-H showed a little less bed voidage compared to Chiralcel OD. This may be attributed to the fact that OD-H columns are packed with smaller diameter of 5 μm particles compared to OD columns which are packed with 20 μm particles.

Table 5.1: Overall void fraction of the columns.

Column name	Type	Specification	particle size	ε_t	% error
Chiralcel OD	Preparative	10 cm $\times$ 1 cm	20 μm	0.71	< 5%
Chiralcel OD-H	Analytical	15 cm $\times$ 0.46 cm	5 μm	0.68	< 5%

5.3.2 Isotherm

Chromatograms for increasing feed concentrations of guaifenesin enantiomers have been shown in Fig. 5.4.

Figure 5.4: Pulse chromatograms of the enantiomers of guaifenesin at increasing feed concentration.

Adsorption parameters from these experimental runs were obtained using nonlinear direct inverse method as elaborated in Chapter 4 and the results are furnished in Table 4.5. In this case, we consider the adsorbent structure as non-homogeneous. Therefore, we used bi-Langmuir isotherm to describe the adsorption properties for ISCC system.

It may be noted that NDIM requires the solution of an optimization problem for which

Henry's constants as calculated from Eq. 5.2, provides a good initial guess (102).

$$H_i = \frac{\varepsilon_t}{1 - \varepsilon_t} \left(\frac{t_{R,i} - t_0}{t_0} \right) \quad (i = A, B) \quad (5.2)$$

Where t_0 is the residence time of the tracer and $t_{R,i}$ is the retention time of solute molecules in the column. The nonlinear adsorption behavior is determined by injecting solutions with increasing concentrations of the guaifenesin, in Fig. 5.4 a shift in retention time is observed.

5.4 Vial test

A schematic diagram of the arrangement of the vial tests is shown in Fig. 5.5. These tests are carried out to check for the level of mixing and cross contamination in the vials. A pulse of feed is injected into the system without any HPLC column (Fig. 5.5).

Figure 5.5: Arrangement of vial test.

The vial is pressurized and sufficient time is given for mixing. A small portion of the vial contents is sent to the UV detector for analysis. A typical example of analysis is given in Fig. 5.6. Note that a blank injection is provided at the end of the experiment. Mass injected as feed is related to the concentration in the vial liquid holdup as:

$$c_H^t = \frac{c_T^F V_{inj}^F}{V_H} \quad (5.3)$$

where V_{inj}^F and V_H are the volume of the feed injected and the volume of the liquid holdup, respectively.

On the other hand, experimentally obtained concentration in the vial liquid holdup is:

$$c_H^e = \frac{A_S}{A_F} \frac{c_T^F V_{inj}^F}{V_{inj}^S} \quad (5.4)$$

where A_F and A_S are the areas under absorbance curves of the feed injected and sample taken from the liquid holdup, respectively. V_{inj}^S is the volume of the sample taken from the liquid holdup.

We define:

$$\alpha = \frac{c_H^e}{c_H^t} \quad (5.5)$$

α will be unity for perfect mixing, and in case of blank injections, will be zero for no cross-contamination.

Experimental conditions and calculated α values are given in Table 5.2 and Table 5.3, respectively. For majority of runs, α is very close to unity, which means, 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, we injected a second blank, no peak could be identified within the sensitivity of the UV detector. This means that contamination is only carried to the next cycle. In other words, this monitoring system would have a dynamic with one cycle transient response until it gives accurate readings.

Table 5.2: Values of parameters involved in the vial test.

Parameter	Value
c_T^F	10 g/L
V_{inj}^F	50 μ l
V_{inj}^S	20 μ l
V_H	2 ml
ω	150 RPM

Figure 5.6: Testing mixing and cross-contamination in the intermediate vial. The mobile phase is heptane-ethanol (65:35, v/v). See Table 5.2 for the values of parameters. Note that the last peak is for a blank injection.

Table 5.3: The results of testing mixing and cross-contamination in the vial. Note that the last run is a blank injection.

Run	1	2	3	4	5	6	7	8	9	10
α	0.94	0.98	0.98	1.01	0.99	0.99	0.96	0.97	0.93	0.04

5.5 Open-loop (uncontrolled) operation of ISCC process

The purpose of open-loop operation is to test and verify the separation performance of the ISCC process and the automated online monitoring system without imposing the controller. The operating parameters for the experiments are summarized in Table 5.5. After injecting feed into the system, the separation performance is monitored by observing the elution profile obtained from the UV detectors. Products were collected in the intermediate vials and analyzed in the analytical columns after ensuring proper mixing. In the open-loop mode, we considered two case studies. The summary of the case studies is given in Table 5.4. From the table of operating points it is obvious

Table 5.4: Purity requirement constraints for open-loop operation case studies.

Case	Purity of A	Purity of B
A	98%	98%
B	99.9 %	99.9%

that we can attend higher purity by changing only the cut intervals in expense of recovery. It also suggests that cut intervals are the important decision variables to fulfill the product quality. The purity of the products were calculated by measuring the underneath area of the analytical curves of the detectors.

Table 5.5: Operating parameters for open-loop run of ISCC process for both case studies.

Parameter	Case study A	Case study B
c_T^F	10 g/L	10 g/L
t_{cy}	170s	170s
dt_{c1}	70s	75s
dt_{c2}	10s	5s
dt_{c3}	80s	90s
V_{inj}	2ml	2ml
V_{inj}^S	20 μ L	20 μ L
V_H	2ml	2ml
ω	150 RPM	150 RPM

5.5.1 Case study A

In case study A, our target was to achieve 98% purity for both products. Cut intervals and flow rates were chosen based on offline optimization. Steady state elution profile of this experiment is shown in Fig. 5.7. For brevity and clarity only a part of the elution profile is presented here. Fig. 5.7 indicates significant separation of the guaifenesin enantiomers with certain extent of intra-profile 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 performances of the online monitoring system are shown in Fig. 5.8 and Fig. 5.9. The analytical response of the products in vial 1 (Fig. 5.8) shows that there are small peaks of more retained compound (Product A) compared to less retained compound (Product B) which shows that the ISCC process was able to deliver 98% purity for Product B in vial 1. Similar observations were made for the product in vial 2 (Fig. 5.9).

Figure 5.7: Elution profile of open loop uncontrolled operation of ISCC process (case study A).

Figure 5.8: Analytical response of product in vial 1 (case study A).

Figure 5.9: Analytical response of product in vial 2 (case study A).

5.5.2 Case study B

In case study B, we targeted for more stringent product requirement than case study A. The operating parameters and cut intervals were set to achieve 99.9% purity for both products. In Fig. 5.10, the detector's signal (elution profile) indicates the desired level of separation. The analysis of product in vial 1 (Fig. 5.11) and vial 2 (Fig. 5.12) shows that there are apparently no second peak implying that there are only product B and product A, respectively. This results show that complete separation of the enantiomers was achievable in the ISCC process. This study also established the fact that selection of cut intervals significantly affect the process performance and bolstered the need for an efficient fraction collection system.

5.6 Optimizing controller design for ISCC process

The concept of using an optimizing controller for chromatographic processes has received a lot of attention lately (12, 27, 31, 34, 36, 37, 103–108). The idea is to operate the process near or at the optimal operating point after meeting the process

Figure 5.10: Elution profile of open loop uncontrolled operation of ISCC process (case study B).

Figure 5.11: Analytical response of product in vial 1 (case study B).

Figure 5.12: Analytical response of product in vial 2 (case study B).

Figure 5.13: Schematic diagram of the implementation of model predictive control (MPC) concept on the process.

and product constraints.

In chromatographic process, the controller design is quite challenging due to its nonlinearity with lagged response and also for its mixed behavior of being continuous and discrete. This type of processes are difficult to handle with classical knowledge of process control. Purity and productivity are the main performance indicators of this process which are closely related with the operational limitations of equipment and other factors which clearly indicate the necessity of constrained optimization. The optimal operating region usually falls close to the constraints and this requires effective control schemes to keep the process at optimal point without violating the constraints. Again, an accurate continuous online monitoring system for chiral separation to date is unavailable and is a challenge due to its lack of accuracy or slowness of sampling. These limitations cannot be overcome unless standard systems are customized to suit the process condition and controller demands which inspired us to design an innovative online monitoring system with the use of HPLC.

It is evident that the online monitoring system which we developed returns the average concentration of each cycle, a ‘cycle to cycle’ optimization and control variant of MPC (model predictive control) will be a suitable option for this process (12). A schematic diagram of the control concept is given in Fig. 5.13. We have implemented a ‘cycle to cycle’ MPC scheme for the proposed ISCC process. MPC has been widely used in chemical and pharmaceutical industries including continuous chromatographic separation (12, 32, 106, 108). Although our process is operated in semi-batch mode, it reaches steady state similar to continuous processes with proper formulation of the inputs and outputs. In this control formulation, the manipulated variables (i.e., inputs) are injection volume, desorbent flow rate and three cut intervals whereas the controlled variables (i.e., outputs) are the process performance indicators. The performance function has been formulated as Equation 5.6, which represents the profitability of the operation:

$$F_{PD} = \lambda_1 (Pr - Pr_s) - \lambda_2 (Dr - Dr_s) \quad (5.6)$$

Pr_s and Dr_s are steady state values around which the process is linearized.

MPC depends on a model for decision making, the accuracy of the model plays an important role in the overall performance of the controller. Here, we have used a linear empirical model to fit the dynamic behavior of the ISCC process on a ‘cycle

to cycle' basis. MPC heavily relies on solving dynamic optimization problem. In this case the optimization problem has been formulated as follows:

$$\Delta u(k|k), \dots, \Delta u^{min}(m-1+k|k), \epsilon \left\{ \sum_{i=0}^{p-1} \left(\sum_{j=1}^{n_y} |w_{i+1,j}^y (y_j(k+i+1|k) - r_j(k+i+1))|^2 + \sum_{j=1}^{n_u} |w_{i,j}^{\Delta u} \Delta u_j(k+i|k)|^2 + \sum_{j=1}^{n_u} |w_{i,j}^u (u_j(k+i|k) - u_{jtarget}(k+i))|^2 \right) + \rho \epsilon^2 \right\} \quad (5.7)$$

subject to the following constraints:

$$u_{jmin}(i) - \epsilon V_{jmin}^u(i) \leq u_j(k+i|k) \leq u_{jmax}(i) + \epsilon V_{jmax}^u(i) \quad (5.8)$$

$$\Delta u_{jmin}(i) - \epsilon V_{jmin}^{\Delta u}(i) \leq \Delta u_j(k+i|k) \leq \Delta u_{jmax}(i) + \epsilon V_{jmax}^{\Delta u}(i) \quad (5.9)$$

$$y_{jmin}(i) - \epsilon V_{jmin}^y(i) \leq y_j(k+i|k) \leq y_{jmax}(i) + \epsilon V_{jmax}^y(i) \quad (5.10)$$

for $i = 0, \dots, p-1$, and

$$\epsilon \geq 0 \quad (5.11)$$

u and y are the array of inputs and outputs, respectively. The subscript j is the j th element of a vector. The expression $k+i|k$ means predicted value at time $k+i$ based on the information available at time k . $r(k)$ is the reference (setpoint) trajectory at time k , which can be a function of time. $u_{jtarget}(k)$ is the setpoint value for input j . The controller tries to minimize the difference between this value and the j th input if it is necessary to fix any of the inputs.

$w_{i,j}$ values are weights associated with y , u , and Δu to adjust the relative importance of their respective variables in the objective function defined above. The weight ρ_ϵ regulates the importance of violating the constraints. The slack variable, ϵ which is a positive scalar here, takes the value of the largest constraint violation.

The model predictive toolbox of MATLAB 2010a was used for implementing the MPC scheme and a virtual plant was implemented in Simulink. We also used Kalman filtering for online updating and state estimation.

A detailed development of the MPC controller was done in a parallel work in our group and can be found elsewhere (109).

5.7 Close-loop operation of ISCC process

In close-loop controlled operation, the designed MPC controller was implemented on the ISCC process. We assessed the performance of the controller for set point tracking and disturbance rejection through simulation studies. This was followed by experimental evaluation of the controller on the laboratory ISCC unit. During the experiments, it was noticed that sometimes the detector connected to the ISCC process lost communication to the HMI when the MPC was running. This data loss prevented us from running the process with the controller in a continuous fashion. This is an implementation issue and we clearly point out this limitation of the current integrated ISCC (with online monitoring and MPC controller) process. We believe that a fast and robust detector such as one that comes with the uHPLC unit will be able to overcome this problem and include this as a suggestion for future works.

We nonetheless, implemented and checked the performance of the controller experimentally in an offline fashion. Some of the operating points from the simulation studies were implemented and purity values of the product streams were calculated. They are shown along with the simulated performance of the controller for set point tracking and disturbance rejection in the following case studies:

5.7.1 Set point tracking

Table 5.6: Operating parameters for close-loop run of ISCC process for set point tracking.

Parameter	Initial point	Final point
Purity of A	95%	98%
Purity of B	95%	98%
Recovery of A	75%	78%
Recovery of B	75%	78%

The aim of set-point tracking is to demonstrate the ability of the controller to fulfill the product specifications under different set points. The set-points are changed after 45th injection while other system parameters are kept constant. The MPC is activated immediately after start up and tries to maintain the purity and recovery

values given, and simultaneously maximize productivity and minimize desorbent requirement. Results shown in Fig. 5.14, demonstrate that initially the set-point of 95% purity and 75% recovery for both of the products were fulfilled. Controller took about 20 cycles to fulfill these product specification. After 45th injection, setpoint was changed to 98% purity and 78% recovery values.

The change in the set point resulted in changing the operating points of the ISCC unit and the subsequent action of the controller was able to take the process to a region where the purity and the recovery requirements were fulfilled. It took about 15 cycles to achieve this. However, a small offset in the purity requirement when tracking the second set point is observed. This is due to highly non-linear interactions of the purity and recovery parameters. Similar observations were made by other investigators when attempts were made to simultaneously track these inter-related quantities (110). Operating points where experiments were conducted are shown in the same figure using solid symbols. It is very clear to observe a close match between experiments and simulation results.

Apart from delivering the product requirements, the MPC algorithm also aims to optimize the process performance. Fig. 5.15 shows the performance function, F_{PD} , along with productivity, Pr , and desorbent consumption, Dr , as a function of time in cycle unit. It is observed from the Fig. 5.15 that before the introduction of the set point change at cycle 45, the action of the controller maximized the process performance while the product requirement remained fulfilled. After the change in the set points to SP_2 , performance function decreased, i.e. Pr decreased and Dr increased. This is expected since the product requirement settings for the second set points (SP_2) were more stringent compared to the first set points SP_1 . The change in the operating points, i.e. input parameters namely injection volume and cut intervals are shown in Fig. 5.16. This figure shows the trajectories of controller actions before and after the change of the set points.

5.7.2 Disturbance rejection

The performance of the controller in terms of disturbance rejection is shown in Figs. 5.17 and 5.18. The ISCC process was started up with the controller on and at the same initial operating condition of the set-point tracking. The results are divided

(a)

(b)

Figure 5.14: The results of set-point tracking (case study 1); after 45th injection the set-point values of purity (P) and recovery (Y) for both products are changed from SP_1 ($P_i = 95\%$, $Y_i = 75\%$) to SP_2 ($P_i = 98\%$, $Y_i = 78\%$): (a) purities; (b) recoveries.

Figure 5.15: The results of set-point tracking (case study 1); after 45th injection the set-point values of purity (P) and recovery (Y) for both products are changed from SP_1 ($P_i = 95\%$, $Y_i = 75\%$) to SP_2 ($P_i = 98\%$, $Y_i = 78\%$): performance function (F_{PD}), productivity (Pr) and desorbent requirement (Dr).

Figure 5.16: The results of set-point tracking (case study 1); after 45th injection the set-point values of purity (P) and recovery (Y) for both products are changed from SP_1 ($P_i = 95\%$, $Y_i = 75\%$) to SP_2 ($P_i = 98\%$, $Y_i = 78\%$): manipulated variables (injection volume and three cut intervals).

into two parts. In the first part, i.e. from start-up to cycle 45, the evolution of the purity and recovery values over time is shown, demonstrating that the controller is able to satisfy the product specifications and at the same time it is able to optimize the process performance. Disturbance was introduced at cycle 45 in the form of a deliberate decrease in the feed concentration from 20 g/L to 19 g/L. This was unknown to the controller. The effect of this decrease in feed concentration was a loss of purity of component A and recovery of component B. Besides, productivity of the process decreased and the desorbent requirement increased as seen in Fig. 5.18 as a consequence of change in the feed concentration. The overall performance function (F_{PD}) also decreased for controllers subsequent actions to maintain the product requirements. Fig. 5.19 shows the trajectories of controller actions before and after the introduction of the disturbance.

5.8 Concluding remarks

In this chapter, the experimental implementation of the ISCC process is presented for the separation of guaifenesin enantiomer. At first, the characterization of the ISCC process was accomplished. We measured the overall bed void fraction for all the columns (one preparative and two analytical columns). Isotherm parameters obtained by the nonlinear direct inverse method mentioned in Chapter 4. The importance of mixing in the intermediate vials was discussed along with the vial test results. We have performed open-loop uncontrolled operation of ISCC process to ensure that all sections can operate seamlessly. It also verified the performance of the online monitoring system. In close-loop operation, the performance of ‘cycle to cycle’ optimizing controller was presented by simulation results followed by experimental verification of selected points. The proposed MPC scheme was tested for set point tracking and disturbance rejection. It was noted that sometimes the detector lost its communication with the HMI, when MPC was running. Therefore, it was not possible to evaluate controller’s performance in an online way for all operating points. We believe that a fast and robust detector such as one that comes with the uHPLC unit will be able to overcome this problem and include this as a suggestion for future works. In future more experimental runs may be designed to challenge the robust performances of the control scheme with improvements in the integration of the

(a)

(b)

Figure 5.17: The results of disturbance rejection (case study 2); after 45th injection the feed concentration is changed from 20 g/L to 19 g/L: (a) purities; (b) recoveries.

Figure 5.18: The results of disturbance rejection (case study 2); after 45th injection the feed concentration is changed from 20 g/L to 19 g/L: performance function (F_{PD}), productivity (Pr) and desorbent requirement (Dr).

Figure 5.19: The results of disturbance rejection (case study 2); after 45th injection the feed concentration is changed from 20 g/L to 19 g/L: manipulated variables (injection volume and three cut intervals).

building blocks of the closed-loop ISCC process. Nonetheless, the designed ISCC process with the online monitoring system is able to run at the optimal operating conditions for the separation of a mixture of enantiomers and deliver the product requirements as confirmed by open-loop and close-loop experiments.

Nomenclature

A_F	Area under feed absorbance peak [mAU.s]
A_S	Area under sample absorbance peak [mAU.s]
c_T^F	total feed concentration [g/L]
D	column diameter [cm]
Dr	desorbent requirement [L/g]
d_P	particles diameter [μm]
dt_{ci}	cut intervals [s]
F_{PD}	performance function [-]
H_i	Henry constant of species i [-]
K_i	equilibrium constant in Langmuir isotherm of species i [L/g]
L	column length [cm]
N_{cy}	number of experimental cycles [-]
P	purity [%]
Pr	productivity [g/(min g)]
S	peak area [mAU.s]
Q	volumetric flow rate [mL/min]
$q_{s,i}$	saturation capacity of species i [g/L]
t	time [s]
t_{cy}	cycle time [s]
$u(k)$	inputs [-]
V_{inj}^F	feed injection volume [μL]
V_{inj}^S	sample injection volume [μL]
V_H	volume of vial liquid holdup [μL]
V_d	setup dead volume [μL]
V_{inj}	injection volume [μL]
$w_{i,j}$	weight factors in formulating the MPC cost function [-]
$x(k)$	model states [-]
$\hat{x}(k)$	estimated states [-]
$y(k)$	measured outputs [-]
$\hat{y}(k)$	estimated/simulated outputs [-]
y_{UV}	UV signal [mAU]
Y	recovery [%]

Greek letters

α	parameter defined in Eq. 5.5 [-]
ω	shaker speed [RPM]
ϵ	slack variable [-]
ε	overall void fraction of column [-]
λ	wave length [nm]
ρ_ϵ	weight factor of slack variable [-]

Subscripts and superscripts

A	more retained component
B	less retained component
exp	experimental
F	feed
i	component index
inj	injection
s	steady state
sp	setpoint

Chapter 6

Conclusions and outlook

This thesis introduced an improved single-column chromatographic (ISCC) separation process with the final objective to make this process distinct from existing single-column chromatographic separation processes by physical modifications and conceptual advances. The performance of this ISCC process was evaluated by experimental implementation to separate a mixture of guaifenesin enantiomers.

In ISCC process, different standard HPLC peripherals were used as building blocks and some standard parts of the commercial HPLC system were redesigned to overcome the existing limitations for better performance. Fraction collection schemes and mechanism are the important features of this improvement. This fraction collection system allows accommodation of overlapped peaks from adjacent cycles and reduce the overall time delay of the process. These process design modification provide a wider degree of freedom: injection volume, cycle time, desorbent flow rate, feed concentration and fraction collection intervals. A robust online monitoring system was designed which was relatively inexpensive and was able to offer high frequency and accurate analysis of the samples compared to other devices. The proposed ISCC process was assembled in a laboratory and commissioned successfully.

Process performance was optimized by a multi-objective stochastic optimization technique based on genetic algorithm (GA). The optimization problem was appropriately formulated with the aim of maximization of productivity and minimization of desorbent requirement. Performance of the ISCC process was also compared with a similar SMB process. This study provided the basis for reaping the full potential benefits of a single column process that adopts cyclic injection. Besides, relative contribution of the decision variables were ascertained through the study of

their effects on the performance indicators.

Detector calibration and determination of adsorption isotherm parameters were done simultaneously by adopting a method named nonlinear direct inverse method, which is relatively fast, and economical technique compared to existing alternatives. A ‘cycle to cycle’ model predictive control (MPC) scheme was developed in-house to guarantee product and process specifications for obtaining optimized profitability. The performance of this MPC scheme was demonstrated through simulation studies. Finally, the cycle-to-cycle optimizing controller is developed for the ISCC process for the separation of a mixture of guaifenesin enantiomers. Key implementation issues were accuracy of the online measurement system and integration and automation of the ISCC process with online measurement system and controller. This was achieved by designing and developing a human machine interface (HMI) that was able to effectively communicate among the three essential components of the control loop. The performance of the controller was tested for set point tracking and disturbance rejection. Results indicate that the designed ISCC process with the online monitoring system was able to run at the optimal operating conditions and deliver the product requirements as confirmed by open-loop and close-loop experiments.

6.1 Outlook

In our proposed ISCC process, we have two waste streams, which are not recycled back to the feed. Therefore, a direct extension of this work would be steady state recycling (SSR) to boost the performance of the ISCC process. We have found that overlapped peaks (either from the same cycle or from adjacent cycles) can enhance the performance of the separation under reduced purity. This will be useful since only one fraction is recycled and no overlapping from adjacent cycles is allowed in the existing SSR processes. However, adding recycling streams to the ISCC process may cause complex dynamic behavior, which must be carefully investigated for controller design.

This process can be extended to fields where we need moderate purity requirement such as purification of pesticides, purification of macromolecules, etc since ISCC can compete well with other continuous chromatographic processes under reduced product

requirement. The study may be extended to separations characterized by a generalized Langmuir isotherm..

There appears to be a gap in research regarding detector calibration in overlapped conditions for generic compounds, not just enantiomers, which can be a useful subject for future studies.

Appendix A

List of Abbreviation

CPU	central processing unit
CSP	chiral stationary phase
EA	evolutionary algorithm
FV	finite volume
GA	genetic algorithm
HMI	human machine interface
HPLC	high performance liquid chromatography
ISCC	improved single-column chromatography
MPC	model predictive control
NSGA	non-dominated sorting genetic algorithms
ODE	ordinary differential equation
PDE	partial differential equation
PFD	process flow diagram
RPM	rounds per minute
SMB	simulated moving bed
TMB	true moving bed
WENO	weighted essentially non-oscillatory

Appendix B

Publications

Patent

- Medi B., M. K. Kazi, and M. Amanullah. Design of an improved single-column chromatographic separation process and its online monitoring system, filed on 6 March 2012 (patent pending).

Journal publications

- Kazi, M. K., B. Medi and M. Amanullah. Optimization of an improved single-column chromatographic process for the separation of enantiomers. J. Chromatogr. A, 2012. 1231: p. 22-30.
- Medi B., M. K. Kazi, and M. Amanullah. Nonlinear direct inverse method: a shortcut way for isotherm determination and calibration, Adsorption, 2013, p. 1-12.
- Medi, B., M. K. Kazi, and M. Amanullah. Analytical Comparison of Single-Column Chromatography and Simulated Moving Bed Process at Optimal Operating Points, In Preparation.
- Kazi, M. K., B. Medi and M. Amanullah. Experimental implementation of improved single-column chromatographic separation process, In Preparation.

Conference proceedings

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- Medi B., M. K. Kazi, and M. Amanullah. Optimization of an Improved Single-Column Chromatographic Process for the Separation of Enantiomers. AIChE Annual Meeting, Minneapolis, USA, 2011
 - Kazi, M. K., B. Medi and M. Amanullah. Nonlinear direct inverse method: a way to combine nonlinear calibration with isotherm determination. AIChE Annual Meeting, Pittsburg, USA, 2012
 - Medi B., M. K. Kazi, and M. Amanullah. Optimal Performance of Single-Column Chromatography and Simulated Moving Bed Processes for the Separation of Optical Isomers. MOIME, Jakarta, Indonesia, 2013.

Poster presentations

- Medi B., M. K. Kazi, and M. Amanullah. Comparison of single-column chromatography and simulated moving bed process at optimal operating points. In AIChE Annual Meeting, page 630f, Minneapolis, USA, 2011.

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