GREENER SOLVENT SELECTION, SOLVENT RECYCLING AND OPTIMAL CONTROL FOR PHARMACEUTICAL AND BIO-PROCESSING INDUSTRIES

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ABSTRACT

This paper proposes the simultaneous integration of environmentally benign solvent selection (chemical synthesis), solvent recycling (process synthesis) and optimal control for the separation of azeotropic systems using batch distillation. The previous work performed by Kim et al. (2004) combines the chemical synthesis and process synthesis under uncertainty. For batch distillation, optimal operation is also important due to the unsteady state nature of the process and high operating costs. Optimal control allows us to optimize the column operating policy by selecting a trajectory for the reflux ratio. However, there are time-dependent uncertainties in thermodynamic models of batch distillation due to the assumption of constant relative volatility. In this paper, the uncertainties in relative volatility are modeled using Ito processes and the stochastic optimal control problem is solved by combined maximum principle and non-linear programming (NLP) techniques. Then the previous work of optimal solvent selection and recycling is coupled with optimal control. As a real world example for this integrated approach, a waste stream containing acetonitrile-water is studied. The optimal design parameters obtained by Kim et al. (2004) for this separation are used and the optimal control policy is computed first without considering uncertainties by variable transformation technique. The deterministic optimal control policy improves the product yield by 4.0% as compared to the base case. A higher recovery rate is expected when the uncertainties are incorporated into in the model.

1. Introduction

Solvents are widely used in bulk chemical, specialty chemical and pharmaceutical industries. However, waste solvents released from these industries deteriorate the environmental quality and reduce the material economy. In order to recover the solvents from waste streams, separation processes are employed. Batch distillation is one of the separation processes used for solvent recovery in many chemical industries especially those related to the production of high value, low volume specialty chemicals, pharmaceuticals and bio-chemicals. This process offers great flexibility for small scale production, where there are variations in feed stock and product specifications. On the other hand, the unsteady state nature of this process creates challenging design and operational problems.

One of the most difficult problems is to optimally design and operate batch columns for the separation of systems showing non-ideal mixture behavior. For many industrially important mixtures and some waste solvents, the thermodynamics is complex due to the formation of

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azeotropes. One way to separate an azeotropic mixture is to use an entrainer to break the azeotrope by changing vapor-liquid equilibrium. The question following this is how to select an effective separating agent or entrainer (chemical synthesis) which complies with environmental regulations and how to synthesize this distillation process for solvent separation and recycling. In recent years, researchers have realized the importance of integrating chemical synthesis (i.e. environmentally benign solvent (EBS) selection) with process synthesis (i.e. in-process solvent (IPS) recycling) to ensure improved economic performance and environmental quality. However, this integrated approach poses a big problem of combinatorial explosion of alternatives in EBS selection and IPS recycling as well as the difficulties caused by thermodynamically complex systems and complex process configurations. In addition, uncertainties in the property prediction models in EBS selection and variability in IPS recycling results in additional complexities to this integrated approach. Recently, Kim and Diwekar (2004) derived an innovative batch campaign using the integrated chemical synthesis and process synthesis approach.

Furthermore, for batch distillation, we should also consider another important factor: optimal operation. Due to its unsteady state nature, operation is much more difficult and the operating costs are higher for this process. Therefore, optimal operating policies should be found for batch distillation. This results in an optimal control problem where an optimal trajectory for the control variable is found so as to optimize an index of performance. An optimal trajectory would be obtained if the mathematical model accurately captures the dynamics of the batch distillation process. However, for many mixtures the thermodynamic model is not exact and this results in time-dependent uncertainties. Rico-Ramirez et al. (2003) and Ulas et al. (2003) modeled these time-dependent uncertainties by making use of Real Options Theory based on Ito's Lemma (Ito, 1951) and derived the necessary equations for solving stochastic optimal control problems in batch distillation. The usefulness of this approach was demonstrated by case studies with known thermodynamic systems where the optimal reflux profiles obtained resulted in better process yield and product purity.

The aim of this work is to combine the previous work of computer-aided environmentally benign solvent selection and in-process recycling with optimal control in one platform considering the uncertainties at each stage. This complete integrated approach enables us to optimally design and operate batch distillation processes for azeotropic systems under uncertainty.

2. Integrated Framework for Waste Solvent Reduction

As mentioned above, the integrated framework consists of three stages:
(1)   Environmentally benign solvent selection (EBS)
(2)   In-process solvent recycling (IPS)
(3)   Optimal control and operation

2.1. Solvent Selection – Product Design

The first stage of this integrated framework is product design which is an approach to generate candidate solvent molecules that have desirable physical, chemical, and environmental properties. Computer-aided molecular design (CAMD) is one commonly used method. Based on the reverse use of group contribution methods, CAMD can automatically

generate promising solvent molecules from their fundamental building blocks or groups (Kim and Diwekar, 2002). Solvent selection model includes properties such as (a) distribution coefficient (b) solvent selectivity (c) solvent loss (SL), (d) physical properties like boiling point, ash point, density, and viscosity, (f) toxicology, (g) environmental properties like $LC50$(lethal concentration at 50%), $LD50$ (lethal dose at 50%), BCF (bio-concentration factor), and persistence, and (h) cost. The basic diagram of CAMD is given in Figure 1. This method can generate a list of candidate solvents with reasonable accuracy within a moderate time scale. However, CAMD is limited by the availability and reliability of property estimation methods and there are uncertainties in the prediction of environmental properties. These uncertainties will be mentioned in Section 3.
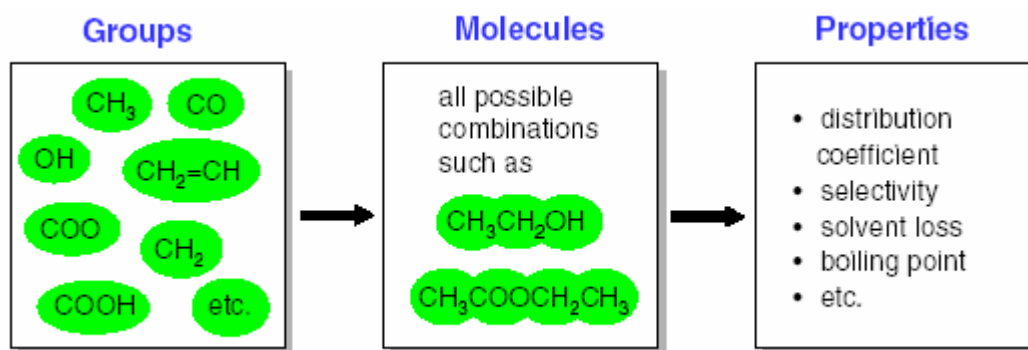

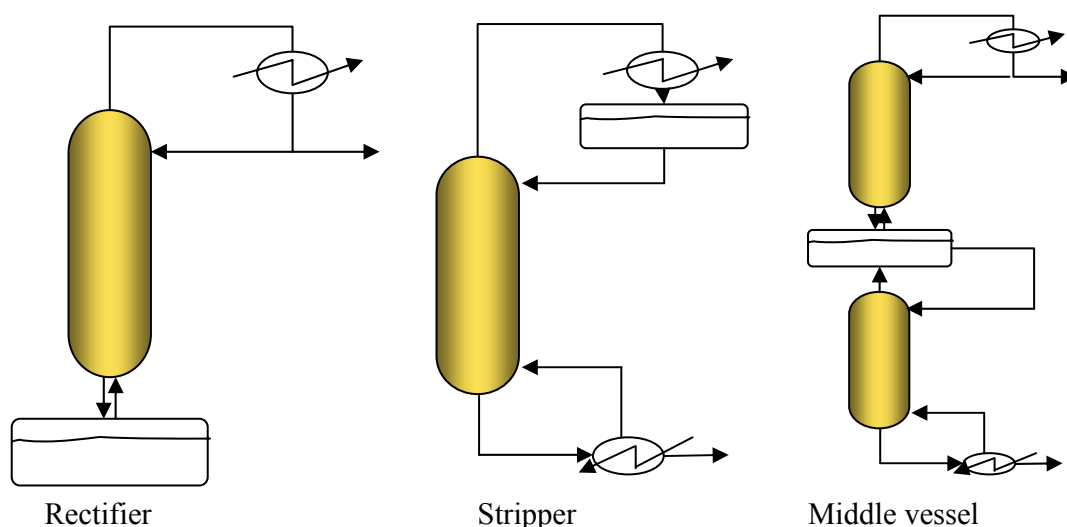**Figure 1.** Basic diagram of CAMD based on group contribution methods (Kim and Diwekar (2002)

Rectifier   Stripper   Middle vessel

Figure 2. Batch column configurations

2.1.   Solvent Recycling – Process Design

At this stage the EBS selection and in-process solvent (IPS) recycling models are simultaneously integrated. Three competing batch column configurations: the rectifier, the stripper, and the middle vessel column are considered which are given in Figure 2. Heuristics and optimization are used to find the best possible column configuration. A multi-objective optimization framework with possible objectives: maximum product recovery, maximum column feasibility and minimum heat duty provide the various trade-offs necessary for a smooth and robust operation. Kim et al. (2004) applied this framework to an industrial case study involving acetonitrile and water and derived two innovative batch campaigns. In this paper, to further improve waste reduction, optimal operation is also considered as well as product and process design, which is described in the following subsection. The same case study will be used to see the effect of optimal operation on process recovery in Section 4.

2.2.   Optimal Control – Optimal Process Operation

The final stage of this integrated framework is to apply optimal operation strategies to achieve maximum product yield and profit in solvent recycling. This is an important issue in batch and bio-processing because of the dynamic nature of these processes and the uncertainties associated with operation. The implementation of optimal operating strategies is important to maximize the amount of solvents recovered and to reduce the operating costs.

Optimal reflux policy in batch distillation is a trade-off between the two operating modes of variable reflux and constant reflux, based on the ability to yield the most profitable operation. The conceptual representation of optimal reflux policy is given in Figure 3. The computation of this policy relies on optimal control theory. Optimal control problems in batch distillation involve finding an open loop solution for the reflux ratio profile. The trajectory for reflux ratio is followed by the controller to optimize the chosen performance index. This trajectory is optimal when the mathematical model accurately represents the physical phenomena.
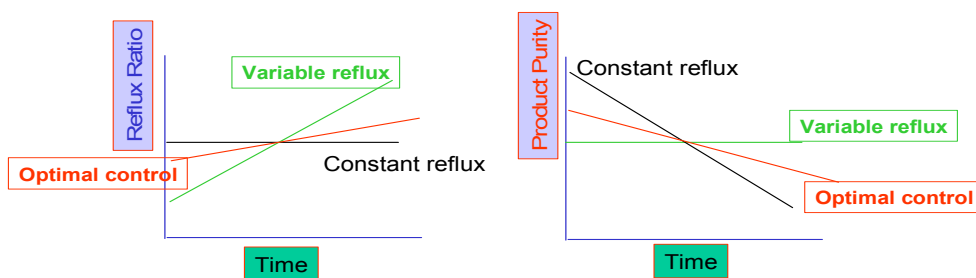

Figure 3. Representation of three operating modes in batch distillation

For inverted columns (strippers) operating policies are constant reboil, variable reboil and optimal reboil. Lotter and Diwekar (1997) studied emerging batch distillation columns such as the batch stripper and middle vessel columns (shown in Figure 2) and derived shortcut models for these complex column configurations. Although the constant and variable reboil policies have been studied before, the stripper optimal reboil policy was not presented. In a similar fashion to optimal reflux policy of batch rectifier (Diwekar, 1992), the optimal reboil policy can be derived from optimal control theory for the stripper.

3. Uncertainties in Integrated Framework

The uncertainties in this integrated framework can be classified into two groups: static uncertainties and time-dependent uncertainties.

3.1. Static Uncertainties

The solvent selection model predicts parameters such as the solvent selectivity, distribution coefficient and solvent loss using UNIFAC. The interaction parameters between groups in the UNIFAC equation are obtained from regressions of experimental data and are thus subject to uncertainty due to experimental and regression errors. Furthermore, the activity coefficient at infinite condition is, by definition, extrapolated to an infinite dilution activity coefficient in which large discrepancies.

For example, Figure 5 show how the uncertainties in more than 1800 interaction parameters present in the UNIFAC model to predict the solvent selection objectives for the acetic acid-water separations, collapsed in terms of three parameters in a case study by Kim and Diwekar (2002). In this figure, the uncertainty factor is defined as the ratio of experimental values of γ^∞, which is defined as the activity coefficient at infinite dilution to the γ^∞ values predicted by the UNIFAC model.
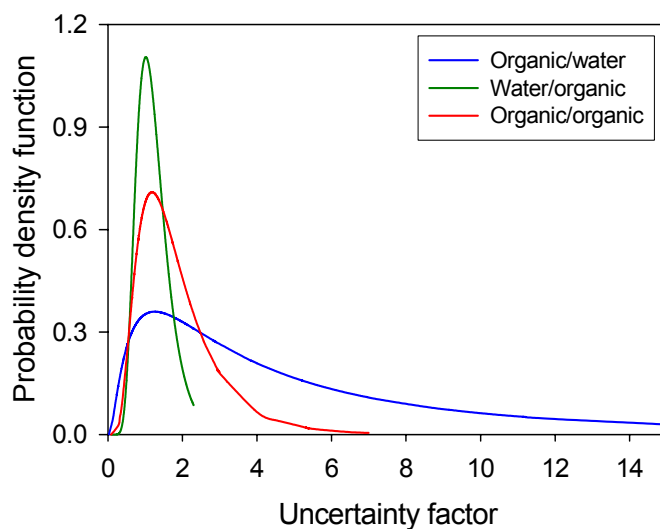

Figure 5. Probability density functions of uncertainty factors (UFs) for the organic-water, water-organic and organic-organic families

Thermodynamics is used to identify three kinds of interactions, organic-water (lognormal distribution), organic-organic (lognormal distribution), water-organic (normal distribution). This division considers the difference between properties of water and those of organic chemicals. In order to deal with this uncertainty, an efficient sampling technique called the Hammersley Sequence Sampling (HSS) (Kalagnanam and Diwekar, 1997) was applied to this model and to solve this stochastic combinatorial optimization problem of solvent selection, Hammersley Stochastic Annealing (HSTA) algorithm was developed. For details of this work please refer to Kim and Diwekar (2002).

3.2. Time-Dependent Uncertainties

For many mixtures encountered in pharmaceutical, specialty chemical and biochemical industries, the thermodynamic models are not exact or there is not enough data to predict the behavior caused by non-idealities. These thermodynamic uncertainties are static uncertainties, which in most cases can be represented by probability distributions functions. However, since batch distillation is of unsteady state nature, static uncertainties are translated into time-dependent (dynamic) uncertainties which affect the optimal operating conditions.

Recently a paper by Rico-Ramirez et al. (2003) presented a new approach to optimal control problems in batch distillation. In this paper, Real Options Theory from finance literature was used to include time-dependent uncertainties in current formulations of batch distillation optimal control. It was proved to be very useful for an ideal system of pentane-hexane (Ulas et al., 2003) as well as non-ideal systems (Ulas and Diwekar, 2004). These time-dependent uncertainties were included in the process models by using a class of stochastic processes called Ito processes. The uncertainties in group contribution methods (UNIFAC) used for the estimation of phase equilibria and their effects on the model parameters were also illustrated in this work using extensive experimental data available in literature.

Two examples of Ito processes are given in Equations 1 and 2. The first equation represents geometric Brownian motion, which was used previously for ideal systems and the second equation is for geometric mean reverting process, for non-ideal systems.

$$dx = \alpha x dt + \sigma x dz \tag{1}$$

$$dx = n(\bar{x} - x)dt + \sigma x dz \tag{2}$$

In these equations $dz = \varepsilon_t \sqrt{dt}$, where ε_t is a random number drawn from a unit normal distribution. It was shown that the stochastic reflux ratio profile improves the process performance significantly as compared to the reflux ratio profile computed by deterministic approaches. An improvement in product yield of 69% was reported (Ulas and Diwekar, 2004) in a case study involving the non-ideal mixture of ethanol-water. In the case of ideal systems such as pentane-hexane, the product purity was improved by 11% (Ulas et al., 2003).

4. Case Study

4.1.   Acetonitrile-Water Separation – Campaign I & II

Acetonitrile is a commonly used solvent in pharmaceutical and specialty chemical industries. For example ACN is consumed to purify peptide drugs in liquid chromatography columns (Mallinckrodt Chemicals, St. Louis, MO), however at the end of the process a mixture of water and acetonitrile is produced as a waste stream which forms an azeotrope. Kim et al. (2004) studied the separation of this mixture in two campaigns where the solvent selection and solvent recycling steps of this framework were simultaneously integrated. In this paper, we are also considering optimal operation and the effects of stochastic optimal control on solvent recovery and waste reduction.

The two campaigns can be summarized below:

Campaign I: Water Separation/Purification:

In this campaign, pure water is separated from the ACN-water mixture for direct disposal of water to sewers. The water is the lower volatile component and the composition of the mixture is such that the ACN mole fraction is low (x_{ACN}= 0.2235, x_{water} = 0.7765).

Campaign II: Acetonitrile Separation:

In this campaign ACN is separated using an entrainer that is designed by CAMD approach as described in Section 2.1 and a batch extractive distillation process is employed to separate acetonitrile. The candidate solvents that were found by Kim et al. (2004) were acetone and propyl amine.

This paper focuses on the first campaign where the pure water is obtained from ACN-water mixture. Since water is the lower volatile component (LVC), general heuristics presented by Kim and Diwekar (2000) suggest that a middle vessel or a stripper can be used for this operation. Considering the remaining performance indices suggests the use of a middle vessel column. A middle vessel with an infinite reflux ratio and a finite reboil ratio is designed to obtain the best performance. The middle vessel column has five theoretical equilibrium stages at the top and bottom sections. At the end of batch stripping operation, the optimal design has the following parameters: R_B=5.1, V_T=V_B=77.8 kmol/h, t=4.08 hr. We have simulated this operation with MultiBatchDS$^®$ (Diwekar, 1996), using a semi-rigorous simulator, with zero holdup and 83.05% recovery was obtained from this operation.

This high recovery was obtained for a constant reboil ratio of 5.1. In this paper we suggest the use of an optimal reboil policy to increase the product recovery. First we need to show that the optimal reboil policy indeed results in the most profitable operation by increasing the product yield. The following section presents a derivation of the optimal reboil policy similar to optimal reflux policy reported by Diwekar (1992) where the shortcut method for the batch stripper is used to simplify the problem and to decrease the number of state variables and the optimal control problem is solved using the combined maximum principle and NLP approach.

4.2. Optimal Reboil Policy – Deterministic Case

The formulation of the maximum bottom product problem for the deterministic case is given below based on Pontryagin's maximum principle. The aim is to find the optimal trajectory of the reboil ratio to maximize the yield of the key component, (LVC), for a given purity. In the formulation given below, S is the amount remaining in still which is also the first state variable x_1, Bot is the bottom product, $x_s(k)$ is the still composition of the key component which is the second state variable x_2, $x_{bot}(k)$ is the bottoms composition of the key component, V_B is the vapor boil-up rate and R_B is the reboil ratio.

Maximize
$$J = \int_0^T \frac{dBot}{dt}$$
R_b

or

Maximize $J = -\int_0^T \frac{dS}{dt}$
R_b

Maximize $- x_1(T)$
R_b (1)

subject to:
$$\frac{dx_1}{dt} = \frac{dS}{dt} = \frac{-V_b}{R_{bU}} \qquad x_1(0) = S_0 = F \tag{2}$$

$$\frac{dx_2}{dt} = \frac{dx_s^{(k)}}{dt} = \frac{V_b}{R_{bU} x_1}(x_2 - x_{bot}^{(k)})dt \qquad x_2(0) = x_F^{(k)} \tag{3}$$

and the batch stripper column model. (Table 1)

Hamiltonian:

$$H_t = -z_1 \frac{V_b}{R_b} + z_2 \frac{V_b(x_2 - x_{bot}^{(k)})}{R_b x_1} \tag{4}$$

The adjoint equations are:

$$\frac{dz_1}{dt} = z_2 \frac{V_b}{R_b x_1^2}(x_2 - x_{bot}^{(k)}) \qquad z_1(T) = -1 \tag{5}$$

$$\frac{dz_2}{dt} = -z_2 \frac{V_b}{R_b x_1}(1 - \frac{\partial x_{bot}^{(k)}}{\partial x_2}) \qquad z_2(T) = 0 \tag{6}$$

Combine z_1 and z_2 $\qquad z_t = z_2/z_1$

$$\frac{dz_t}{dt} = \frac{1}{z_1}\frac{dz_2}{dt} + z_2\frac{d(1/z_1)}{dt} = \frac{1}{z_1}\frac{dz_2}{dt} - \frac{z_2}{z_1^2}\frac{dz_1}{dt}$$

(7)

$$\frac{dz_t}{dt} = -z_t\frac{V_b}{R_b x_1}\left(1 - \frac{\partial x_{bot}^{(k)}}{\partial x_2}\right) - (z_t)^2\frac{V_b}{R_b x_1^2}(x_2 - x_{bot}^{(k)})$$

(8)

For stripper:
$$R_b = \frac{x_1 - z_t(x_2 - x_{bot}^{(k)})}{z_t\dfrac{\partial x_{bot}^{(k)}}{\partial R_b}}$$

(9)

This solution is obtained by minimizing the Hamiltonian which does not incorporate the purity constraint. Hence the use of final boundary condition ($z_T=0$) provides the limiting solution resulting in all the still charge instantaneously going to the bottoms pot ($R_B = -\infty$) with lowest overall purity. Since the formulation of the purity constraint is imposed external to the Hamiltonian, the final boundary condition ($z_T=0$) is no longer valid.

TABLE 1:
Short-cut method for the stripper (Lotter and Diwekar, 1997)

Differential Material Balance Equation
$x_{s_{new}}^{(i)} = x_{s_{old}}^{(i)} + \dfrac{\Delta x_s^{(k)}(x_{bot}^{(i)} - x_s^{(i)})_{old}}{(x_{bot}^{(k)} - x_s^{(k)})_{old}}$
Hengestebeck – Geddes Equation
$x_{bot}^{(i)} = \left(\dfrac{\alpha_i}{\alpha_k}\right)^{-C_B}\dfrac{x_s^{(i)}}{x_s^{(k)}}x_{bot}^{(k)}, \quad i = 1,2,3...,n$
Summation of Fractions
$\displaystyle\sum_{i=1}^{n} x_{bot}^{(i)} = 1 \qquad x_{bot}^{(k)} = \dfrac{1}{\displaystyle\sum_{i=1}^{n}\left(\dfrac{\alpha_i}{\alpha_k}\right)^{-C_B}\dfrac{x_s^{(i)}}{x_s^{(k)}}}$
Fenske Equation
$Nb_{min} \approx C_B$
Underwood Equations
$\displaystyle\sum_{i=1}^{n}\dfrac{\alpha_i x_s^{(i)}}{\alpha_i - \varphi} = 0 \qquad -Rb_{min\,u} = \displaystyle\sum_{i=1}^{n}\dfrac{\alpha_i x_{bot}^{(i)}}{\alpha_i - \varphi}$
Gilliand Correlation
$X = \dfrac{Rb - Rb_{min\,g}}{Rb}\ln(\alpha_{LK}/\alpha_{HK}) \qquad Y = \dfrac{Nb - C_B}{Nb+1}$ $Y = 0.2478 - 0.0965\ln(3.784X)$ $Gb_c = \dfrac{Rb_{min\,u} - Rb_{min\,g}}{Rb}$

In order to show that the optimal reboil policy results in an increase in product yield, the maximum bottom product problem was implemented in MultiBatchDS® batch process simulator. The problem was solved for a binary system having 100 k-moles of feed, where the feed composition is $x_F(1) = 0.4$, $x_F(2) = 0.6$, the relative volatilities are $\alpha_1 = 2.5$, $\alpha_2 = 1.0$, vapor boilup rate is $V_B = 40$, and five theoretical equilibrium stages. First the constant and variable reboil policies were implemented. Note that component 2 was chosen as the key component. The results are shown in Table II. From Figure 4, where the three operating policies are shown, it can be seen that the optimal reboil policy is in between the variable and constant reboil policies resulting in the most profitable operation. For this case study, the improvement in product yield compared to constant reboil policy was 1.7% and compared to variable reboil policy was 4.32%. These values may change according to the system parameters, but the optimal reboil policy always results in an improvement in product yield.

Table 2: Results for the three operating policies for the stripper

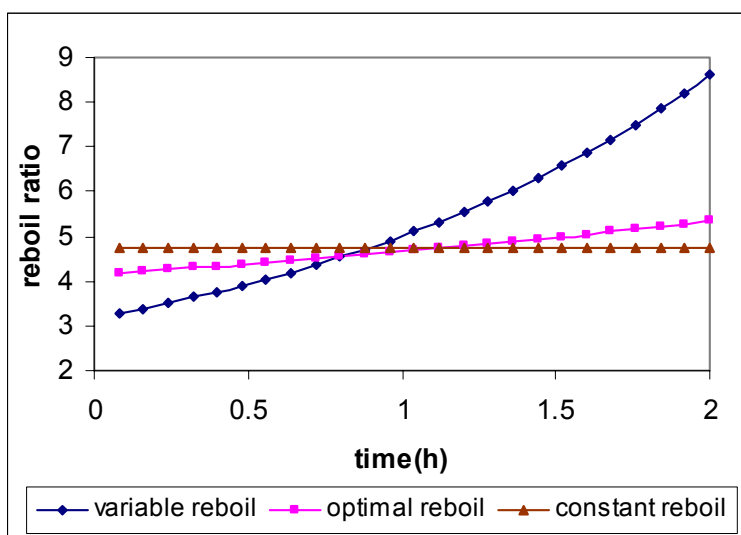|	Constant Reboil Policy	Variable Reboil Policy	**Optimal** Reboil Policy
Reboil ratio	4.75	----	----
Batch time	2 hrs	2 hrs	2 hrs
Product yield	16.8421	16.4148	17.1242
Product purity	0.99	0.99	0.99

Figure 4. Optimal reboil policy for the batch stripper

4.3.   Implementation of Optimal Reboil Policy to ACN-Water Separation

As mentioned earlier, the optimal design with a constant reboil ratio of 5.1 results in 83.05% recovery for ACN-water separation. In order to see the effects of optimal reboil policy on this process, the formulation for the stripper was slightly changed in order to incorporate the fact that a middle vessel with an infinite reflux ratio was used for this separation. At each time step the distillate composition was found using Hengestebeck-Geddes equation for the top portion of the column.

$$x_D^{(i)} = \left(\frac{\alpha_i}{\alpha_k} \right)^{C_T} \frac{x_s^{(i)}}{x_s^{(k)}} x_D^{(k)} \tag{10}$$

In this equation C_T should be equal to N_T (number of theoretical equilibrium stages for the top portion of the column, since we are using infinite reflux ratio. Also the differential material balance equation for the still composition is changed:

$$x_{S_{new}}^{(i)} = x_{S_{old}}^{(i)} + \frac{\Delta x_s^{(k)} (x_{bot}^{(i)} - x_s^{(i)})_{old}}{(x_{bot}^{(k)} - x_s^{(k)})_{old}} + \frac{\Delta x_s^{(k)} (x_D^{(i)} - x_s^{(i)})_{old}}{(x_D^{(k)} - x_s^{(k)})_{old}} \tag{11}$$

Finally the Gilliand correlation is also different for the middle vessel. The equations for X and Y for the bottom portion of the column are given below:

$$X = \frac{Rb - Rb_{\min g}}{Rb} \qquad Y = 0.6187 - 0.5655 X \tag{12}$$

The rest of the equations are the same with the stripper since the reflux ratio is infinite.

It is known that acetonitrile-water mixture forms an azeotrope. The vapor liquid equilibrium data for a pressure of 760 mmHg (Gmehling and Onken, 1977) suggests that the azeotrope occurs at a composition around 70%. The vapor liquid equilibrium data is shown in Figure 5.
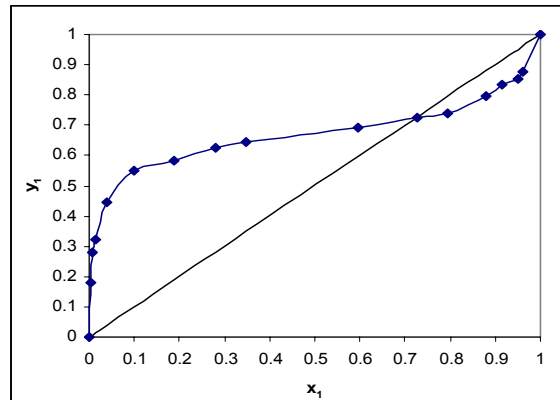

Figure 5. The vapor-liquid equilibrium for acetonitrile-water system

The shortcut method for the stripper is based on the assumption of constant relative volatility throughout the column. In case of azeotropic systems, the relative volatility becomes unity at the azeotropic point so this assumption is no longer valid. In order to deal with this problem, variable transformation approach is used. This approach has been presented by Anderson and Doherty (1984) for continuous columns and Diwekar (1991) applied this method to batch distillation columns. According to this method, the equilibrium curve is split into two parts as shown in Figure 6. Then the variables are transformed using the azeotropic composition.
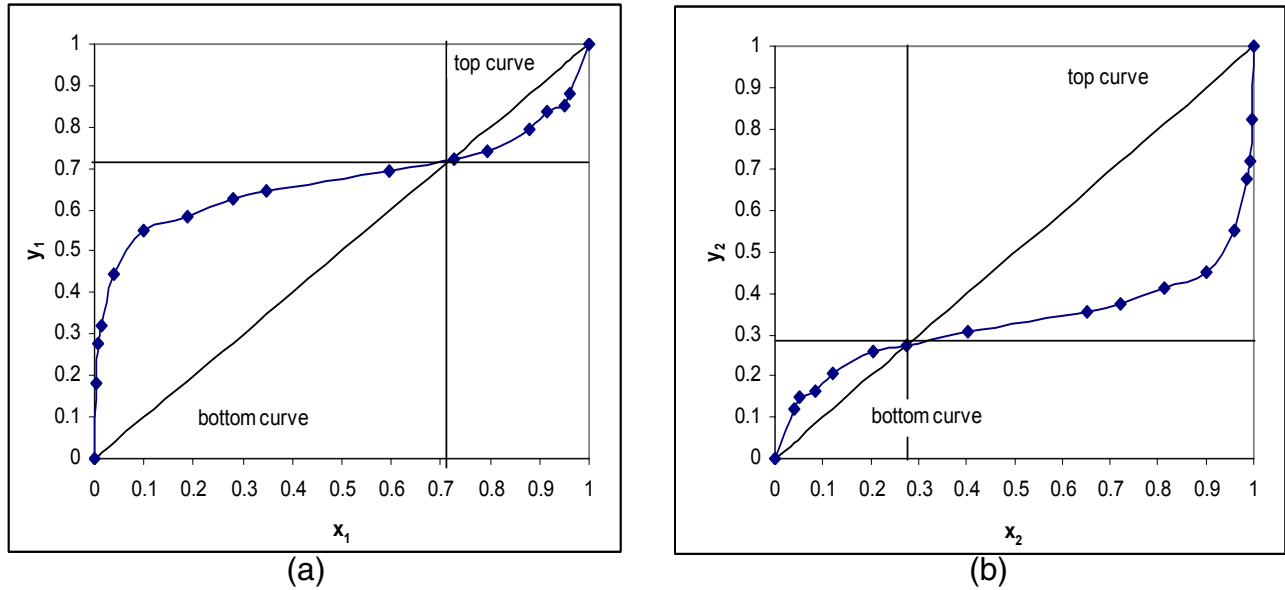

(a)   (b)

Figure 6. The vapor-liquid equilibrium for acetonitrile-water system

The bottom curve represents:

$$x_1^* = \frac{x_1}{x_1^{az}} \qquad\qquad x_2^* = 1 - x_1^* \tag{13}$$

$$y_1^* = \frac{y_1}{y_1^{az}} \qquad\qquad y_2^* = 1 - y_1^* \tag{14}$$

The top curve represents:

$$x_1^* = \frac{x_1 - x_1^{az}}{1 - x_1^{az}} \qquad\qquad x_2^* = 1 - x_1^* \tag{15}$$

$$y_1^* = \frac{y_1 - y_1^{az}}{1 - y_1^{az}} \qquad\qquad y_2^* = 1 - y_1^* \tag{16}$$

The equilibrium relationship for the binary system in terms of the transformed variables is represented by:

$$y_1^* = \frac{\alpha_1 x_1^*}{1 + (\alpha_1 - 1)x_1^*} \tag{17}$$

After variable transformation is applied to the acetonitrile-water system with azeotropic composition of the more volatile component being 70%, the relative volatility of the system was found as 17.02. Then this variable transformation was incorporated into the optimal control problem for the middle vessel with infinite reflux ratio. Since water (LVC) is separated using a stripping operation, the key component is 2, thus the top and bottom curves are reversed in Figure 6(b). The variable transformation is applied choosing the azeotropic composition as 30% and equations 15 and 16 for the top curve. The equations for transforming the still composition, bottoms composition and distillate composition are given below.

Variable Transformation

$$x_{az} = 0.30$$

$$x_s^{(2)} = (x_s^{(2)} - x_{az})/(1 - x_{az}) \tag{18}$$

$$x_s^{(1)} = 1 - x_s^{(2)}$$

After the reflux ratio is found at each time step, the variables are retransformed.

Variable Retransformation

$$x_s^{(2)} = x_s^{(2)} - x_{az}(x_s^{(2)} - 1) \quad x_s^{(1)} = 1 - x_s^{(2)}$$

$$x_{bot}^{(2)} = x_{bot}^{(2)} - x_{az}(x_{bot}^{(2)} - 1) \quad x_{bot}^{(1)} = 1 - x_{bot}^{(2)} \tag{19}$$

$$x_D^{(2)} = x_D^{(2)} - x_{az}(x_D^{(2)} - 1) \quad x_D^{(1)} = 1 - x_D^{(2)}$$

For the next time step, the still compositions are calculated using the differential material balance equations. After that, the variables are again transformed. The details of this method can be found in detail for rectifying operation in Diwekar (1991, 1995).

After applying variable transformation to ACN-water separation using the middle vessel with the optimal design variables $V_T = V_B = 77.8$, batch time = 4.08, 94.5 k-moles of feed with a composition of $x_{ACN} = 0.2235$, $x_{water} = 0.7765$, five theoretical equilibrium stages at the top and bottom and an infinite reflux ratio, the optimal reboil policy was computed. A recovery of 87.12% was achieved with this operation. The optimal reboil profile is shown in Figure 7.

As mentioned earlier 83.05% recovery was achieved with optimal design. Integration of optimal design and optimal operation results in 4.07% improvement in product yield. The comparison of profiles for the bottoms product and results for product purity and yield are shown below in Figures 8, 9 and Table 3. Note that the semi-rigorous models were used to compare the results of constant reboil and optimal reboil cases, where the column holdup effects are not considered.

Table 3. The comparison of results for constant reboil and optimal reboil cases

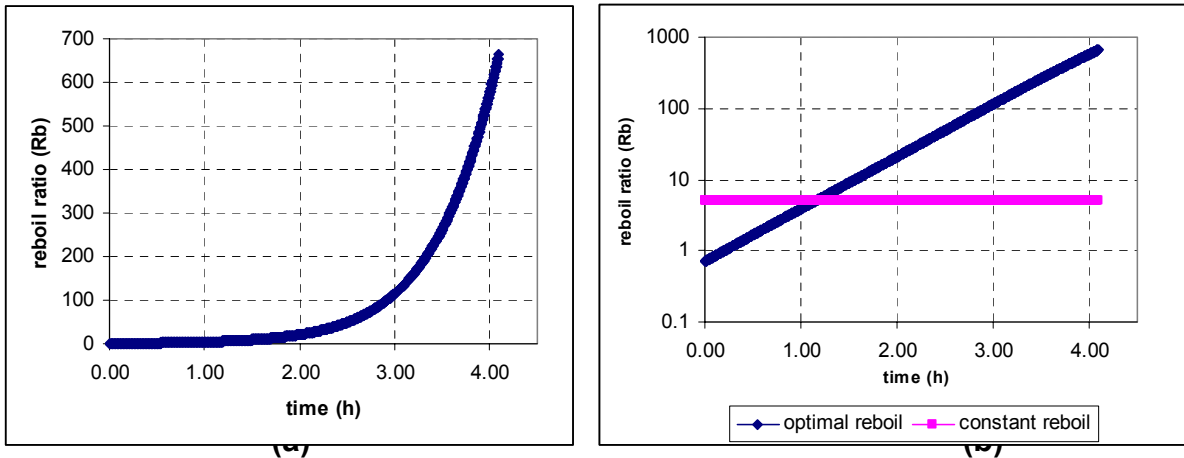|	Constant Reboil	**Optimal Reboil**
Bottoms Product (Bot)	62.30	**65.14**
Bottoms Purity ($x_s^{(2)}$)	97.8%	**98.1%**
Recovery	83.05%	**87.12%**

Figure 7 (a) Optimal reboil policy for the stripper, **(b)** comparison of constant reboil and optimal reboil policies on a log scale
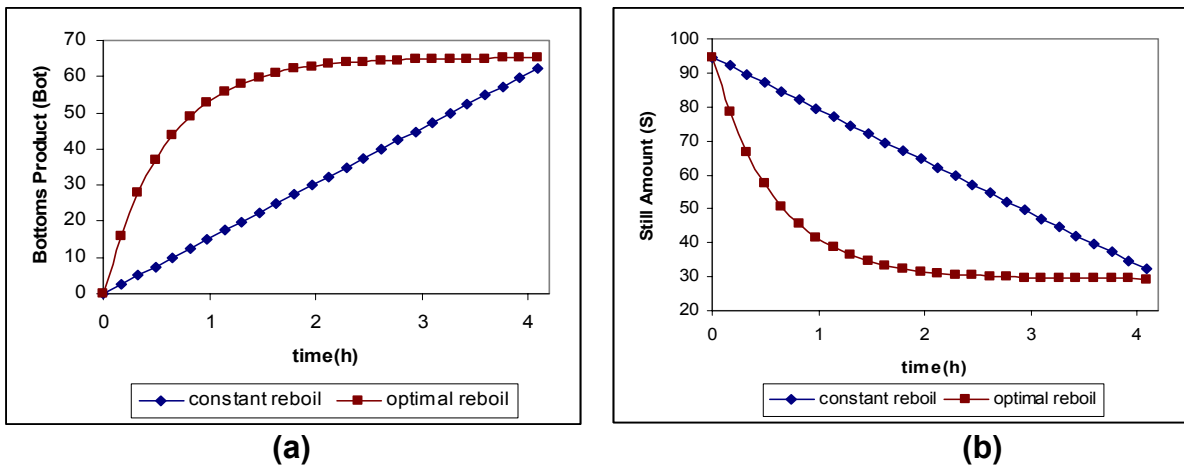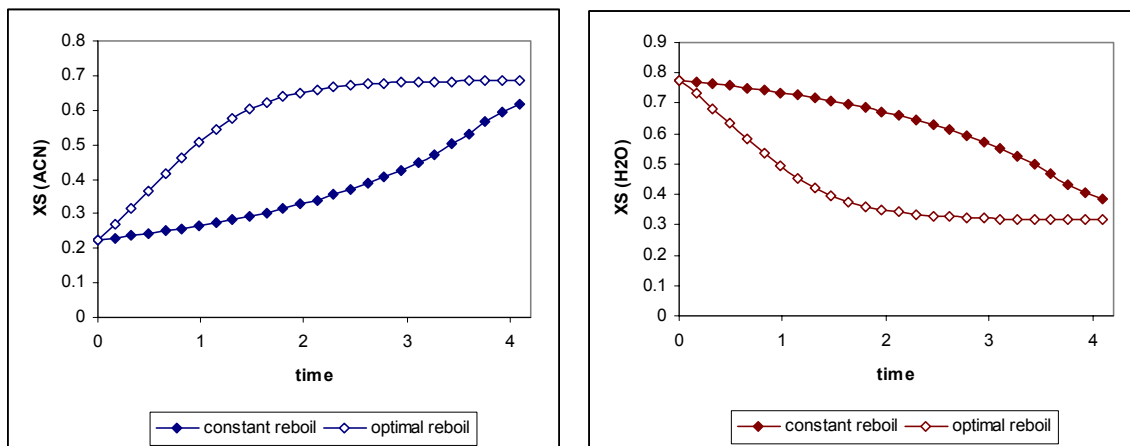

Figure 8 (a) Profiles for the bottoms product for constant reboil and optimal reboil cases, **(b)** Profiles for the amount remaining in still (middle vessel) for constant reboil and optimal reboil cases

<div align="center">(a)   (b)</div>

Figure 9 (a) Profiles for the still composition of acetonitrile for constant reboil and optimal reboil cases, **(b)** Profiles for still composition of water for constant reboil and optimal reboil cases

4.4.   Time-Dependent Uncertainties in ACN-Water Separation

We have shown in the previous section that, optimal reboil policy results in an improvement in product yield for the separation of a low volatile component from an azeotropic binary mixture. For the azeotropic system of ACN-water, an approximate model, namely variable transformation was used to recognize the azeotropic point as an impassable barrier, which the column composition profile cannot reach beyond. The recovery from the middle vessel can be increased even more when the relative volatility is considered as a time-dependent uncertainty and modeled accordingly.
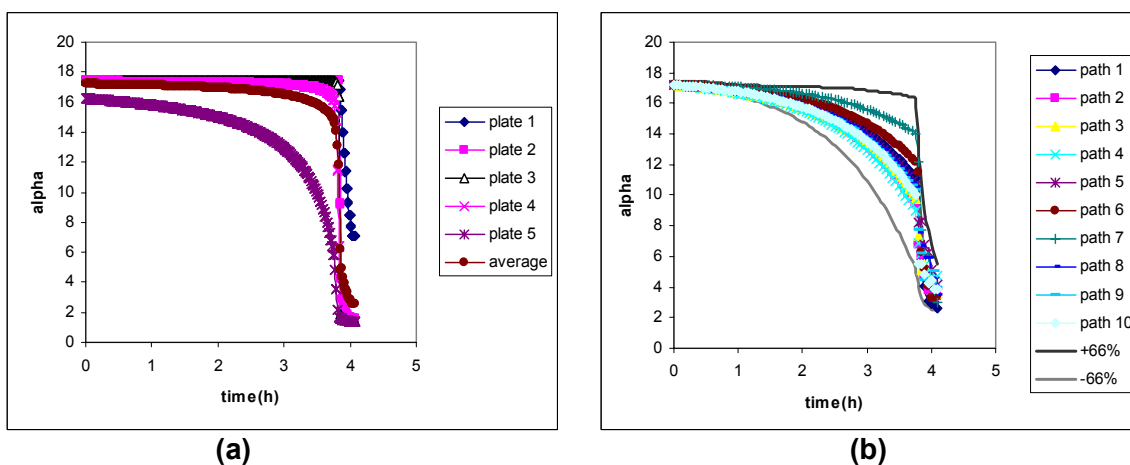
<div align="center">(a)   (b)</div>

Figure   10 (a) Time dependent changes in relative volatility with respect to time and plate taken from a semi-rigorous model **(b)** Representation of relative volatility as a geometric mean reverting process with 66% confidence intervals

Previously, for azeotropic systems such as ethanol-water the time-dependent changes in relative volatility were modeled using the geometric mean reverting process, as shown in Equation 2 (Ulas and Diwekar, 2004), which resulted in significant improvement in product recovery.

Applying the same principle here for the ACN-water, the variation of relative volatility with respect to time and each plate was found using the semi-rigorous model of MultiBatchDS as a proxy for real experiments. The result of the simulation is shown in Figure 10 (a).

Two different sets of parameters for two time periods were used to model the changes in relative volatility as a geometric mean reverting process, which is shown in Figure 10(b), because of the sudden decrease in relative volatility when the batch time is 3.08 hours. For the first time period, at the end of regression analysis the parameters were found as $\eta = -0.86$, $\overline{\alpha} = 17.5$, $\sigma = 0.003$, for the second time period the parameters were, $\eta = 7.0$, $\overline{\alpha} = 3.0$, $\sigma = 0.4$. It should be highlighted that $\overline{\alpha}$ represents the value which α tends to revert, is the speed of the reversion and σ is the standard deviation.

4.5. Optimal Reboil Policy – Stochastic Case

Since we have modeled the time-dependent uncertainties with the geometric mean reverting process, we can revisit the maximum bottom product problem. The uncertainties in relative volatility affect one of the state variables, the still composition. This can be derived from Hengestebeck-Geddes equation similar to the rectifier case. Therefore, the still composition can also be represented by an Ito process. The maximum bottom product problem becomes:

Maximize $\quad -x_1(T)$

$\qquad R_{bU}$

subject to:

$$\frac{dx_1}{dt} = \frac{-V_b}{R_{bU}} \qquad -x_1(0) = S_0 = F$$

$$\frac{dx_2}{dt} = \frac{-V_b}{R_{bU} x_1}(x_2 - x_{bot}^{(k)})dt + \sigma_2 x_2 dz \quad x_2(0) = x_F^{(k)}$$

and the batch stripper column model. (Table 1)

Hamiltonian:

$$H_t = \frac{-V_b}{R_{bU}} \frac{\partial L}{\partial x_1} + \frac{V_b}{R_{bU} x_1} (x_2 - x_{bot}^{(k)}) \frac{\partial L}{\partial x_2} + \frac{\sigma_2^2}{2} (x_2)^2 \frac{\partial^2 L}{(\partial x_2)^2}$$

The adjoint equations are:

$$\frac{dz_1}{dt} = z_2 \frac{V_b}{R_{bU} x_1^2} (x_2 - x_{bot}^{(k)})$$

$$\frac{dz_2}{dt} = -z_2 \frac{V_b}{R_{bU} x_1} (1 - \frac{\partial x_{bot}^{(k)}}{\partial x_2}) - \sigma_2^2 x_2 \frac{\partial^2 L}{(\partial x_2)^2}$$

$$\frac{\partial L}{\partial x_1} = z_1 \qquad \frac{\partial L}{\partial x_2} = z_2 \qquad\qquad \frac{\partial^2 L}{(\partial x_2)^2} = \omega_t$$

$$\frac{d\omega_t}{dt} = \frac{d}{dt}\left(\frac{\partial^2 L}{(\partial x_2)^2} \right)$$

negligible

$$\frac{d\omega_t}{dt} = -\omega_t \frac{V_b}{R_{bU} x_1} (1 - \frac{\partial x_{bot}^{(k)}}{\partial x_2}) + z_2 \frac{V_b}{R_{bU} x_1} \frac{\partial^2 x_{bot}^{(k)}}{\partial x_2^2} - \omega_t \sigma_2^2 - 2\sigma_2^2 x_2 \frac{\partial^3 L}{(\partial x_2)^3}$$

$$R_{bU} = \frac{\frac{-\partial L}{\partial x_2}\left(\frac{x_2 - x_{bot}^{(k)}}{x_1} \right) + \frac{\partial L}{\partial x_1}}{\frac{\partial x_{bot}^{(k)}}{\partial R_{bU}} \frac{1}{x_1} \frac{\partial L}{\partial x_2}} + \frac{\sigma_2 \frac{\partial \sigma_2}{\partial R_{bU}} x_2^2 \frac{\partial^2 L}{\partial x_2^2}}{\frac{\partial x_{bot}^{(k)}}{\partial R_{bU}} \frac{1}{x_1} \frac{\partial L}{\partial x_2}} \frac{R_{bU}^2}{V}$$

Define:

$$\xi = \frac{\frac{\partial^2 L}{\partial x_2^2}}{\frac{\partial L}{\partial x_1}} = \frac{\omega_t}{z_1} \qquad \text{and} \qquad z = \frac{z_2}{z_1} = \frac{\frac{\partial L}{\partial x_2}}{\frac{\partial L}{\partial x_1}}$$

$$\frac{dz}{dt} = -z^2 \frac{V_b}{R_{bU}} \frac{1}{x_1^2} (x_2 - x_{bot}^{(k)}) - z \frac{V_b}{R_{bU}} \frac{1}{x_1} (1 - \frac{\partial x_{bot}^{(k)}}{\partial x_2}) - \xi \sigma_2^2 x_2 \qquad\qquad z_2(T) = 0$$

$$\frac{d\xi}{dt} = -\xi \frac{V_b}{R_{bU} x_1} (1 - \frac{\partial x_{bot}^{(k)}}{\partial x_2}) + z \frac{V_b}{R_{bU} x_1} \frac{\partial^2 x_{bot}^{(k)}}{(\partial x_2)^2} - \xi \sigma_2^2 - \xi z \frac{V_b}{R_{bU}} \frac{1}{x_1^2} (x_2 - x_{bot}^{(k)}) \qquad\qquad \xi(T) = 0$$

The final solution is:

$$R_{bU} = \frac{x_1 - z(x_2 - x_{bot}^{(k)})}{\dfrac{\partial x_{bot}^{(k)}}{\partial R_{bU}} z} + \frac{x_1 \left[\sigma_2 \dfrac{\partial \sigma_2}{\partial R_{bU}} (x_2)^2 \xi \right]}{\dfrac{\partial x_{bot}^{(k)}}{\partial R_{bU}} z} \frac{R_{bU}^2}{V}$$

where:

V_b = boilup rate
R_{bU} = reboil ratio (uncertainty)
x_{bot} = bottoms composition
x_s = still composition
α_i = relative volatility
N_b = number of bottom plates
F = feed

The effects of stochastic optimal reboil policy on acetonitrile-water separation remains to be studied. Considering the excellent results from the stochastic optimal reflux policy for the rectifier, it is expected that this approach will be very useful in solvent recycling problems in batch processing industries.

5. Conclusion

An integrated framework has been developed that involves solvent selection, solvent recycling and optimal operation under uncertainty for batch processing industries. This framework was applied to a solvent recycling problem in peptide drug production. For binary azeotropic systems, this framework selects candidate solvents based on computer-aided molecular design. Then the optimal batch column configuration is selected based on the parameters for separation and heuristics. Finally the optimal operation policy is found for the best column configuration. It was shown that similar to the optimal reflux policy for the rectifier, the optimal reboil policy improves the product yield significantly for the stripper and middle vessel column configurations and results in the most profitable operation.

Uncertainties are considered in two categories in this framework: static uncertainties and time-dependent uncertainties. The static uncertainties constitute the uncertainties in UNIFAC which have a significant effect on the CAMD model. An efficient sampling technique, the HSS sampling is used to deal with static uncertainties. Since batch distillation is a dynamic process, the static uncertainties are translated into dynamic uncertainties, which in turn affect the optimal operating profiles. These dynamic uncertainties are modeled using Ito processes in this paper.

The effect of time-dependent uncertainties on the optimal reboil policy is yet to be explored. It is expected that the product recovery will exceed the recovery found using an approximate variable transformation technique for the separation of azeotropic mixture acetonitrile-water.

This integrated framework promises to be very useful for waste reduction in pharmaceutical and specialty chemical industries, to achieve the most efficient,

environmentally friendly and profitable separation process both at the stages of design and operation.

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