1-14-2014

A new software tool to environmentally and economically evaluate solvent recovery in the pharmaceutical industry

Eduardo Cavanagh

Recommended Citation

Cavanagh, Eduardo, "A new software tool to environmentally and economically evaluate solvent recovery in the pharmaceutical industry" (2014). *Theses and Dissertations*. 295.
https://rdw.rowan.edu/etd/295

A NEW SOFTWARE TOOL TO ENVIRONMENTALLY AND ECONOMICALLY EVALUATE SOLVENT RECOVERY IN THE PHARMACEUTICAL INDUSTRY

by
Eduardo Juan Cavanagh

A Thesis

Submitted to the
Department of Chemical Engineering
College of Engineering
In partial fulfillment of the requirement
For the degree of
Master of Science in Engineering
at
Rowan University
November, 14, 2013

Thesis Chairs: Mariano Savelski, Ph.D., C. Stewart Slater, Ph.D

Dedication

To my family Eduardo Cavanagh, Elena Martinez Vivot, Glubi Cavanah, Lola Cavanagh and Helena Cavanagh. To Esther Cornejo Butler. To Lucas Mendos, Nicolás Ferretti, Juan Pablo Kunz, Ignacio Espinosa, Diego Filpo, Patricio Barciela, Juan Simonelli, Carolina Olascoaga, Diego Rhode, Paula Bruni, Mariela Pistasoli, Silvina Fernandez Vidal, Alejandro Corizzo, Maria Schoendfel and Francisco Ferretti.

Acknowledgments

To my advisors Dr. Mariano Savelski and Dr. C. Stewart Slater. To Frank Urbanski and Carlos Junco from Pfizer, Inc. To Leland Vane and Nora Lopez from U.S. EPA. To Harold Wandke from Sulzer. To former and current Rowan University students Mike Raymond, Dave Hitchcock, Molly Russell, Stephen Montgomery, Mihika Padia, Matt Bucchanan and Bill Hoffman.

Abstract

Eduardo Juan Cavanagh
A NEW SOFTWARE TOOL TO ENVIRONMENTALLY AND ECONOMICALLY EVALUATE SOLVENT RECOVERY IN THE PHARMACEUTICAL INDUSTRY
2012/13
Mariano Savelski, Ph.D., C. Stewart Slater, Ph.D.
Master of Science in Chemical Engineering

The environmental impact reduction and operating costs savings associated with the purification and recuse of solvent waste in the manufacture of active pharmaceutical ingredients (API's) were investigated. A software toolbox has been developed that combines Aspen Plus® process simulation with SimaPro® and Ecosolvent life cycle assessment (LCA) databases. The feasibility of a relatively small flexible skid capable of recovering multiple solvent waste streams was evaluated. Fractional distillation and pervaporation were considered to separate binary solvent waste mixtures. Optimum distillation reflux ratio and feed stage were determined to maximize the environmental impact reductions and operating cost savings. The optimum reflux ratio was significantly higher than suggested by traditional heuristics. The emissions and cost reductions obtained were as much as 43 % and 59 % higher, respectively, as compared to using the conventional optimum reflux ratio. A comprehensive cash flow analysis showed that the recovery of low volume solvent waste streams can be economically feasible, despite traditional thinking. It has been demonstrated that the flexibility of a skid to recover solvent waste streams of different thermodynamic nature and volume is a key issue to increase profitability. Four case studies from Pfizer are presented to show how our software tool can aid in green engineering decision making.

Table of Contents

List of Figures

Figure Page

List of Tables

Chapter 1

Introduction

The manufacture of active pharmaceutical ingredients (API's) has an E-factor (mass of waste per mass of product) usually between 25 and 100[1]. Although waste composition varies and is not homogeneous throughout the pharmaceutical industry, an average organic solvent composition of around 58% has been reported, while the rest is composed of water (30%), reactants (5%) and other byproducts (7%)[2,3]. Solvent recovery and reuse has been an economic drive for pharmaceutical companies since their inception. However, the toxicity and large quantities of API manufacturing waste, combined with social, political, and economic pressure to move towards a sustainable existence, has led pharmaceutical companies to pursue pollution prevention (P2) and waste reduction strategies in a greater extent. This project is the result of Rowan University's efforts to partner with pharmaceutical and fine chemical companies, and the United States Environmental Protection Agency (EPA), to develop green engineering solutions for the current state of API manufacturing.

The majority of drug substances made through organic synthesis routes require many sequential reaction steps, large quantities and multiple organic solvents (with varying degrees of toxicity), and are typically made in batch processes[4]. Solvents are used to facilitate reaction, separation, and purification steps of the API manufacturing process. Because they, for the most part, do not become part of the final product, they are removed in further separation, extraction, crystallization, purification, and drying steps and the spent solvent is finally collected as waste (Figure 4). Other processes that generate liquid waste streams containing organic solvents are solid washing and equipment cleaning processes, as well as byproducts from reactions inefficiencies. The multistep chemistry and batch nature of a typical API manufacturing process is the reason multiple solvent waste streams are generated.

In 2010, the pharmaceutical industry sector (NAICS codes 325411 and 325412) reported the generation of approximately 168 million pounds of waste to EPA's Toxic Release Inventory (TRI)[5]. Figure 1 shows the mass of typical solvents not recovered in 2010 in the US, as reported by the TRI. However, some solvents widely used in the pharmaceutical industry are not included in the TRI, such as acetone, isopropyl alcohol (IPA) and tetrahydrofuran (THF).

Figure 2 shows the percentage of solvent waste management methods used in the United States in 2010, based on data from the Toxic Release Inventory (TRI) of the USEPA. The most typical waste management practices implemented by pharmaceutical companies are incineration for energy recovery to produce steam, electricity or heat, and incineration for destruction. The least common practice is the direct release to surface or underground waters; although this poses an environmental concern since organic solvents used in pharmaceutical manufacturing have varying degrees of toxicity[6]. Some are known or possible carcinogens. Toluene and dichloromethane have been designated as priority pollutants by the United States Environmental Protection Agency (EPA)[7]. Table 1 shows the toxicity to aquatic life of typical organic solvents used in API manufacturing. They also can produce undesired environmental impacts as air, water and soil pollutants. Furthermore, these compounds have varying degrees of biodegradability thereby requiring approaches to reduce their release.

Organic solvents also result in wastes released into the environment through the life cycle of their production and disposal which extend beyond the pharmaceutical plant boundaries but significantly impact the environment in a negative way.

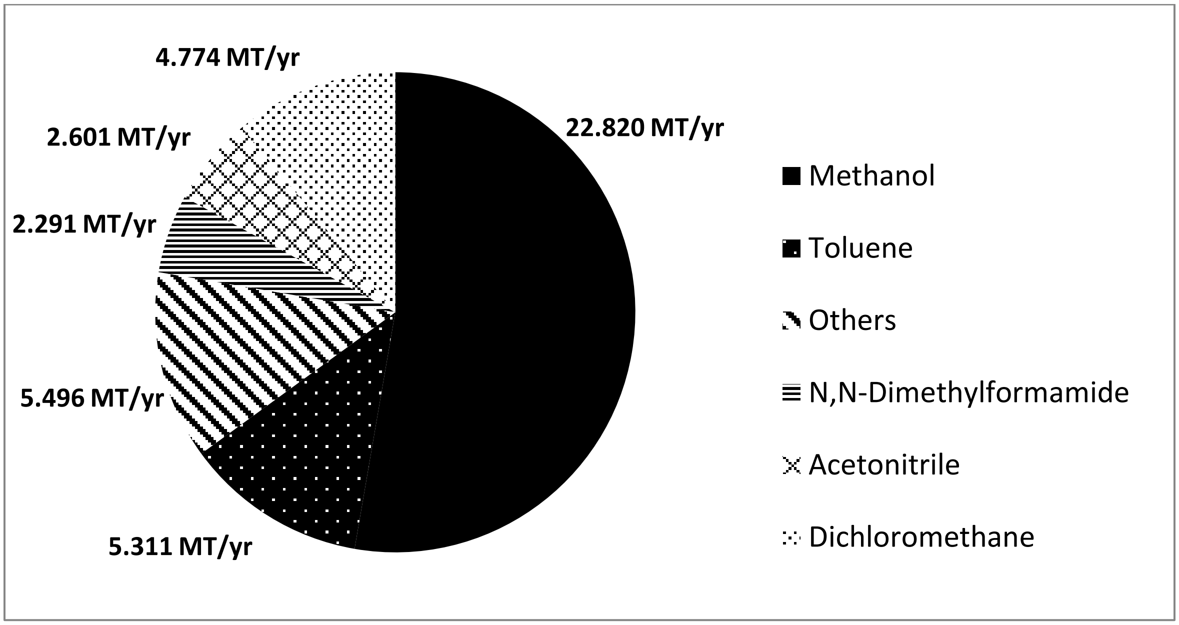


Figure 1. Mass of organic solvents not recovered (incinerated or released) in the pharmaceutical industry in the United States, EPA's TRI, 2010 Data[5]. Not all solvents are included in the TRI, such as acetone or tetrahydrofuran.

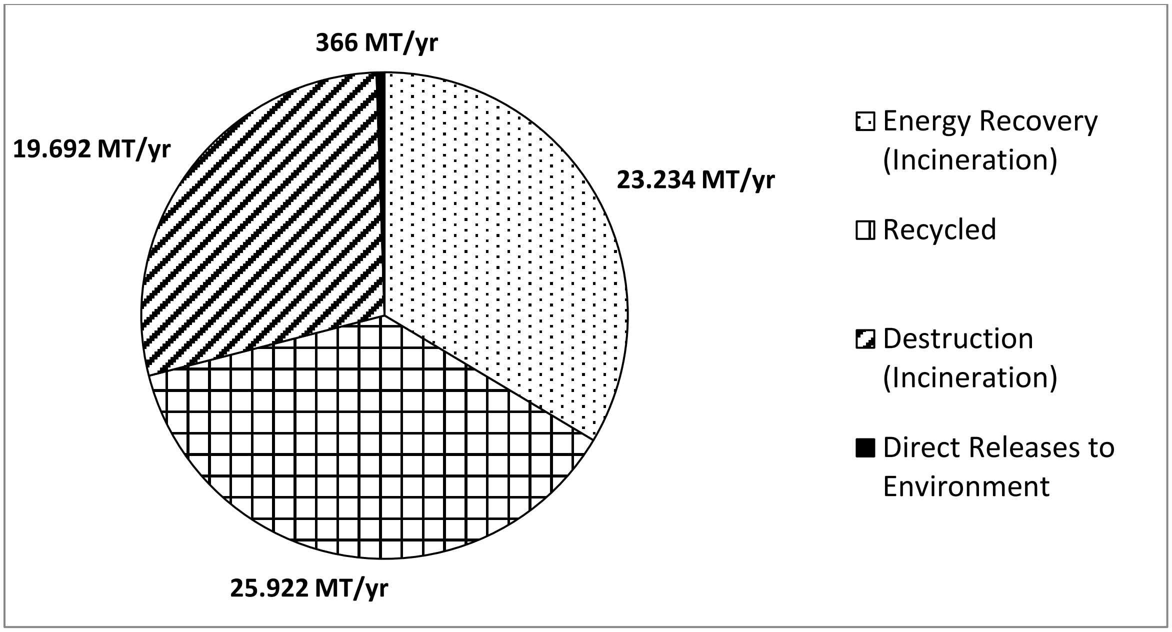


Figure 2. Solvent Waste Management in the United States, EPA's TRI, 2010 Data[5].

Table 1. Aquatic toxicity of organic solvents typically used in the pharmaceutical industry[8,9].

Organic solvent	Toxicity in Fish		
	Fish	Test	Concentration (mg/L)
Toluene	Goldfish Zebra Fish Fathead minnow	24h-LC_{50} 48h-LC_{50} 32d-EC_{50}	58 60 6
Methanol	Fathead minnow	96h-LC_{50}: 96h-EC_{50}:	29,400 28,900
Tetrahydrofuran (THF)	Fathead minnow	96h-LC_{50}	2,816
Isopropanol (IPA)	Fathead minnow	96h-LC_{50}	11,130
Dichloromethane	Bluegill sunfish Fathead minnow	96h-LC_{50}:	220 193
Acetone	Rainbow trout,: Fathead minnow, Bluegill sunfish	96h-EC_{50} 24h-LC_{50}: 96h-LC_{50}	5.54-6.10 5,000 8,300
N-methyl-2-pyrrolidone	Fathead minnow	96h-LC_{50} 96h-LC_{100}	1,072 5,000
Acetonitrile	Fathead minnow Bluegill sunfish	96h-LC_{50}	1,000 1,850

*LC_{50}: Lethal concentration for 50% of the organisms exposed, EC_{50}: Concentration necessary for 50% of aquatic species to show abnormal behavior or visible injury.

Approaches to reduce organic solvents usage and environmental impact in API manufacturing, and thus the E-factor, are:

1) solid phase manufacturing, which produces almost no waste[2];
2) biosynthetic production routes, which consists of using enzymes as biocatalysis, producing thus little to no solvent waste[2];
3) telescoping, which reduces the number of steps and therefore solvent use[2,4];
4) switching to a continuous production mode, which is known to be more mass efficient[2];
5) “Greener” chemical synthetic routes and/or operating conditions, which result is avoiding large and/or toxic wastes or intermediates (e.g.: Using more efficient catalysts that reduce solvent use. Other examples can be found in Butters et al.[4]);
6) using water as a solvent, since water is the least toxic solvent[10]; and
7) recycling organics solvent waste[2].

Since green engineering in the pharmaceutical industry gains more attention each year, these approaches are increasingly implemented, and are one of the reasons total waste managed in United States industry sectors NAICS 325411 (Medicinal and Botanical Manufacturing) and 325412 (Pharmaceutical Preparation Manufacturing) has decreased 67.4 % from 2001 to 2010, as shown in Figure 4. An additional reason for this descent is the moving of API manufacturing to off-shore sites[11].

In many cases, the listed measures are not possible to implement and new developments would be required. Our study focuses on the 7th approach, solvent recycling.

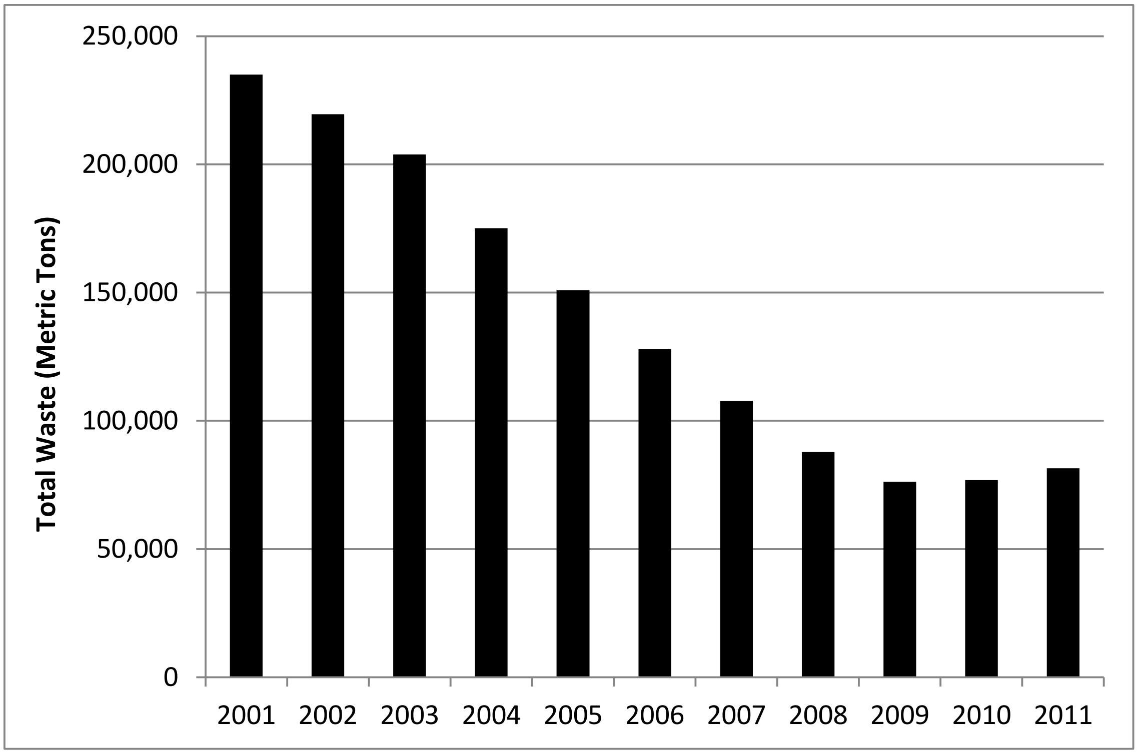


Figure 3. Annual waste from the pharmaceutical sector in the United States, as reported by the TRI5

From a mass balance point of view, it is easy to see that the mass of virgin solvent purchased by a pharmaceutical facility is essentially the same as the solvent waste mass, since solvents are not normally consumed in the process or contained in the final API. Therefore, the recovery of solvent waste comes as an opportunity to reduce the operating costs associated with its purchase and waste management; although these costs have to be weighed against the capital, material, labor, and energy costs associated with the recovery of spent solvents. In this paper, the term "recovery" is defined as "recovery and reuse": the extraction and purification of a solvent from a solvent waste stream to be reused for its original purpose. Another common term for "recovery and reuse" is "recycling", although the latter usually means turning waste into valuable resources for new products.

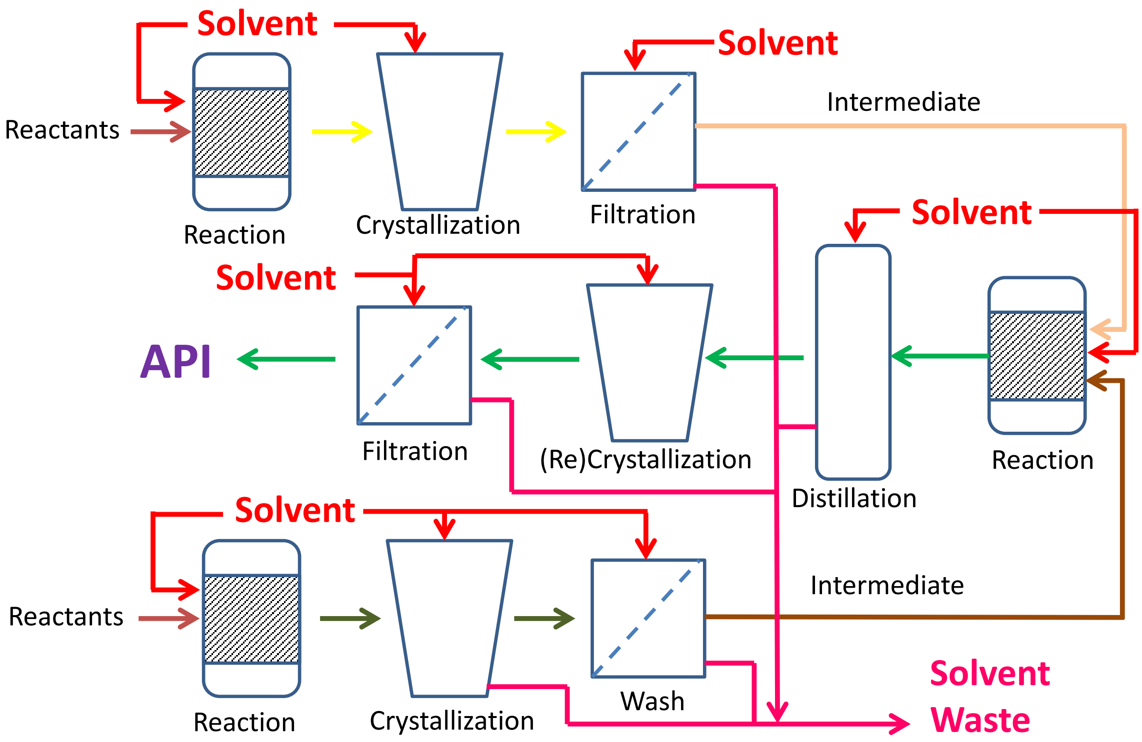


Figure 4. Illustrative process diagram of a multistep API manufacturing process and solvent waste generation.

United States EPA's pollution prevention act determines source reduction as the most desired waste management practice, followed by recycling, energy recovery, destruction or treatment, and disposal or other releases (Figure 5)[12]. Other environmental organizations also suggest source reduction as the priority spent solvent management method[13]. Source reduction and recycling are considered two different approaches to reduce waste when the system boundaries are set around a single equipment or process, such as a reactor. However, when solvent are recovered and reused for its original purpose, this distinction blur when the boundaries are set around a manufacturing plant. Source reduction means to reduce the mass entering the reactor to achieve the same mass of product, therefore reducing the mass of waste exiting it. Recycling does not change the reactor's mass input or output, but it takes the waste and reintroduces it back into the reactor as an input. If the boundaries of the system were set around the manufacturing plant, the raw materials entering the plant would be reduced if recycling was applied. With these boundary settings, recycling could be considered a source reduction measure.

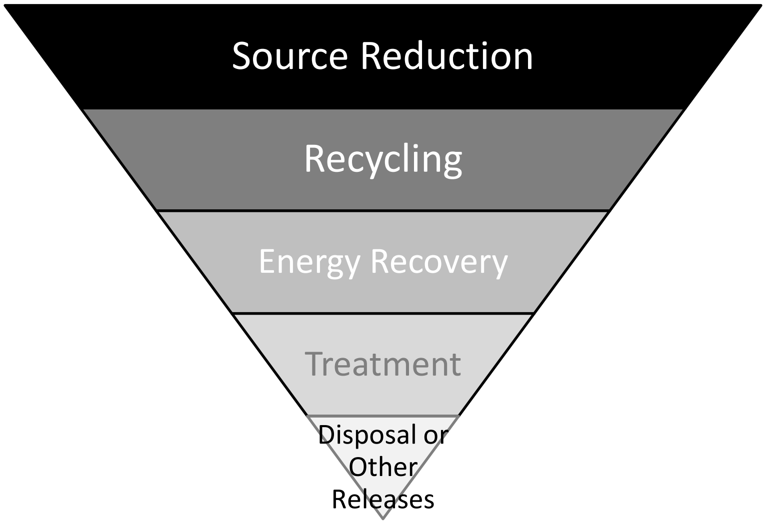


Figure 5. EPA's Waste Management Hierarchy. Adapted from EPA's website[12].

Solvent recovery and reuse complies with principles # 2: prevention of waste instead of treatment, and # 4: maximize mass and energy efficiency, of the American Chemical Society's (ACS) 12 principles of Green Engineering[14]. In 2007, representatives of pharmaceutical companies came together in the Pharmaceutical Roundtable of the ACS and did a brainstorming to list key green engineering research areas. Solvent recycling was on the top 5 of this list[15]. Based on these principles, solvent recycling is a worth endeavor to pursue. The *"2009-2014 EPA Strategic Plan Change Document"* asks for industries to reduce hazardous materials, carbon dioxide (CO_2) emissions, and water use[16].

Life Cycle Assessment of Organic Solvents Recovery in the Pharmaceutical Industry

The virgin solvents' life cycle corresponds to raw material extraction, raw material transportation, and solvent production and transportation to the API manufacturing plant. When solvents are recovered, less virgin solvent is purchased; therefore, less solvent life cycle emissions are generated. At the same time, waste disposal emissions are reduced, as well as the associated waste transportation emissions. However, the recovery process generates emissions from the utilities used such as steam, electricity, and cooling water.

From an environmental point of view, solvent recovery can significantly reduce the emissions associated with the waste management and the life cycle of solvents[17,18]. In this paper, the term "emissions" is referred to any compound released to the environment (water, soil, and air) by an anthropogenic activity. Organic solvents have significant cradle to gate life cycle emissions, most of which are CO_2 emissions. The production carbon footprint of tetrahydrofuran, acetonitrile, dichloromethane, acetone, isopropanol (IPA), toluene and methanol is 5.51, 2.86, 2.81, 1.98, 1.71, 1.32 and 0.68 kg of CO_2eq per kg, respectively; while the production carbon footprint of natural gas, light fuel oil, heavy fuel oil and hard coal is 0.47, 0.33, 0.29 and 0.12 kg of CO_2eq per kg, respectively (Pre Consultants, 2012). Organic solvent manufacture has also significant Cumulative Energy Demand (CED). (Figure 6). Therefore, solvent recovery reduces the carbon footprint of the pharmaceutical industry by avoiding the manufacture of virgin solvents. The higher emissions associated with the production of organic solvents as compared to those of fuel indicates that burning solvent waste for energy recovery may have a net negative environmental impact. Since incineration is the most frequent solvent waste management method, its emissions are also avoided when solvents are recovered and reused. Not all recycled solvents are used back in the process that generated it, some are not purified enough and are used for other industrial purposes of lower value. Furthermore, solvent waste incineration sometimes requires ancillaries such as hydrochloric acid and sodium hydroxide, whose life cycle emissions contribute to the total waste disposal emissions. For example, the incineration of 1 kg of dichloromethane uses 2.42 kg of sodium hydroxide as an ancillary to neutralize acidic combustion byproducts[19]. In a net balance, the production and incineration avoided emissions should be weighed against those associated with utility used (i.e. steam and electricity) when operating the recovery process.

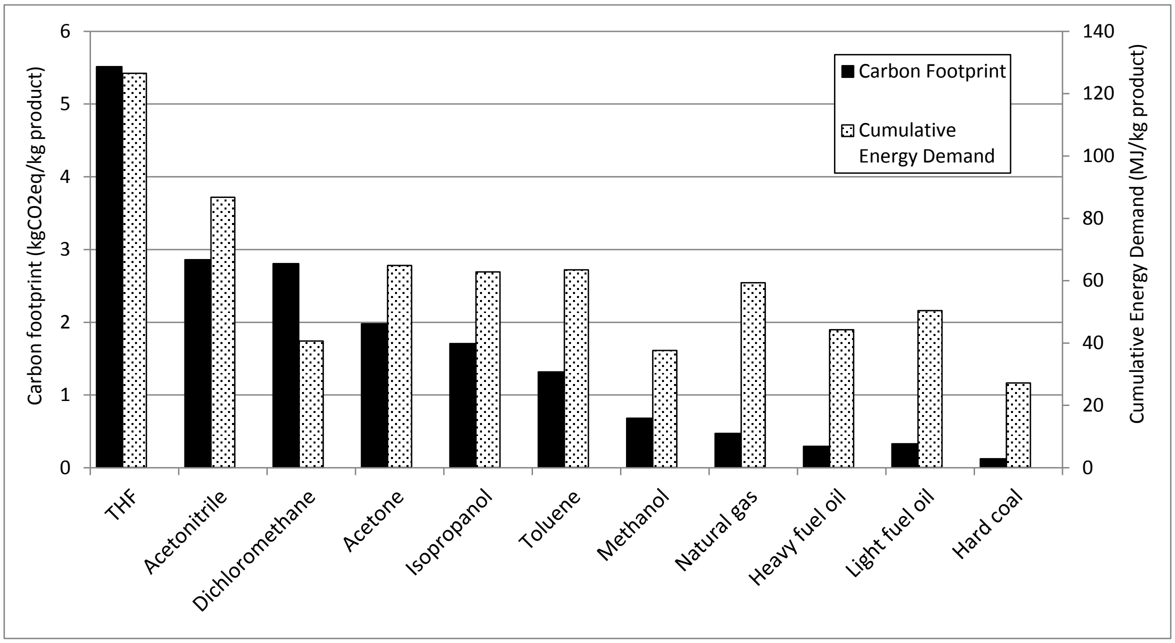


Figure 6. Life cycle carbon footprint and cumulative energy demand of the production of organic solvents and conventional fuels[20].

A diagram of the LCA of the use of solvents in the pharmaceutical industry is presented in Figure 7. Similar LCA flow charts for solvent use can be found elsewhere[10]. The diagram shows four waste disposal methods: energy recovery (by incineration), destruction (by incineration), direct release to the environment, and recycling. The waste management emissions may include the waste transportation emissions in cases where solvent waste is incinerated off site. The recycling waste process avoids the emissions of the raw materials extraction, raw materials transportation, and organic solvent production and transportation processes, as well as the emissions of the waste management method. Additionally, waste energy recovery avoids steam, electricity or heat emissions that would be generated otherwise using conventional fuels.

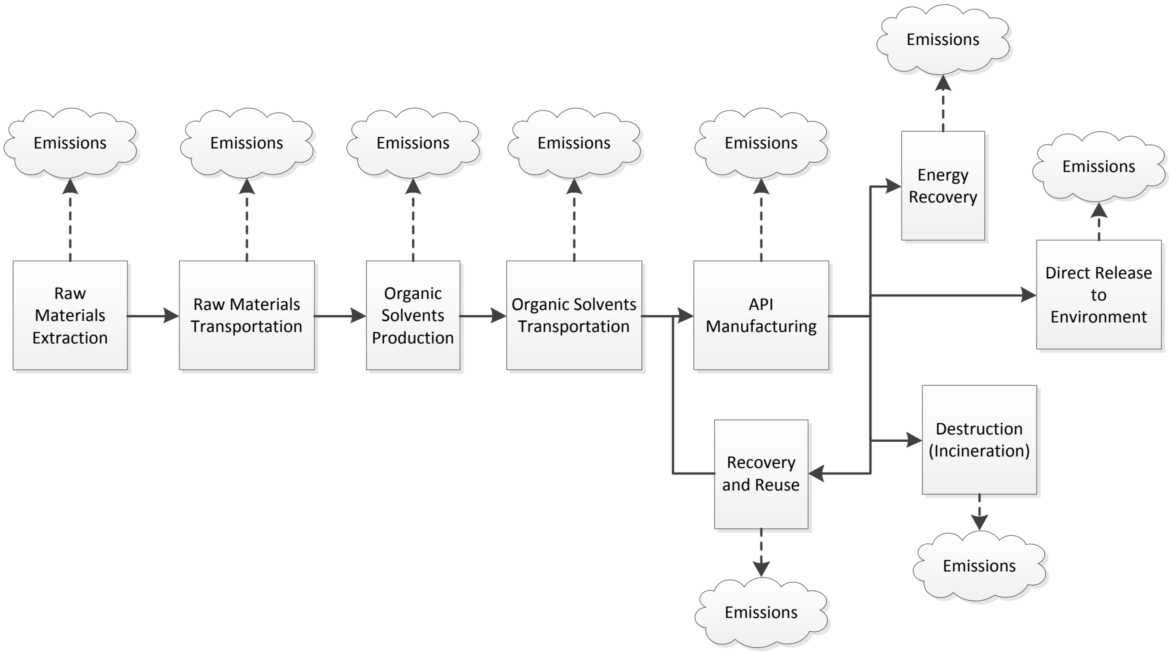


Figure 7. Life cycle flow diagram of organic solvent use in the pharmaceutical industry.

The impact of solvent recovery in the life cycle of solvent use in the pharmaceutical industry is shown in Figure 8. Solvent recovery is the only waste management method that reduces the production of virgin solvent. It also reduces the emissions of the other waste management methods, such as incineration or direct release to the environment of solvent waste. On the other hand, solvent recovery requires energy to run the recovery process. It will be later shown in the results chapter that a small increase in the recovery process emissions reduces the overall life cycle emissions of solvent usage significantly. In the same way, a small increase in the steam and electricity cost generates important operating cost savings.

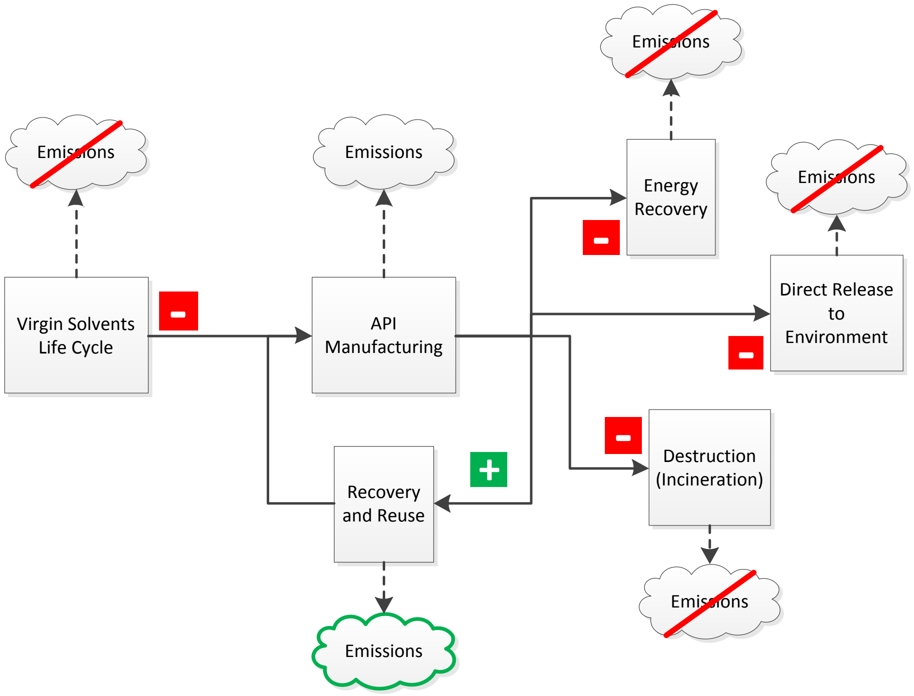


Figure 8. The impact of solvent recovery in the life cycle in the pharmaceutical industry.

Life Cycle Emissions Avoided in Solvent Recovery. Life cycle emissions avoided in solvent recovery are determined by comparing the base case life cycle emissions with the recovery case life cycle emissions. The objective is to measure the environmental impact (positive or negative) of solvent recovery, using a LCA.

The base case corresponds to the current situation in which solvent are not recovered, but otherwise incinerated, in most cases. The base case life cycle emissions are composed of the manufacture and incineration life cycle emissions of the solvents present in the solvent waste, as shown in Equation 1. M_1 and M_2 are the mass of the solvents in the binary mixture waste, LCI_{m1} and LCI_{m2} are the manufacture life cycle inventories (LCI's) of the solvents, LCI_{i1} and LCI_{i2} are the incineration LCI of the solvents; D is the distance the waste is transported; and $\mathrm{LCI_t}$ is the LCI of the transportation method.

Equation 1:

$$\mathrm{LCE_{base\ process}} = \mathrm{M_1} \cdot (\mathrm{LCI_{m1}} + \mathrm{LCI_{i1}}) + \mathrm{M_2} \cdot (\mathrm{LCI_{m2}} + \mathrm{LCI_{i2}}) + (\mathrm{M_1} + \mathrm{M_2}) \cdot \mathrm{D} \cdot \mathrm{LCI_t}$$

A LCI corresponds to the unitary life cycle emission of a product or process, and its units depend on the type of product or process. For example, the units of a solvent or steam LCI are “mass of emissions/mass of solvent”, while the units of waste transportation LCI are “mass of emissions/mass transported/distance”. The manufacture LCI takes into account all of the raw materials and chemicals used for production, including the emissions from raw material extraction to the transport of materials to the API manufacturing plant. LCI's are usually normalized to a unit of mass, e.g.: 1 kg.

The incineration of solvents after use is the most common waste management practice in the pharmaceutical industry. When solvents are recovered and reused, the manufacture of virgin solvents is avoided, as well as the incineration of used solvent. The recovery process LC emissions are composed of the manufacture and incineration LC emissions of the solvent not recovered, minus the manufacture LC emissions of the steam and electricity used in the recovery process; as shown in Equation 2, where R_1 and R_2 are the mass of the solvents recovered in the recovery process; S and E are the mass of steam and quantity of electricity used in the recovery process, respectively; and LCI_S and LCI_E are the manufacture LCI of steam and electricity, respectively. The units of electricity LCI are "mass of emissions/energy".

Equation 2:

$$\mathrm{LCE}_{\text{recovery case}} = (\mathrm{M}_1 - \mathrm{R}_1)\cdot(\mathrm{LCI}_{\mathrm{m}1} + \mathrm{LCI}_{\mathrm{i}1}) + (\mathrm{M}_2 - \mathrm{R}_2)\cdot(\mathrm{LCI}_{\mathrm{m}2} + \mathrm{LCI}_{\mathrm{i}2}) + (\mathrm{M}_1 - \mathrm{R}_1 + \mathrm{M}_2 - \mathrm{R}_2)\cdot \mathrm{D}\cdot \mathrm{LCI}_{\mathrm{t}} + \mathrm{S}\cdot \mathrm{LCI}_{\mathrm{S}} + \mathrm{E}\cdot \mathrm{LCI}_{\mathrm{E}}$$

The life cycle emissions avoided are the difference between the base case and recovery case life cycle emissions, as shown in Equation 3.

Equation 3:

$$\mathrm{LCE}_{\text{base case}} - \mathrm{LCE}_{\text{recovery case}} = \mathrm{R}_1\cdot(\mathrm{LCI}_{\mathrm{m}1} + \mathrm{LCI}_{\mathrm{i}1}) + \mathrm{R}_2\cdot(\mathrm{LCI}_{\mathrm{m}2} + \mathrm{LCI}_{\mathrm{i}2}) + (\mathrm{R}_1 + \mathrm{R}_2)\cdot \mathrm{D}\cdot \mathrm{LCI}_{\mathrm{t}} - \mathrm{S}\cdot \mathrm{LCI}_{\mathrm{S}} - \mathrm{E}\cdot \mathrm{LCI}_{\mathrm{E}}$$

Manufacture life cycle emissions avoided alone are:

$$LCE_m\ Avoided = R_1 \cdot LCI_{m1} + R_2 \cdot LCI_{m2}$$

Incineration life cycle emissions alone are:

$$LCE^I\ Avoided = R_1 \cdot LCI_{i1} + R_2 \cdot LCI_{i2} + (R_1 + R_2)\cdot D \cdot LCI_t$$

If only one solvent in a binary mixture is recovered, the incineration life cycle emissions become:

$$LCE^{I}\ Avoided = R_1 \cdot [x \cdot LCI_1^I + (1-x) \cdot LCI_2^I] + R_1 \cdot D \cdot LCI_t$$

where x is the mass composition of the solvent in the stream recovered.

The recovery process life cycle emissions are:

$$Recovery\ Process\ LC\ Emissions = S \cdot LCI_s + \ E \cdot LCI_E$$

The emissions due to the use of cooling media are included in electricity used in process cooling (cooling tower, chillers, etc.) and pumping to storage tanks and heat exchangers. The life cycle emissions of a recovery process using a fractional distillation column will include the LC emissions used to generate the steam for the reboiler, and the electricity used for the condenser cooling water.

Solvent Recovery Economics. The monetary value of solvents not recovered in 2010 as reported by the TRI (Figure 2) is more than US$90 million, which indicates that significant operating cost savings can be generated with solvent recovery projects. The solvent prices were obtained from ICIS pricing[21]. Recovering solvents also decreases the dependency on solvents' price instability. Most organic solvents are derived from crude oil, of which price volatility has been high in recent decades[22], therefore directly impacting organic solvents' prices.

Recovering solvents from high volume waste streams (HVWS) may require large dedicated equipment and, therefore, large capital expenditures. Previous studies showed that the application of fractional distillation combined with membrane systems could significantly improve recovery and reuse opportunities in HVWS and produce significant cost savings despite the upfront capital investment. These studies proved that design strategies of solvent reuse not only carried a significant reduction in greenhouse gases emissions, water, and energy use but made financial sense as well.

In the case of low volume waste streams (LVWS), the problem of investing in solvent recovery systems is usually related to the impossibility of full utilization of such equipment because of the on-off nature of campaign production cycles. A campaign is defined as a fixed mass or volume production of a certain API, thus related to batch production. Equipment dedicated to a campaign (or even multiple campaigns generating small streams) may result in too onerous investments.

In summary, the problem of solvent recovery being not profitable often arises by the fact that solvent wastes streams are have too little mass or the solvent purchase cost is too low to justify the capital or operating costs of recovery processes. This capital cost problem could be overcome if the recovery equipment was used for solvent wastes of higher monetary value as well, in which case the capital cost was justified. Therefore, a recovery unit flexible enough to accommodate LVWS from many campaigns and/or products would be desirable to minimize idle time, rendering such investment profitable and environmentally sound. The operating costs could be overcome by optimizing the recovery process, or developing a more efficient process.

As with life cycle emissions avoided, operating cost savings (OCS) are the difference between the operating costs of the base case and the operating costs of the recovery case. Equation 4 is used to calculate the OCS. It should be noted that the OCS could be negative, if the operating costs are too high and/or the solvent purchase cost is too low, in which case the "savings" would be an additional cost to the industrial plant.

Equation 4:

$$OCS = \$_{S,1} \cdot R_1 + \$_{S,2} \cdot R_2 + (R_1 + R_2) \cdot \$_w - \$_{steam} \cdot S - \$_{cm} \cdot M_{cm} - \$_{el} \cdot E$$

where $\$_S$, $\$_w$, $\$_{steam}$, $\$_{cm}$ and $\$_{el}$ are the unitary costs of solvent, waste management, steam, cooling media and electricity, respectively. R_1, R_2, S and E were previously defined, while M_{cm} is the mass of cooling media used.

The goal of these calculations is to determine if the savings from buying less virgin solvent and the reduction in costs of incinerating the solvents will be greater than the costs generated from recovering the solvents.

Solvent Recovery Barriers

Based on these findings, one might ask "*Why aren't solvents more frequently recovered?*" The answer to this question may vary across industrial plants. Raymond et al.[18] suggest the analyst's lack of knowledge on the environmental and economic beneficial impact of solvent recovery and reuse as a possible cause. A LVWS may be perceived as not cost-effective and less environmentally friendly waste management options are prioritized. Also, solvent waste mixtures may require very complex separation processes that make them economically unfeasible to recover. Other reasons may be the lack of consistency with existing facilities, lack of recovery techniques "know-how"[13], and/or "fear of change"[2]. Furthermore, and industrial plant with a limited budget may decide to use the capital to install a recovery equipment for a better financial end.

Furthermore, there is a lack of tools to allow for easy or simple pre-screening and evaluation of P2 opportunities within manufacturing facilities. This shortcoming becomes more apparent when dealing with LVWS and the perception that P2 initiatives in such streams are not cost-effective. The lack of P2 evaluation tools prevents companies from considering those streams as feasible candidates for purification and reuse of the solvents. Without the proper tools, solvent recovery assessment can be a very time-consuming task that does not fit pharmaceutical companies’ priorities and may deter form investigating novel P2 strategies.

As an answer to these solvent recovery barriers, we have developed a software toolbox to assess the recoverability of solvents in binary mixtures from an environmental and economic standpoint. The main objective of our tool is to enable decision makers to rapidly and easily assess the implementation of green engineering practices. This tool is described in Chapter 3.

Recovery Technologies Analysis

In this section, several separation and purification techniques are analyzed for the purpose of recovery and reuse of solvent waste.

Fractional Distillation. Fractional distillation (from this point forward referred to as just “distillation”) is a unit operation in which the components of a mixture are separated based on a difference in the volatility of the components. The mixture enters the column at a specific feed location along the height of the tower, based on the conditions of the stream. The mixture is separated because the component with the higher volatility, or light key (LK), is vaporized at a higher rate than the heavy key (HK), and travels vertically through the column. Once the distillate vapor, rich in the LK, leaves through the top of the column, it is condensed and a portion of the distillate is returned to the column as reflux. The returned liquid reflux increases the efficiency of the distillation column by enriching the rising vapors.[23] Separation of components by distillation is limited, as condensers for distillate and reboilers for the reflux run continuously, causing the process to be highly energy intensive. Distillation is also limited by the difference in component boiling points and the presence of azeotropes, which occur in many solvent mixtures.[24]

Even with the limitations associated with distillation, it is currently applied in 95% of all solvent separations[2]. Distillation can be found in waste solvent treatment and recovery both on-site and off-site. Multiple variations of distillation make it a viable solution to a wide range of solvent recovery situations. Distillation is an established and well-known techonology, is usually available at industrial facilities. Despite being energy intensive, its use may be justified in many solvent recovery processes because of the resulting virgin solvent cost savings and virgin solvent's life cycle emissions avoided.

Fractional Crystallization. Crystallization is the formation of a pure solid phase from a gas or liquid solution. Separation by crystallization is important in manufacturing because of the high demand for materials marketed as solids. When a crystal is formed within an impure mixture, the crystal will consist almost entirely of a pure component unless mixing of crystals occurs. Mixing of crystals occurs when temperatures lower than the melting points of multiple components are achieved simultaneously. Crystallization may be applied for solvent separation provided difference in the freezing points of the solvents is significant. This becomes useful when separating solvents with similar structures, but widely varied physical properties, such as isomers. One application of this process is the separation of *para*-xylene from *ortho*-xylene and *meta*-xylene. *Para*-xylene freezes at 13.3 °C, while *ortho*-xylene and *meta*-xylene freeze at -25.2 °C and -47.9 °C, respectively. By cooling the mixture below 13.3 °C but maintaining a temperature above -25.2 °C, the *para* isomer will crystallize and may be physically separated from the other isomers. A competing operation for separating isomers of xylene involves the use of a molecular sieve which has a pore size that allows adsorption of *para*-xylene but not the other isomers.[25]

Fractional crystallization is generally used on a small scale to separate components with melting points greater than 0 °C. When a component has a melting point lower than this, the cost to provide cooling and perform crystallization outweighs the cost saved by the separation.[26]

The most common organic solvents used in the pharmaceutical industry have melting points lower than 0°C, as shown in Table 2. Hence, this separation technique was considered unfeasible for solvent recovery.

Table 2. Solvents melting points at 1 atm

Solvent	**Melting Point (°C)**
Acetone	~ -94
Acetonitrile	-46
Isopropanol (IPA)	-89
Tetrahydrofuran (THF)	-108
Toluene	-95
Water	0

Extraction. Extraction separates a homogenous feed mixture by adding an extraction solvent to partition the mixture into two distinct phases by utilizing differences in the relative solubility of the components. The two phases are chemically different, resulting in separation of the components according to chemical and physical properties. Some applications that frequently use solvent extraction are the separation of acetic acid from water, high-molecular-weight fatty acids from vegetable oil, and the separation of penicillin from complex fermentation mixtures.[27]

In this process, a third solvent that is miscible with one of the components in the feed is contacted with the feed solution. The target component is extracted from the feed and exits the unit with the extraction solvent, thereby reducing the target component's concentration in the original mixture. As a result, the feed mixture exits the unit with significantly less of the target component.[28]

The additional solvent in extraction has associated economic and environmental costs. Essentially, it becomes another component that must be recycled to achieve economic and environmental benefits. Thus the total process proves to be more complex and expensive than single distillation. It is also considered not "green" as the solvent used for extraction must be manufactured and, after its use, it usually becomes a toxic waste. Solutions with components that have different chemical structures – but relatively close boiling points – are ideal for extraction[26].

Extractive Distillation (or Azeotropic Homogeneous Distillation). Extractive distillation is a process by which an entrainer (solvent) is added to a mixture to increase the relative volatilities of the key components of the feed.[29] It is usually employed to separate mixtures with close boiling points or with an azeotrope presence, which cannot be separated with fractional distillation alone[30]. Extractive distillation requires the selection of an optimal entrainer to effectively increase the relative volatilities of the key components of the feed. The entrainer selected must have some or all of the characteristics listed below:[31,32,33,34]

- ability to change the relative volatility between the key components of the feed
- low volatility to exit the bottom of the distillation column
- thermally stable
- non-reactive with the components of the feed
- economically
- non-corrosive
- relatively low toxicity
- easily separated from the other bottoms product
- completely miscible with key components of the feed

Extractive distillation has the same drawbacks as an extraction technology due to the additional cost and environmental burden of the entrainer.

Pervaporation. In recent years, pervaporation has gained popularity as an alternative to azeotropic distillation and pressure swing distillation for separating azeotropic mixtures, because it is less energy intensive, more cost-effective and environmentally friendlier[35]. In pervaporation, the separation is not based on the relative volatility of the components in the mixture as it is in distillation; hence it is not limited by vapor-liquid equilibrium but only depends on the relative permeability of the components in the membrane. This membrane process can be used following distillation to take advantage of the benefits of each technology. A dehydration pervaporation system is more economically used to remove the minor component of a feed mixture. Therefore, distillation would normally precede pervaporation when dehydrating organic solvents with relatively small water concentration at the azeotrope. Often, these hybrid processes are seen to reduce energy and eliminate the use of chemical entrainers, both leading to economic and environmental savings.

A vacuum is kept on the permeate side of the membrane while the feed side of the membrane is kept at atmospheric or elevated pressure. Therefore, a pressure difference is created over the membrane which is the driving force for the pervaporation process. The component(s) that preferentially permeates through the membrane evaporates while passing through the membrane because the partial pressure of the permeating component(s) is kept lower than the equilibrium vapor pressure. A sweep gas can also be used to keep a low vapor pressure of the permeating component. The driving force is due to the fact that on the feed side, the chemical potential is higher than on the permeate side, similar to what is found in gas separation membranes. The gradient in chemical potential is maximized by using high feed temperatures and low pressures on the permeate side.

Pervaporation is a separation process in which a compound of a mixture selectively permeates through a membrane and is evaporated on the other side. The concentration of the compound must be low on the permeate side to promote mas transfer, so a vacuum or a sweep gas are used on the permeate side. Pervaporation is very commonly used in the dehydration of organic solvents, especially because organic solvents and water almost always form azeotropes and cannot be purified with distillation alone. For example, it is used in the production of ethanol.

Furthermore, it is considered a greener technology and more cost effective than traditional schemes used to separate these complex mixtures, such as azeotropic distillation[36,37,38,39,40].

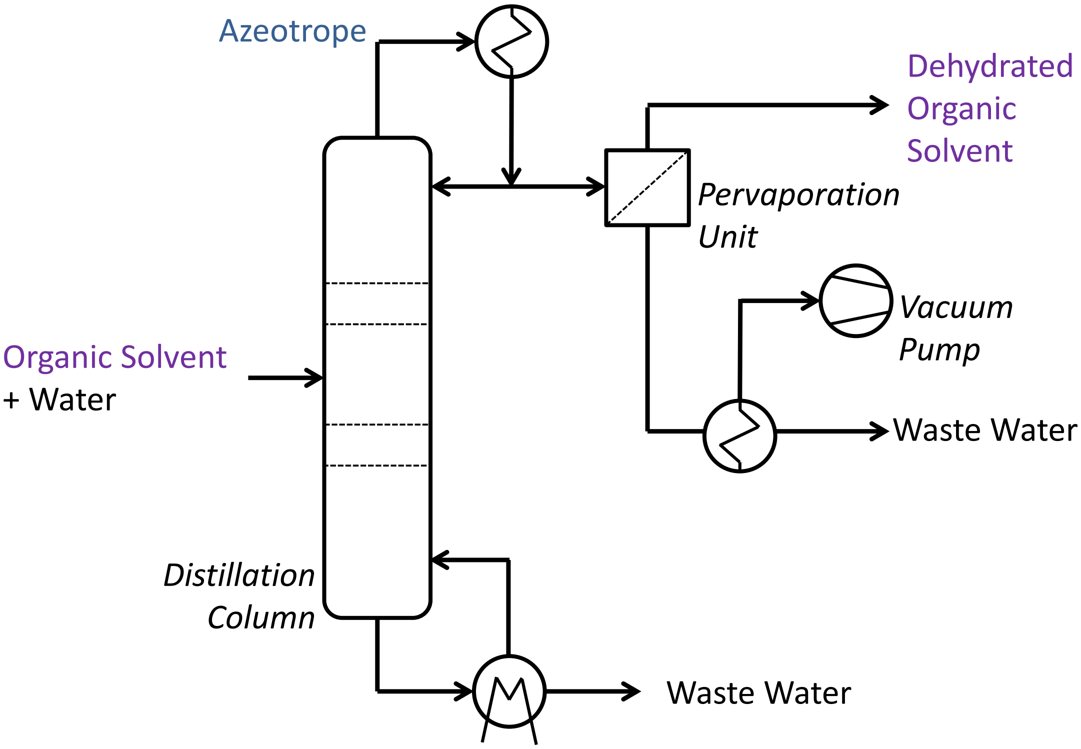


Figure 9. Integration of pervaporation with distillation for solvent recovery from azeotropic aqueous-solvent waste system. *A*: Distillation Column, *B*: Pervaporation Unit.

Chapter 2

Solvent Recovery Assessment Software Toolbox: R.SWEET

As mentioned earlier, a software toolbox was developed to environmentally and economically assess solvent recovery. The toolbox was named R-SWEET (*R*ecovery of *S*olvent *W*aste *E*nvironmental and *E*conomic *T*oolbox). R-SWEET combines process simulation, LCIs, and economic information to become an environmental and economic evaluation tool.

The main idea for the development of this tool was to enable the pharmaceutical industry to overcome two solvent recovery barriers: a steep learning curve to understand its implementation and the potential preconception that solvent recovery is not cost-effective. Therefore, R.SWEET was provided with the following capabilities:

- Identification of suitable recovery processes based on solvent binary mixture thermodynamics.
- Simulation of solvent waste separation processes.
- Calculation of life cycle emissions avoided.
- Calculation of operating cost savings.
- Determination of the optimum distillation reflux ratio and feed stage that maximizes life cycle emissions avoided and operating cost savings.
- Cash flow analysis.

Additional objectives for the development of R.SWEET were to:

- assist pharmaceutical industries in source reduction, pollution prevention, design for the environment, and green manufacturing;

- providing a ready-to-use design tools to facilitate the understanding and implementation of cost-effective pollution prevention strategies in the pharmaceutical industry;
- assist process engineers, manufacturing engineers, EHS personnel, and decision makers, with the need for pre-screening and evaluation of pollution prevention opportunities within manufacturing facilities;
- evaluate solvent recovery feasibility and readily obtain environmental impact determination;
- provide the industry and other NGOs with a design tool to help them determine and evaluate source reduction opportunities with minimum effort;
- make possible for pharmaceutical companies and Non-Government Organizations (NGOs) to design greener processes and retrofit existing ones using LCA as primary driving force;
- assist industry with "adopting more efficient, sustainable practices and technologies";
- show that recovery and reuse of solvents in LVWS could be cost effective and that the associated environmental footprint reductions are significant;
- make possible the development of new "green solvent recovery";
- make possible for pharmaceutical plants to design P2 strategies for multiple manufacturing campaigns, thereby reducing design cost and improving process flexibility; and
- guide decision making to reduce process waste as well as to reduce emissions from the life cycle, as less fresh solvent will be needed.

A total of 31 typical solvents present in pharmaceutical industry's solvent waste streams are included in our tool, as observed in Appendix A. To allow for environmental determinations, the toolbox contains life cycle inventories (LCIs) of virgin solvents, transportation, and utilities (steam, electricity, and cooling water), obtained from SimaPro®'s database. Solvent incineration emissions were calculates using the Ecosolvent tool (Ecosolvent). The LCI's can be modified by the user.

R.SWEET combines a non-traditional separation technique, pervaporation, with the more traditional separation methods, decanting and distillation, which are naturally supported by commercial process simulator. Pervaporation is a membrane-based separation process typically used to efficiently separate azeotropic and close boiling point mixtures, commonly present in solvent waste. The ability to simulate continuous distillation, decanting, and pervaporation, gives the user the flexibility to evaluate homogeneous, heterogeneous, zeotropic, and azeotropic systems purification.

Process simulators are extensively used in industry, universities, and other NGOs, making our development easier to implement and increasing its transferability. Process simulators also offer comprehensive chemical data banks for the necessary solvent properties.

R.SWEET's interface is Microsoft Excel® (Excel). Distillation and decanting are modeled with Aspen Plus®. Excel add-in Aspen Simulation Workbook™ (ASW) is used to communicate Aspen Plus® simulation with Excel. Through sensitivity analyses, distillation operating variables (reflux ratio and feed stage) can be optimized to maximize operating cost savings and minimize life cycle emissions. A model to simulate pervaporation was developed and included in Excel.

R.SWEET software requirements are Aspen Plus® Version 8.0 or earlier, and Microsoft Excel 2010 or earlier.

Recovery Process Selection Guide

Waste solvent commonly show thermodynamic non-ideal behavior and the formation of azeotropes, which may difficult the design of solvent recovery. Vapor-liquid equilibrium data may be unavailable or expensive to obtain. To overcome these problems, this guide uses the thermodynamic information of a binary mixture to find the most suitable recovery process. Three things need to be defined: 1) the solvents present in the mixture, 2) which one is the primary or desired solvent, and 3) what is the composition of the mixture.

Solvent mixtures in pharmaceutical processing can have complex thermodynamic interactions, which can play a large role in the complexity of the separation process required to recover the solvents. Depending on the components present; the mixtures can be homogeneous or heterogeneous, and zeotropic or azeotropic. When purifying a mixture, it is desirable to obtain a final solvent mass fraction close to 1. There are different ways to achieve the final purity, which depend on the system thermodynamics and the initial composition of the system. For this reason, the first step in the solvent recovery assessment is to analyze the thermodynamic behavior of the mixture, since it will define the separation. The user must input the mixture composition and the tool will detect the presence of azeotropes at 1 atm and heterogeneity at 1 atm and 25 °C. Based on the results, a separation process is suggested.

As solvent binary mixtures can be homogeneous or heterogeneous, and zeotropic or azeotropic, a Recovery Process Selection Guide is included to guide the design of the separation train. The user must input the mixture composition and the Recovery Process Selection Guide detects the presence of azeotropes at 1 atm and liquid heterogeneity at 1 atm and 25 °C. Based on the results, the separation process is defined. As an example, to recover isopropanol from a 50-50 %wt. mixture of isopropanol (IPA) and water, the tool recommends an azeotropic distillation or distillation followed by pervaporation. This is because this mixture presents an azeotrope at 87.8 % wt. IPA. If, however, the isopropanol composition were 90 % wt., the recommended process would only indicate distillation since it is past the azeotrope. Another example is the recovery of methyl acetate from water at equal mass compositions. At 1 atm and 25 °C, the system is heterogeneous with aqueous and organic phases containing 23 % wt. and 91 % wt. of methyl acetate, respectively. Additionally, the mixture forms an azeotrope at an organic composition of 98.9 % wt. which calls for a decanter followed by azeotropic distillation or pervaporation. If the original methyl acetate composition were 92 % wt., the recommended recovery train would be azeotropic distillation or pervaporation. If it were less than 23 % wt., the separation process would be distillation followed by decanting and further azeotropic distillation or pervaporation.

The Recovery Process Selection Guide uses a decision tree that can be seen in Appendix B. The application of this decision tree to more solvent mixtures, with the aid of vapor-liquid-liquid equilibrium diagrams, is also explained in Appendix B.

Prior to simulate the recovery process, the Recovery Process Selection Guide should be consulted, more so if the thermodynamic behavior of the solvent binary mixture is unknown.

The azeotropes' temperature and composition, and the phase mass composition in heterogeneous mixtures were obtained from Aspen Plus® using the property method UNIQUAC. When possible, this information was corroborated with VLE and LLE experimental data available on scientific literature. A comparison between UNIQUAC thermodynamic behavior prediction and experimental data for some mixtures of solvents widely used in the pharmaceutical industry can be seen in Appendix C. The user can modify the azeotrope and heterogeneous information.

Process Simulation

How it Works. The tool uses an excel interface, but it communicates with commercial simulator ASPEN Plus in real time, which provides the simulation capabilities for distillation and decanting. This communication is possible with an excel add-in called Aspen Simulation Workbook® (ASW). However, we also have to simulate PV, and because is not simulated by Aspen Plus®, we created a model in excel to simulate PV.

In Aspen Plus®, the rigorous distillation calculation method RadFrac is used. The distillation column design specifications in Aspen Plus® are used to achieve the desired purity of the separation. The thermodynamic property method UNIQUAC was selected, as recommended by Carlson et al.[41]. The accuracy of UNIQUAC to predict thermodynamic behavior was tested for selected binary mixtures formed by the solvents most used in the pharmaceutical industry.

Currently, R.SWEET models the dehydration of THF, IPA, n-butanol, tert-butanol, and 2-butanol using different hydrophilic membranes. Only hydrophilic membranes are considered because pervaporation is more efficient when the component to permeate has the lower concentration in the feed, which in solvent waste mixture is usually water. Hydrophobic membranes are used to remove volatile organic compounds (VOC's) from water stream.

PV is not modeled by commercial simulators because the flux through the membrane is highly dependent on the membrane materials and internal structure, therefore is difficult to create a unified model. The complexity to model pervaporation has been highlighted by Cséfalvay et al.[42] and Verhoef et al.[43]. Dr. Leland Vane commented that the performance of the separation medium changes from one vendor to another, from one solvent to another, and with temperature/concentration[44]. However, we developed our pervaporation simulator using experimental data from different membranes.

Previous studies modeled pervaporation with a user block in Aspen Plus® or ChemCAD®[42,45,46,47,48], in which specific membrane parameters need to be changed manually to accurately model different membranes and solvents. R.SWEET, on the other hand, contains a membrane parameter database; the pervaporation model automatically changes these parameters when different membranes and solvents are selected.

Equation 3 and Equation 4 are used by R.SWEET to calculate the life cycle emissions avoided and the operating cost savings, respectively.

Recovery Process Utilities. Distillation steam, cooling media, and electricity usage are determined with the resulting heat duties from Aspen Plus®. The mass of steam and electricity used in the recovery process is calculated as:

Equation 5:

$$S = \sum_{i=heater} \frac{Heat\ Duty_i}{C_{S,i} \cdot Heater\ Efficiency_i}$$

Equation 6:

$$E = M_{cm} \cdot F_{cm}$$

where C_S is the latent heat of steam, M_{cm} is the mass of cooling media, and F_{cm} a factor accounting for the energy used in pumping and cooling (cooling towers, chillers) after passing through heat exchangers. It is assumed that all exchangers used for process heating use steam as the heat media. M_{cm} is calculated as:

Equation 7:

$$M_{cm} = \frac{Condenser\ Duty}{\Delta T_{condenser} \cdot C_{cm} \cdot Condenser\ Efficiency}.$$

where C_{cm} is the heat capacity of the cooling media.

In pervaporation, the electricity usage is calculated as:

$$E = W_{vacuum\ pump} + W_{chiller}$$

where $W_{vacuum\ pump}$ accounts for the energy required to maintain a low partial pressure in the permeate side, and $W_{chiller}$ is energy required to condense the permeated solvent. The steam usage is calculated as in distillation.

Pervaporation Modeling. The transport equation used to calculate the flux of a component (J_i) across a pervaporation membrane is:

Equation 8

$$J_i = f(x_s) \cdot \exp[-(E_i/R') \cdot (1/T_o - 1/T_F)]$$

This equation accounts for the effect of feed concentration and temperature, where $f(x_s)$ accounts for the effect of organic solvent feed mass composition, E_i is the activation energy of component i, R' is the universal gas constant, T_O is the reference temperature at which the function $f(x_s)$ is derived, and T_F is the feed temperature. The exponential function represents the Arrhenius nature dependence of flux with temperature at a given feed composition[49,50]. $f(x_s)$ is a polynomial function of the feed mass fraction of the organic solvent, since the flux of a component i as a function of the organic solvent feed mass composition at a constant temperature can be well represented by a polynomial equation. The polynomial coefficients of $f(x_s)$ were developed using experimental data on commercially available membranes from the literature. These coefficients are membrane and compound specific. The energy of activation of a component (E_i) is also dependent on the membrane and on the other components present in the mixture and was derived from experimental data as well.

Previous pervaporation models are based on the solution-diffusion theory[42,45,46,47,48]. Our model relies primarily on experimental data. The use of empirical approaches over mass transfer models is not uncommon in chemical engineering, such as in the rules of thumb used for the determination of height equivalent to theoretical plate (HETP) in packed towers used for distillation[51].

Along a pervaporation unit, the temperature and mass composition in the liquid side change since the temperature decreases due to water evaporation and the solvent gets more concentrated as the water is continuously permeated. Accordingly, the flux across the membranes changes as well, as suggested by Equation 8. To account for these changes, the pervaporation membrane is divided into differential elements which physically represent small segments of equal area, as seen in Figure 10. Pervaporation is modeled in a cascade mode, in which the retentate of each area segment is sent to the next area segment as the new feed. The permeate streams, on the other side, are collected. To model an entire pervaporation unit, a mass and energy balance must be solved in each subsequent area segment, until the desired purity of the retentate, concentrated in organic solvent, is achieved. The procedure used to calculate the required membrane area to achieve a desired purity is shown next. The equations referenced in this procedure are included in Table 3.

1. As the starting point, the feed flow rate (F), temperature (T_1), mass composition ($x_{s,1}$) must be defined. The compound properties and the area of the differential segments (A) are already defined in the PV Simulator.
2. T_1 and $x_{s,1}$ are used in equations 9 and 10 to calculate the solvent and water flux, $J_{s,1}$ and $J_{w,1}$.
3. The total flux, J_1, and permeate, P_1, are calculated with Equation 11.
4. Equation 12 is used to calculate the retentate, R_1.
5. Equation 13 is used to calculate the solvent mass fraction of the retentate, $x_{s,2}$.
6. The solvent and water properties are used in Equation 14 to calculate T_2.

7. At this stage, the data needed to calculate the mass and energy balance of the next area segment are available: T_2, $x_{s,2}$, A, R_1 and the solvent and water properties.
8. These steps are repeated as needed to achieve the desired purity, $x_{s,T}$, being T the total number of area block required.

A diagram representation of this procedure can be seen in Appendix E.

Equation 14 was adapted from Ho & Sirkar[52] and Noble & Stern[53]. This procedure to design an industrial pervaporation unit as a continuous flow cascade process agrees with Noble & Stern[53], Lipnizki et al.[46] and Csefalvay et al.[42].

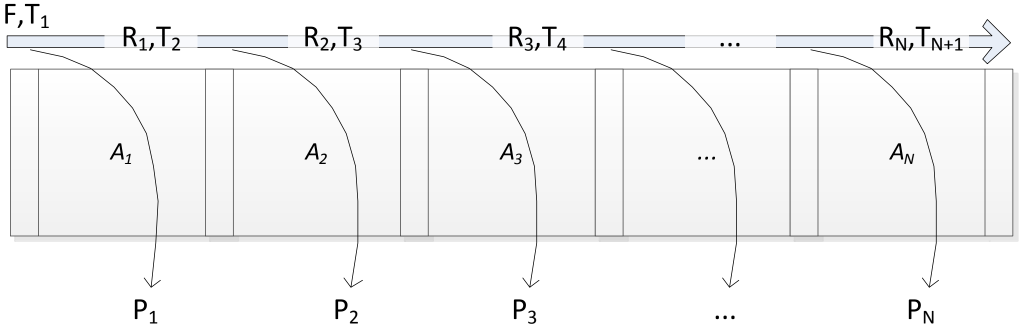


Figure 10. Differential elements (area segments) in a pervaporation membrane. R: Retentate, P: Permeate, F: Feed, T: Retentate temperature. A: differential elements area ($A_1 = A_2 = A_3 = \ldots = A_N = A$).

Table 3. Equations used in the required pervaporation membrane area calculation procedure

Equation	Equation #
$J_{s,N} = f_s(x_{s,N}) \cdot \exp[-(Ei/R') \cdot (1/T_o - 1/T_N)]^a$	9
$J_{w,N} = f_w(x_{s,N}) \cdot \exp[-(Ei/R') \cdot (1/T_o - 1/T_N)]^a$	10
$J_N = J_{w,N} + J_{s,N} = P_N \cdot A$	11
$F = R_1 - P_1\ ;\ R_{N-1} = R_N - P_N$	12
$x_{s,N+1} = \left(R_{N-1} \cdot x_{s,N} - J_{s,N} \cdot A\right)/R_N$	13

$$\mathrm{P_N} \cdot \left(\mathrm{y_{s,N}} \cdot \Delta \mathrm{H_{vap,s,T_N}} + \mathrm{y_{w,N}} \cdot \Delta \mathrm{H_{vap,w,T_N}}\right) = \mathrm{R_{N-1}} \cdot \left(\mathrm{x_{s,N}} \cdot \mathrm{Cp_{s,T_N}} + \mathrm{x_{w,N}} \cdot \mathrm{Cp_{w,T_N}}\right) \cdot (\mathrm{T_N} - \mathrm{T_{N+1}})^{a} \qquad 14$$

[a]. Notation previously not defined: $\Delta H_{vap,s,T_N}$ and $\Delta H_{vap,w,T_N}$: heat of vaporization of the organic solvent and water, respectively, at temperature T_N; Cp_{s,T_N} and Cp_{w,T_N}: heat capacity of the organic solvent and water, respectively, at temperature T_N.

Industrial pervaporation units contain modules with an already defined membrane area. Therefore, the total area of the pervaporation unit will not be the summation of the *T* number of area segments, but rather the minimum multiple of the industrial membrane modules area that contains this summation. For example, if the total area required to achieve certain purity is 51 m^2 and the modules have an area of 35 m^2, two modules would be required and the total area of the pervaporation unit would be 70 m^2. The final retentate flow rate and mass composition will be that of the last area segment of the pervaporation unit.

Pervaporation energy requirements are to maintain a low partial pressure of the permeating component in the permeate side, and heating the retentate to prevent a drastically reduction in flux. In our model, pervaporation is induced by vacuum on the permeate side generated with a vacuum pump. Because of the temperature decrease of the retentate and the consequent reduction in flux, heating is typically used between membrane modules[38,50]. The tool assumes the use of inter-module heaters, being the outlet temperature the same as the feed temperature.

The effect of concentration polarization has not been considered in the PV Simulator, although its effect in pervaporation has been reported to be small[40,53]. The effect of swelling is assumed to be already considered in the experimental data. The effect of neither permeate nor retentate pressure is considered. Our pervaporation model was used within the experimental mass composition ranges. As for boundary conditions, the flux of water and organic solvents approaches zero when the organic solvent mass fraction in the retentate side approaches one.

When deriving the polynomial coefficients of the polynomial function $f(x_s)$, three boundary conditions need to be considered: water and solvent flux is zero when solvent mass composition in the feed/retentate is 1, and solvent flux is zero when solvent mass composition in the feed/retentate is 0. The following procedure ensured that these boundary conditions were fulfilled in the fitting curve:

1. A preliminary polynomial fitting curve was developed with all experimental points.
2. A number of points equal to the power of the polynomial equations plus one were selected, ensuring that the lower and higher solvent mass composition (the higher being 1) points were selected.
3. A new fitting curve with the experimental points selected in step 2 was developed.
4. The coefficient of determination was calculated to indicate how well the new curve fitted all the experimental points.
5. If the coefficient of determination was acceptable (>0.9), the fitting curve was accepted, otherwise, the process went back to step 2.

Figure 11 shows an example of an original and revised fitting curve of the IPA flux through a Sulzer’s membrane PERVAP 2201 in the dehydration of IPA.

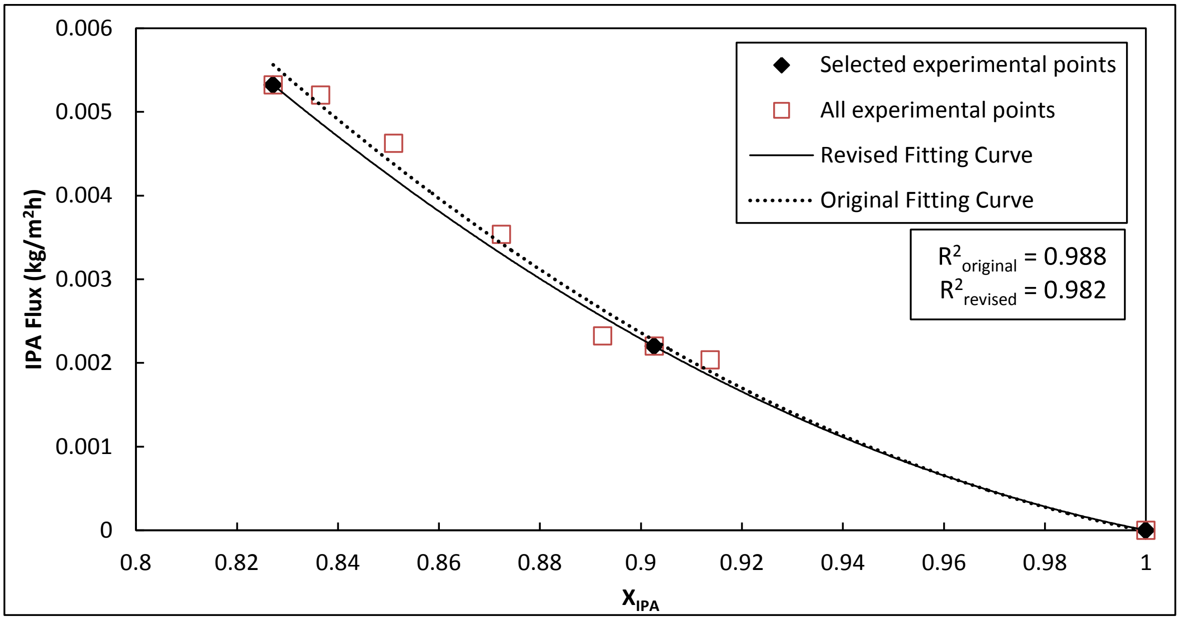


Figure 11. IPA flux across Sulzer's PERVAP 2201 pervaporation membrane as a function of IPA mass fraction in the feed. Adapted from Qiao et al.[54].

Furthermore, the PV simulator does not model pervaporation below the experimental range of solvent mass composition. When the experimental range did not approached a solvent mass composition close to 1 (as in the case of IPA in membrane PERVAP 2201), an artificial point of zero flux was included for both water and solvent at a solvent mass composition of 1.

How to Use it. The steps for designing and optimizing a solvent recovery process are: 1) define base case, 2) define recovery process, 3) simulate separation and optimize distillation (if distillation is part of the recovery process), and 4) obtain final results. The main inputs and results of each step are shown in Table 4.

Table 4. Main inputs and results of the simulation tool

Inputs			
1) Define Base Case		2) Define Recovery Process	
Waste and Costs	Utilities	Distillation	Pervaporation
• binary mixture components • mass composition • waste management method • waste transportation distance • transportation type • total waste (yearly basis) • solvents cost • utilities cost	• Steam characteristics (pressure, temperature, saturation? etc.) • Cooling media characteristics (cooling media energy factor, heat capacity, etc.)	• desired purity • number of stages • feed stage • reflux ratio • feed flow rate • feed pressure • feed temperature • heat exchangers efficiency and heat integration	• solvent to dehydrate • mass composition • flow rate • feed temperature • membrane type • module area • adiabatic or isothermal process • desired purity • heat exchangers efficiency and heat integration

Results			
General		Distillation	Pervaporation
• steam use • electricity use • purity achieved • stream mass flow rates	• stream temperatures • life cycle emissions avoided • operating cost savings	• Column diameter	• membrane area required

By defining the base case we define all the information necessary to define the LCIs that will be used to calculate the life cycle emissions avoided (Equation 3), and the cost information that will be used to determine the operating cost savings (Equation 4). Then, R.SWEET requires information of distillation and pervaporation to define how the recovery process will be simulated. Finally, the results of the simulation are the missing data to calculate the life cycle emissions avoided (Equation 3) and the operating cost savings (Equation 4).

Once we obtain the results of our first simulation, we ask ourselves: "*How do we know that we have selected the best feed stage or reflux ratio?*" To answer this question, sensitivity analysis are available to maximize the operating cost savings and the life cycle emissions avoided.

The ASW can be used to run multiple scenarios simultaneously to perform a sensitivity analysis with the feed stage and reflux ratio as the independent variables. The life cycle emissions avoided and operating cost savings are calculated for each scenario. Then, R.SWEET highlights the optimum reflux ratio and feed stage that maximizes the life cycle emissions avoided and operating cost savings. By selecting these parameters, different recovery scenarios can be examined. Distillation optimization is valuable since it is the most common solvent recovery process in the chemical industry[55]. The sequence for distillation optimization is shown in Figure 12.

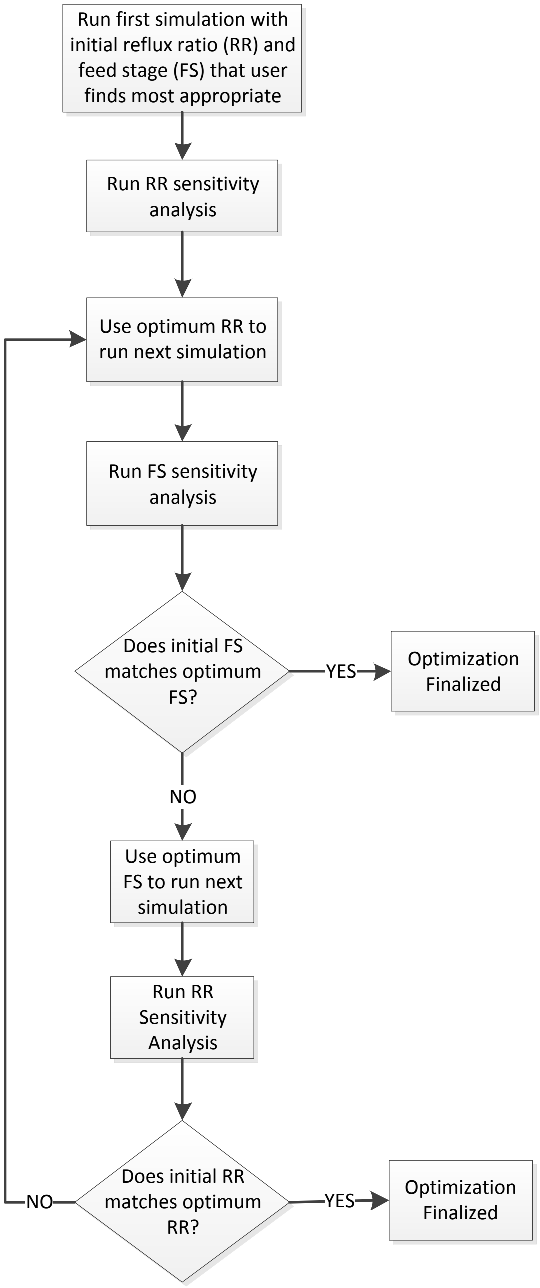


Figure 12. Procedure for solvent recovery optimization

Cash Flow Analysis

R.SWEET's cash flow analysis uses the operating cost savings, the investment and maintenance cost of the recovery process, and financial parameters: discount rate and income tax, to returns three parameters used to financially evaluate projects: net present value (NPV), internal rate of return (IRR) and payback period.

Comparison with Other Tools

Both Ecosolvent and our toolbox are used to environmentally assess the recovery of solvents in waste mixtures by comparing the recovery scenarios to other waste disposal methods, following a life cycle approach. However, the main differences reside in the following additional capabilities of our toolbox:

- Recommends recovery processes;
- Simulate recovery processes;
- Includes pervaporation;
- Performs economic analyses.

Ecosolvent's environmental analysis on distillation is performed with information provided by the user, such as steam and electricity use, or, if this information is missing, uses representative data; but does not run active simulations. Furthermore, our simulation tools have the option to customize the type of steam and electricity used, in order to generate a more representative LCI of a specific chemical plant. Nevertheless, Ecosolvent offers greater detail regarding waste management methods other than waste recovery, such as incineration. Therefore, our toolbox contains incineration LCI's that were obtained from Ecosolvent.

FIZ CHEMIE Berlin, provider of online database products for organic and industrial chemists, developed a software tool that, given a binary mixture, recommends separation processes and finds a suitable entrainer in the case azeotropic distillation is needed[56]. This software is comparable to our Recovery Process Selection Guide tool; however, it does not include pervaporation as an alternative separation process. Furthermore, it does not consider the mass composition of the components in the mixture, which has an impact on recovery process design. Nevertheless, we acknowledge that an entrainer selection guide is very useful tool when pervaporation is not applicable.

Chapter 3

Case Studies

Four solvent waste case studies were provided by Pfizer: 1) a mixture of acetone and acetonitrile from the manufacture of selamectin, the API of the drug Revolution®; 2) an IPA and THF system derived from the production of API Nelfinavir, for the drug Viracept® 3) the production of API hydrocortisone, for the drug TriOptic-S®, generated a toluene and acetone waste solution; and 4) a waste mixture of IPA and water from the API celecoxib of the drug Celebrex®. These cases were environmentally and economically analyzed with our toolbox. More detail on the case studies is provided in Table 4. As mentioned earlier, the adequate recovery process depends on the thermodynamics behavior of the binary mixture. The acetone and acetonitrile (selamectin), IPA and THF (nelfinavir), and toluene and acetone (hydrocortisone) mixtures are homogeneous and do not form an azeotrope; therefore, distillation will suffice as a separation process. IPA and water (celecoxib) forms a homogeneous liquid mixture as well, but it presents an azeotrope at an IPA mass composition of 87.8 % wt., making distillation alone unable to purify IPA. Therefore, a pervaporation unit after distillation was added for the fourth case study. These cases were selected to show the flexibility of the proposed skid and of the simulation tool since they are representative of high and low volume waste streams with different thermodynamic behavior. All the case studies contain solvents that are widely used in the pharmaceutical industry. Therefore, their evaluation sets a good basis for other manufacturing plants.

Table 5. Solvent waste case studies summary

Case Study[a]	Selamectin	Nelfinavir	Hydrocortisone	Celecoxib
Binary Composition (%wt.)	Acetonitrile (72) & Acetone (28)	IPA (86) & THF (14)	Toluene (91) & Acetone (9)	IPA (50) & Water (50)
Drug	Revolution®	Viracept®	TriOptic-S®	Celebrex®
Mass of Solvent Waste (kg/yr)	84,500 (LVWS)	78,700 (LVWS)	257,600 (LVWS)	5,470,000 (HVWS)
Solvent Cost (US$/kg)	Acetone: 1.03 Acetonitrile: 4.07	IPA: 1.49 THF: 2.97	Toluene: 0.92 Acetone: 1.03	IPA: 0.92 Water: NA
Desired Recovery	Acetonitrile, Acetone (98 wt. %)	IPA (98 % wt.)	Toluene (99.8 wt. %), Acetone (98 wt. %)	IPA (99.5 wt. %)
Waste Management Cost (US$/kg)	0.129	0.129	0.129	0.5
Utilities Cost (US$/kg, *US$/kWh)	Steam: 0.02 Electricity: 0.1	Steam: 0.02 Electricity: 0.1	Steam: 0.02 Electricity: 0.1	Steam: 0.04 Electricity: 0.127
Base Case Waste Management Method	Incineration for Energy Recovery	Incineration for Energy Recovery	Incineration for Energy Recovery	Incineration for Energy Recovery
Recovery Process	Distillation	Distillation	Distillation	Distillation + Pervaporation
Recovery Skid Investment (US$)	1,500,000	1,500,000	1,500,000	2,960,000
	Combined: 1,500,000			
	All cases combined: 2,960,000			

[a]: Case studies are named after the API manufactured from which the solvent waste is generated.

The Skid

The ultimate goal was to design a skid of relatively low capital investment cost, small footprint, and be versatile enough so that it can be used to treat different solvent streams. Such a system would allow for the recovery and reuse of multiple organic solvent streams, making the original capital investment viable. This concept fits very well with the batch-and nature of the manufacturing process in pharmaceutical companies. This skid would then be used as the equipment for solvent recovery simulation in all the case studies. Such recovery unit would be flexible enough to purify all solvent waste case studies, minimizing idle time. Finally, the skid would break the solvent recovery barrier: plant not fit for solvent recovery.

The design of this skid resulted in the following characteristics:

- A structured packed distillation column of 20 ft. of height and 1.5 ft of diameter. Assuming a maximum HETP of 2 ft.[57], this column would contain at least 10 theoretical stages
- The type of packing selected in Aspen Plus® was MellapakPlus™ *252.Y* from Sulzer Chemtech. A packed column was selected for distillation because it is recommended for the diameter and operating pressure considered. Furthermore, as compared to trayed and randomly packed columns, structured packed towers usually have less residence time, which minimizes thermal degradation and pressure drop and allow for less height since they are more efficient[58].
- As for pervaporation, a unit using Sulzer's PERVAP® 2510 membranes with an area of 210 m^2 was considered which accounts for 6 modules of 35 m^2 each. We based this design on the commercially available Sulzer plate and frame system, because this type of pervaporation equipment is available at a Pfizer plant in Barceloneta, where one of the solvent waste case studies was generated. The membrane is composed of a polyvinyl alcohol polymer.
- The estimate dimensions for the skid including auxiliary equipment (pumps, pipes, tanks, and heat exchangers) are 15 ft. x 15 ft. x 35 ft. in W x D x H. These

approximate dimensions where obtained from distillation tower vendor quotations and from similar existing pervaporation units at chemical plants. Furthermore, the skid would address the problem mentioned in the introduction regarding the difficulty to implement solvent recovery due to the lack of consistency with existing facilities. - Can be used indoor.

Skid Economics. The economic feasibility of using the recovery skid in each case was investigated with a cash flow analysis. The equipment cost estimation for the distillation system was obtained as the average of three vendor quotations. The installation costs were assumed to be 100 % of the capital cost, resulting in a total investment cost for each selamectin, nelfinavir and hydrocortisone case of US$ 1,500,000. If the same recovery skid was used for the three cases, the cost would be the same as the individual value. It should be noted that these three case studies occurred at the same manufacturing plant. The equipment and installation cost of a pervaporation unit with a membrane area of 210 m^2 was determined to be US$ 1,460,000. Therefore, the investment cost for the Celecoxib case skid would be US$ 2,960,000. A membrane lifetime of 3 years was obtained from Van Hoof et al.35, as well as a polymeric membrane cost of US$740/$m^2$, which would account for US$ 155,400 in our pervaporation unit. All pervaporation costs were obtained from Van Hoof et al.35, and adjusted based on the actual size of the equipment in our model. All the costs were updated to current date with the average inflation rate from the date of the reference to the date of the paper submission, obtained from Trading Economics[59]. If a recovery skid would be used for the four cases, the investment cost would be that of the celecoxib case. A detailed calculation of the recovery skid can be seen in Appendix J.

It is interesting to note that idle equipment suitable for solvent recovery could be available at an API manufacturing plant, in which case the investment cost could be lower.

General Considerations

The following procedures, assumptions and conditions were applied to all of the case studies evaluation.

- All the cases were provided by Pfizer.
- The base case waste management method is incineration for energy recovery in a cement kiln, as all the cases analyzed in this research used a similar method.
- All the cases were evaluated with R.SWEET. R.SWEET was used to simulate the distillation recovery process, calculate the life cycle emissions reduction and the operating cost savings.
- The distillation column reflux ratio and feed stage that maximized the life cycle emissions avoided was selected using R.SWEET.
- The feed temperature to the distillation column is 35 °C.
- The life cycle emissions (LCE) of the reflux pump energy and for the manufacture of the recovery process equipment were not considered.
- Heat exchangers have an efficiency of 90 % and heat integration was not considered.
- Waste transport emissions are zero.

Cooling water was the cooling media. In Equation 7 average cooling water temperature temperature change of 5 °C, and the heat capacity of water is 4.184 kJ/(kg·°C). In

- Equation 6 the cooling water electricity factor (F_{cm}) is 1.71 kWh per ton of cooling water;
- In the distillation column, an atmospheric operating pressure was selected to minimize thermal degradation and operating costs.
- In a conservative approach, 8 theoretical stages were used in all case studies, even though 10 stages are available.
- The flow rate to the distillation column was selected to obtain a column diameter of 1.5 ft, which is the skid's distillation column diameter.
- For the cash flow analysis, the annual maintenance costs of the skid were assumed to be 2.5 % of the total capital cost. The internal rate of return (IRR) was determined for a period of 10 years. An income tax rate of 35 % was considered for the cash flow analysis.

Selamectin Case: Acetone and Acetonitrile

Overview. The first homogenous binary solvent system investigated was an acetonitrile and acetone waste mixture. This case study has been provided by Pfizer, Inc. from their Kalamazoo, Michigan plant. This mixture is a waste stream from the production of selamectin (the active ingredient in the drug Revolution®) that contains 72 % wt. acetonitrile in acetone. Selamectin is the API in the drug Revolution®; a topical monthly parasite treatment for both cats and dogs. The final drug formulation is composed of isopropyl alcohol, dipropylene glycol methyl ether, and selamectin which makes up between 7-14% of the total composition of the drug.[60] Revolution® is effective in killing a number of different parasites, such as fleas and a variety of worms. The drug also controls ear mite, sarcoptic mange, and tick infestations. The drug is applied topically, absorbed through the skin, and is distributed throughout the body by means of the bloodstream.[61]

Selamectin has a molecular weight of 770 g/mol and formula $C_{43}H_{63}NO_{11}$[62]. According to the current patent, the process for preparing selamectin is comprised of four major steps. The first step is the catalytic hydrogenation of doramectin in acetone. This intermediate step yields 25-cyclohexyl-22,23-dihydroavermectin. This product is isolated by filtration and separated from the acetone. Step two involves oxidation of this product in the presence of manganese dioxide in an organic solvent to yield 25-cyclohexyl-22,23-dihydro-5-ovoavermectin. This product may or may not be crystallized depending on the process and the key intermediate. Step three is the reaction of this product with hydroxylamine hydrochloride. This produces the final product. Step four consists of purifying the product by crystallization from toluene. The product is then dried to a powder under a vacuum. The final product is 25-cyclohexyl-22,23-dihydro-5-hydroyimino-avermectin, or selamectin. The yields are based on the activity of the doramectin starting product and whether or not the product from step two is cystallized.[63]

In recent years, Pfizer has on a global basis recovered approximately 60 % of solvents used, and incinerated approximately 40%. A significant portion of this 40 % is not typically recovered because the individual stream volumes are between 10,000 to 20,000 gallons, which is too small for existing solvent recovery systems. The acetone-acetonitrile waste stream was selected for this conceptual study because it had the most economic value and the highest potential for both economic and environmental savings, from a list of such smaller volume waste streams being generated at the time.

Two process waste streams, resulting from a step in the production of an intermediate (called SEL), contain recoverable acetonitrile and acetone that must be separated before reuse. Both streams are distillate waste streams, and are combined to form a stream containing 28 % wt. acetone and 72 % wt. acetonitrile at ambient conditions. Figure 13 shows the output of step 1 for making the API and the waste stream specific to the production of selamectin. Table 6 contains the process specifications, which are based on the combined waste stream to be processed by the recovery system in Figure 13.

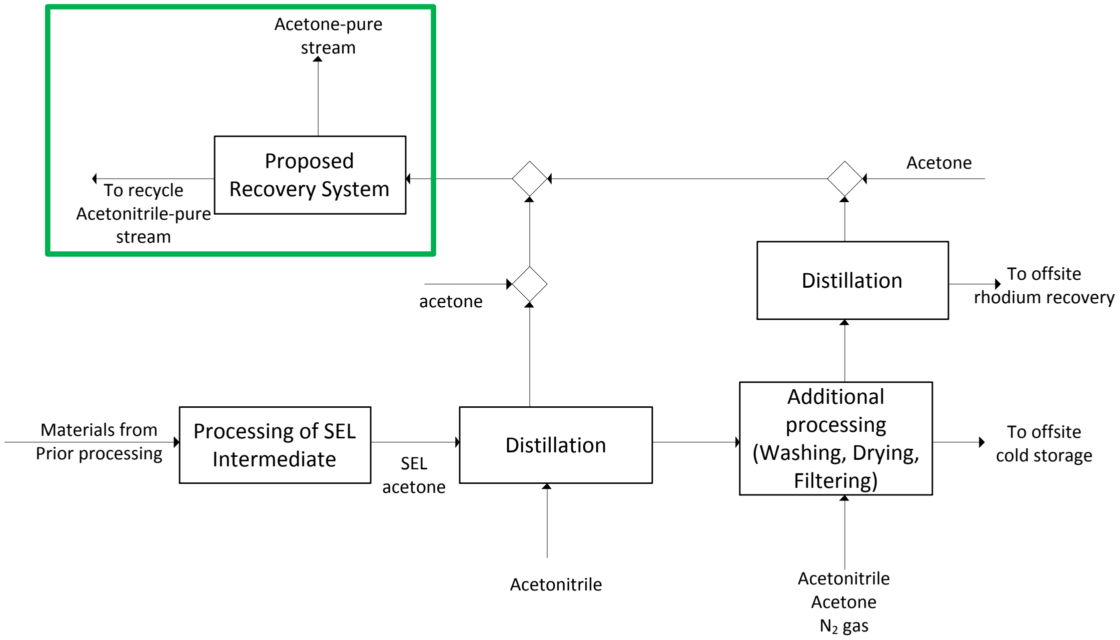


Figure 13. Simple PFD for waste recovery of acetonitrile/acetone. The green square highlights the location of the proposed recovery in the API manufacturing process.

Table 6. Selamectin case waste stream characterization

	Acetone	Acetonitrile	
Mass Fraction	0.28	0.72	
Mole Fraction	0.22	0.78	
Volume Fraction	0.28	0.72	
Purchase Cost (US$/kg)	1.03	4.07	
Incineration Cost (US$/kg)	0.129		Total
Mass (kg/yr)	23,660	60,840	84,500
Cost (US$/yr)	24,370	247,619	271,989

Acetonitrile is a commonly used solvent in many organic and inorganic syntheses. According to the 2010 TRI, acetonitrile ranks fourth for chemical wastes generated by the pharmaceutical and medicinal sectors. Acetone is another common solvent used in the pharmaceutical industry. Acetonitrile is usually acquired as a by-product of the propylene ammoxidation process for acrylonitrile production.[64] This solvent has favorable properties for many chemical reactions. Some of these properties of acetonitrile are low acidity, low boiling point, low viscosity, and low chemical reactivity.[65]

Beginning in fall of 2008, a worldwide shortage of acetonitrile developed. The shortage caused prices for acetonitrile to rise drastically. One of the largest factors affecting the acetonitrile shortage is the current state of the economy. Acrylonitrile is used in manufacturing non-essentials, such as automobiles, carpets, acrylic and carbon fibers, luggage, small appliances, telephones, computer housings, and other products. Since the demand for these commodities has decreased, so has the production of acrylonitrile and thus acetonitrile[65].

Table 7 shows different environmental indicators of acetonitrile and acetone. The physical and chemical properties of acetone and acetonitrile are listed in Table 8. Acetonitrile and acetone are fully miscible in each other and in water.

Table 7. Acetonitrile and acetone toxicity and environmental exposure limits

Solvent	TLV[a]	PEL[b]	LC50[c]	LD50[d]	Carcinogenicity
Acetonitrile	20 ppm	40 ppm	7.551 g/m^3 8 hours (Rat)	50 mg/kg (Rabbit)	EPA Group D (Inadequate evidence for human cancer)[66]
Acetone	500 ppm	1000 ppm	44 g/m^3 4 hours (Mouse)	5340 mg/kg (Rabbit)	EPA Group D (Inadequate evidence for human cancer)[67]

[a] The Threshold Limit Value (TLV) is the amount of a substance that an individual can be exposed to for 8 hours a day and 5 days a week, without adverse health effects.

[b] The Permissible Exposure Limit (PEL) is the legal limit in the United States for the exposure of an individual to a substance.

[c] The discharge limits are given in LC50, which is the lethal concentration of a chemical in the air that kills half of the population.

[d] The LD50 is the lethal dose of a substance that is required to cause death to half of the tested population.

Table 8. Physical and chemical properties

Solvent	Molecular Weight	Density at 25°C	Solubility in water (g/100g)	Boiling Point at 1 atm
Acetonitrile	41.05 g/mole	0.781 g/mL	Miscible	81.6°C
Acetone	58.08 g/mole	0.786 g/mL	Miscible	56.5°C

Thermodynamic Evaluation and Recovery Process Design. A *T-x-y* and *x-y* equilibrium diagrams for the acetone-acetonitrile system is provided in Figure 14 and Figure 15[68]. These diagrams show the absence of an azeotrope, therefore distillation is a viable separation option. The required purity for reuse is 98 wt. % for both solvents. Because the conceptual skid has only one distillation column, the recovery of acetone and acetonitrile cannot be performed simultaneously. It was tried to accomplish but the 8 stages of the skids distillation column were not sufficient. The recovery of acetonitrile through the bottoms of the distillation was simulated first because it is the target solvent. Distillation bottoms products usually contain more impurities than distillates, but it should be reminded that both acetone and acetonitrile streams that compose the final waste mixture come from distillates. The distillate of the first recovery was used later to recover acetone in the same column. The proposed recovery scheme is presented in Figure 16.

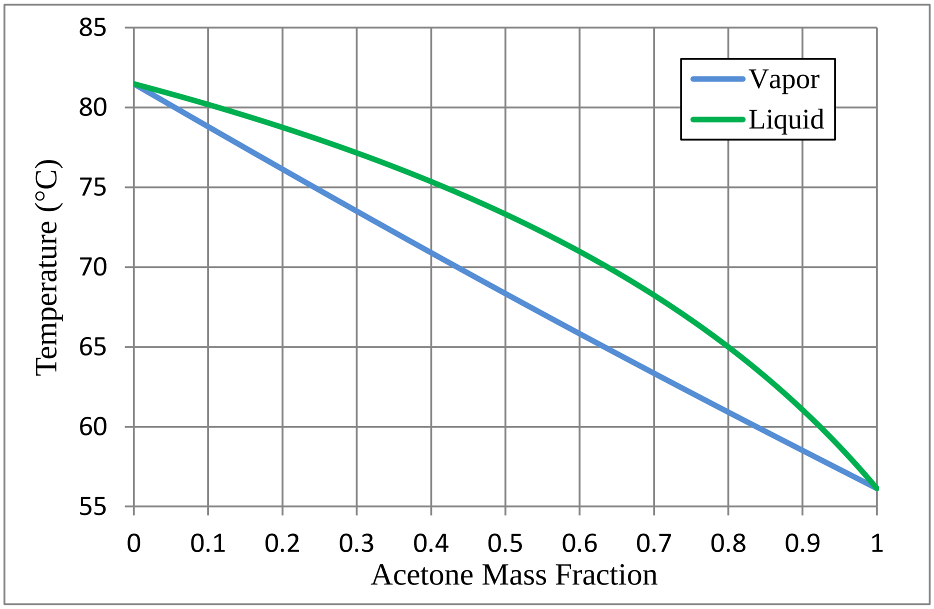


Figure 14. Vapor-liquid equilibrium *T*-*x*-*y* diagram for acetone and acetonitrile at P = 1.0 atm. Generated in Aspen Plus® with UNIQUAC.

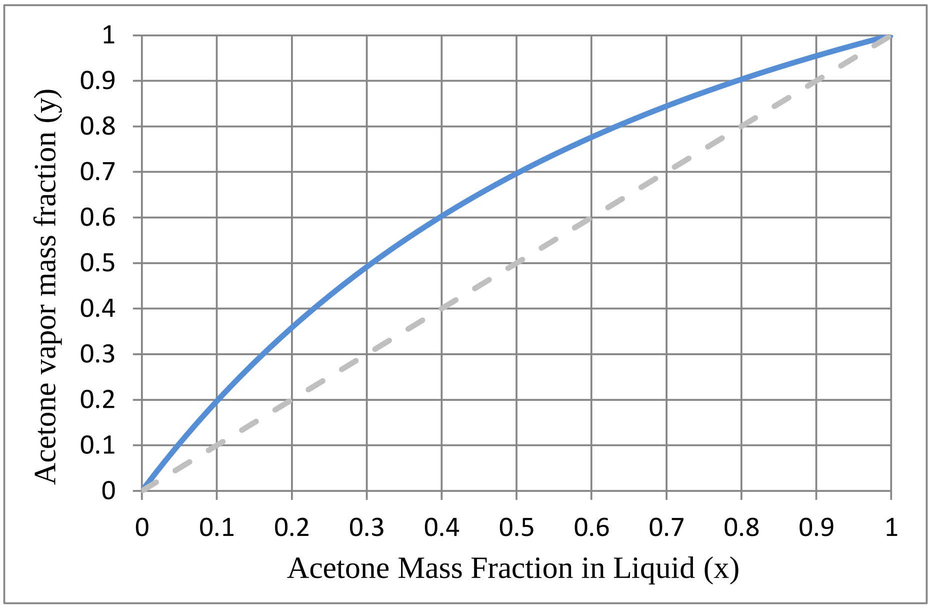


Figure 15. Vapor-liquid equilibrium *x*-*y* diagram for acetone and acetonitrile at P = 1.0 atm. Generated in Aspen Plus® with thermodynamic property method UNIQUAC.

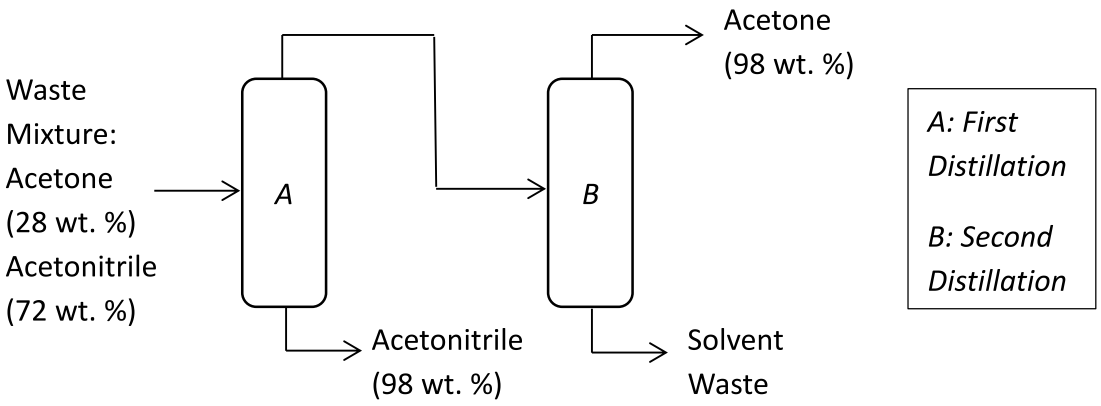


Figure 16. Acetonitrile and acetone recovery scheme in the selamectin case.

Life Cycle Assessment. LCIs for the production and incineration of both acetonitrile and acetone were obtained from SimaPro® and Ecosolvent, respectively. Detailed information regarding acetone and acetonitrile manufacture and incineration LCI's is included in Appendix F. The total emissions for the production of the solvent were opened up in three categories; emissions to air, soil, and water. Major pollutants in each category are shown. Emissions to air include CO_2, carbon monoxide (CO), nitrogen oxides (NO_x), non-methane volatile organic compounds (NMVOCs), particulates, and sulfur dioxide (SO_2). Specified emissions to water are volatile organic compounds (VOCs).

The total emissions to the environment for the production of 1 kg of acetone are 1.86 kg. This value is driven by air emissions, which total 1.83 kg. CO_2 constitutes 98 % of the air emissions with other gases, mostly methane, a greenhouse gas, comprising the remaining 2 %. The total emissions from the manufacture of acetonitrile are 2.12 kg per kg of acetonitrile, comparatively larger than the 1.86 kg of emissions from the manufacture of 1 kg of acetone. Similar to the LCI for acetone, 93% of the total emissions are released to air. 1.95 kg of the 1.97 kg of total air emissions are attributed to CO_2. The other 0.2 kg is made up of a variety of gases, mostly greenhouse gases. The process that is used in the SimaPro® calculation for the emissions of acetonitrile is the SOHIO process, where acetonitrile is actually a by-product of the production of acrylonitrile. Nearly all of the acrylonitrile produced in the world today is produced using the SOHIO process. The primary by-products of the process are hydrogen cyanide, acetonitrile, and carbon oxides.[69]

Both manufacturing processes have high Cumulative Energy Demand (CED). The CED includes energy from both renewable resources such as water, wind or solar, and biomass, and non-renewable energy such as nuclear or fossil fuels. To make 1 kg of acetone and 1 kg of acetonitrile, 64.8 MJ-Eq and 58.6 MJ-Eq of energy are required, respectively.

LCIs were developed for the utilities used by the Kalamazoo plant in SimaPro®. These utilities LCIs will be included in R.SWEET to model recovery processes in the Kalamazoo plant: Selamectin Case, Nelfinavir Case and Hydrocortisone Case. The detailed LCI for the Kalamazoo utilities can be seen in Appendix G.

Nelfinavir Case: IPA and THF

Overview. Nelfinavir Mesylate (Nelfinavir) is the API in the drug Viracept®. Viracept® is an antiretroviral protease inhibitor that is used in the treatment of the human immunodeficiency virus (HIV). The final drug formulation is composed of calcium silicate, colloidal silicon dioxide, magnesium stearate, and Nelfinavir which makes up between 47-61% of the total composition of the drug.

Nelfinavir has a molecular weight of 568 g/mol and formula $C_{32}H_{45}N_3O_4S$.[70,71] According to the chemical's MSDS, as of 2009 the environmental effects of Nelfinavir have yet to be determined. It is suggested that any releases to the environment should be avoided.[71]

The nelfinavir waste stream studied was composed of 86 % wt. isopropyl alcohol (IPA) and 14 % wt. tetrahydrofuran (THF). The IPA in this waste stream must be recovered at 98 % wt. purity to be reused. Table 9 contains the solvent waste specifications.

Table 9. Nelfinavir waste stream characterization

	IPA	THF	
Mass Fraction	0.86	0.14	
Purchase Cost(US$/kg)	1.49	2.97	
Incineration Cost (US$/kg)	0.129		Total
Mass (kg/yr)	67,682	11,018	78,700
Cost (US$/yr)	100,846	32,723	133,569

THF is a common solvent used in the pharmaceutical industry. IPA has favorable properties for many chemical reactions, including the ability to quickly dissolve non-polar compounds, low toxicity, and quick evaporation capability.[72] Table 10 shows different environmental indicators for IPA and THF. Physical and chemical properties of IPA and THF are listed in Table 11. IPA and THF are fully miscible.

Table 10. IPA and THF environmental exposure limits and toxicity information

Solvent	TLV[a]	PEL[b]	LC-50[c]	LD-50[d]	Carcinogenicity
IPA[73]	400 ppm	500 ppm	16000 mg/kg 8 hours (Rat)	3600 mg/kg (Mouse)	IARC Group 3 (Not cancerous to humans)
THF[74]	250 ppm	250 ppm	24 g/m^3 4 hours (Mouse)	1650 mg/kg (Rat)	Group D (Inadequate evidence for human cancer)

[a] The Threshold Limit Value (TLV) is the amount of a substance that an individual can be exposed to for 8 hours a day and 5 days a week, without adverse health effects.

[b] The Permissible Exposure Limit (PEL) is the legal limit in the United States for the exposure of an individual to a substance.

[c] The discharge limits are given in LC50, which is the lethal concentration of a chemical in the air that kills half of the population.

[d] The LD50 is the lethal dose of a substance that is required to cause death to half of the tested population.

Table 11. IPA and THF physical and chemical properties

Solvent	Molecular Weight	Density at 25°C	Solubility in water (g/100g)	Boiling Point at 1 atm
IPA	60.1 g/mole	0.79 g/mL	Miscible	82.5°C
THF	72.11 g/mole	0.89 g/mL	Miscible	66.1°C

Thermodynamic Evaluation and IPA Recovery Process Design. A *T*-*x*-*y* and *x*-*y* equilibrium diagrams for the IPA-THF system are provided in Figure 17 and Figure 18, respectively[68]. As can be seen, the solution forms a homogeneous non-azeotropic mixture. At the vicinity of a THF mass fraction of 1, the relative volatility of both components is close to 1, making the vapor and liquid equilibrium lines to be very close to each other. This suggests that distillation is not a viable separation option for obtaining high purity THF. The vapor-liquid equilibrium close to an IPA mass fraction of 1 is favorable for distillation, which means that high purity IPA can be obtained with this separation technique. The separation scheme for the nelfinavir case is shown in Figure 19.

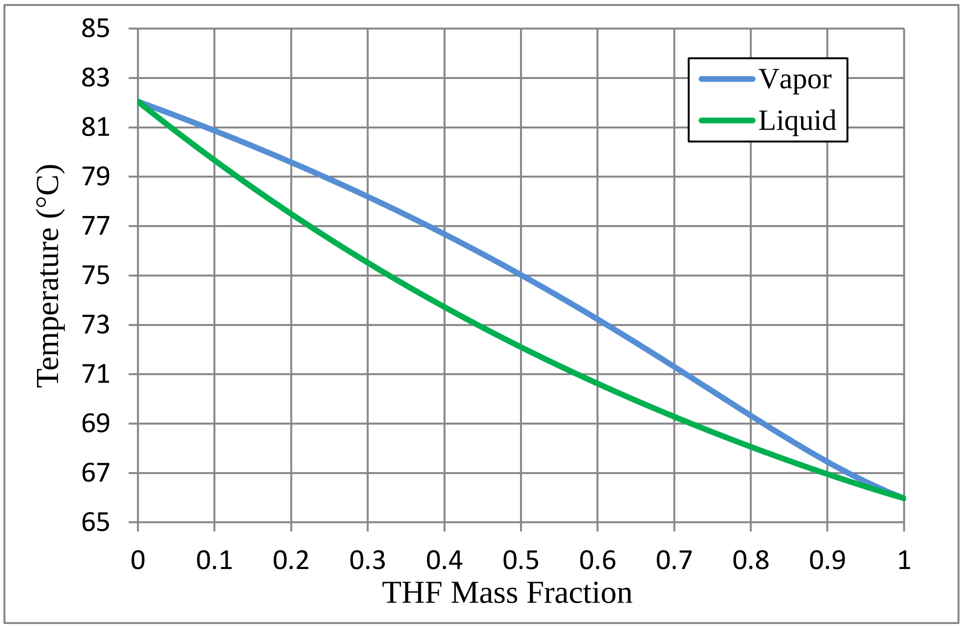


Figure 17. Vapor-liquid equilibrium *T-x-y* diagram for the IPA and THF at P = 1 atm, generated in Aspen Plus® with thermodynamic property method UNIQUAC.

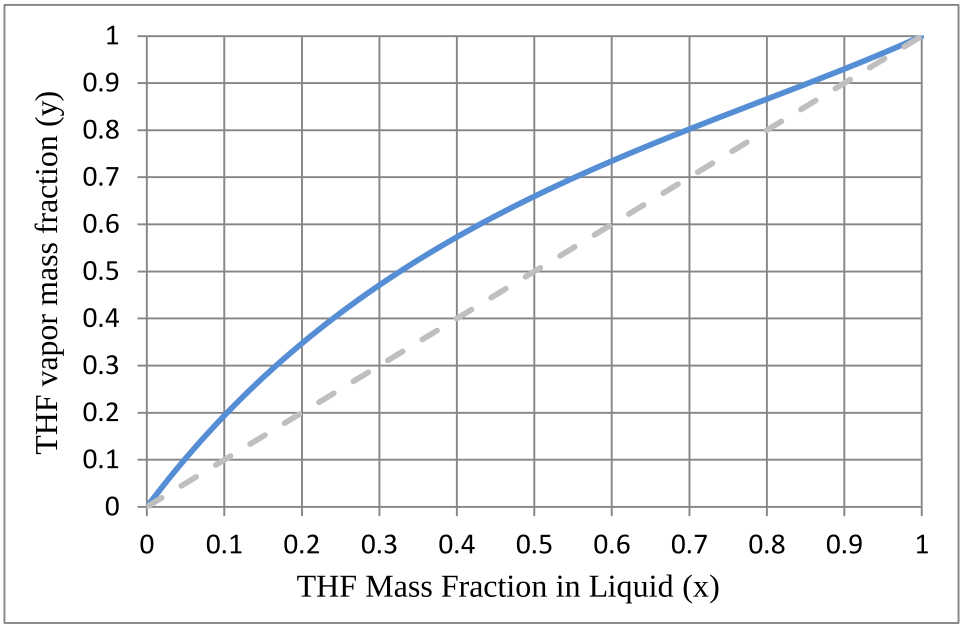


Figure 18. Vapor-liquid equilibrium *x-y* diagram for IPA and THF at P = 1 atm, generated in Aspen Plus® with thermodynamic property method UNIQUAC.

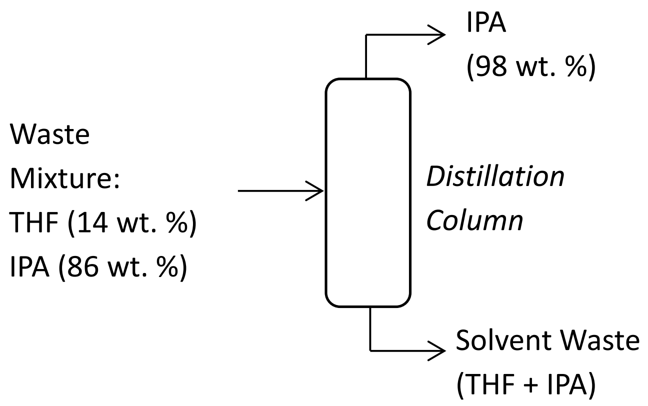


Figure 19. IPA recovery scheme in the nelfinavir case.

Life Cycle Assessment. The total emissions to the environment are 2.20 kg per 1 kg of IPA manufactured. Air emissions make up 1.66 kg of the total emissions with 1.63 kg of emissions from carbon dioxide. The total emissions from the manufacture of 1 kg of THF are 5.65 kg. The majority of the emissions are released to the air. Air emissions attributed to CO_2 are 5.46 kg of the 5.52 kg of total air emissions. The remaining 0.06 kg is made up of a variety of greenhouse gases and other pollutants. Both manufacturing processes have a high CED. The manufacture of 1 kg of IPA and 1 kg of THF require 60.1 MJ-Eq and 128 MJ-Eq, respectively. For both THF and IPA, the majority of this energy is supplied by non-renewable fossil fuels as seen in Appendix G.

The process that is used in the SimaPro® calculation for the emissions of THF is the manufacture of THF from 1,4-butanediol in Europe, while IPA is a readily available organic solvent that is produced from the synthesis of water and propene. The detailed LCIs for THF and IPA can be seen in Appendix F. The LCA for the base process is detailed in Appendix H.

Hydrocortisone Case: Toluene and Acetone

Overview. Hydrocortisone acetate is a topical, oral, or intravenous corticosteroid which works to prevent inflammation. Inflammation or swelling is prevented by lowering the formation, release, and activity of different cells and chemicals in the body. Hydrocortisone is typically used for allergic reactions and skin conditions including eczema, psoriases, and rashes. Hydrocortisone acetate has a molecular weight of 404.5 g/mol and a formula of $C_{23}H_{32}O_6$[75]. Hydrocortisone acetate is an API in the drug TriOptic S®. TriOptic S® is a treatment for bacterial infections in the eyelid and conjunctiva in dogs and cats. The medication is administered 3-4 times daily in a thin film over the cornea. The final drug formula is composed of bacitracin, neomycin, polymyxin, and hydrocortisone acetate which makes up approximately 1% of the total composition of the drug.[76]

TriOptic S is effective in bactericidal action against both gram negative and gram positive bacteria which may infect the eye. TriOptic S® combines the APIs found in Trioptic P along with hydrocortisone acetate, which is an anti-inflammatory agent. TriOptic S allows for bactericidal action and prevention of inflammation in the anterior of the eye.

The process waste stream from the Kalamazoo plant production of hydrocortisone acetate contains toluene and acetone which must be separated before reuse. The solvent waste stream is composed of 79.3 % wt. toluene, 8.0 % wt. acetone, 10.0 % wt. water, and 2.7 % wt. branched octane with trace cyanide at 30 ppm. Branched octane is a term used by Pfizer which refers to an Exxon Mobile product called Isopar™ C. Table 12 shows the process specifications for the solvents of interest in the process waste stream: toluene and acetone.

Toluene is an organic solvent which is used in pharmaceutical syntheses because of its solubility with APIs and intermediates. According to the TRI from 2010, toluene ranks second for chemical wastes generated by the pharmaceutical and medicinal sectors at 5,310,000 kg/year. Toluene is acquired as a byproduct of the production of fuels such as gasoline and coke.

Environmental indicators for acetone and toluene are shown in Table 13.

Table 12. Hydrocortisone solvent waste stream characterization

	Toluene	Acetone	
Mass Fraction	0.79	0.08	
Mole Fraction	0.535	0.085	
Volume Fraction	0.763	0.085	
Purchase Cost (US$/kg)	0.92	1.03	
Incineration Cost (US$//kg)	0.129		Total
Mass (kg/yr)	233,913	23,687	257,600
Cost (US$/yr)	215,200	24,398	239,598

Table 13.Environmental exposure limits for solvents from 5C waste stream

Solvent	TLV[a]	PEL[b]	LC50[c]	LD50[d]	Carcinogenicity
Acetone	500 ppm	1000 ppm	44 g/m^3 4 hours (Rat)	5340 mg/kg (Mouse)	EPA group D (Inadequate Evidence for human cancer)
Toluene	50 ppm	300 ppm	49 g/m^3 4 hours (Rat)	636 mg/kg (Rat)	Group A4 (Not classifiable for human)

[a] The Threshold Limit Value (TLV) is the amount of a substance that an individual can be exposed to for 8 hours a day and 5 days a week, without adverse health effects.

[b] The Permissible Exposure Limit (PEL) is the legal limit in the United States for the exposure of an individual to a substance.

[c] The discharge limits are given in LC50, which is the lethal concentration of a chemical in the air that kills half of the population.

[d] The LD50 is the lethal dose of a substance that is required to cause death to half of the tested population.

Physical and chemical properties of acetone and toluene are listed in Table 14. Only acetone is fully miscible in water; however toluene and acetone are miscible in each other.

Table 14. Physical and chemical properties for hydrocortisone's case waste stream[66]

	Molecular Weight	Density at 25°C	Solubility in water (g/100g)	Boiling Point at P = 1 atm
Acetone	58.08 g/mole	0.786 g/mL	Miscible	56.5°C
Toluene	92.14 g/mole	0.86 g/mL	0.561	110.6°C

Thermodynamic Evaluation and Recovery Process Design. Water and branched octane can be almost fully removed from the mixture by decanting. Additional tanks and a decanter are required. After decanting, the waste stream contains only 0.8 % wt. branched octane and 0.06 % wt. water. These small amounts allow for separation of toluene and acetone by distillation. Therefore, the mixture was assumed to be binary for the purpose of being evaluated with R.SWEET. For the toluene to be recycled back to the process, the contaminants can only make up 0.02 wt. % of the recycled stream. On the other hand, acetone's mass purity specification for recycling is 98 wt. %. A *T*-*x*-*y* and *x*-*y* equilibrium diagrams for the acetone-toluene system are provided in Figure 20 and Figure 21. The absence of an azeotrope and the high relative volatility suggests that both pure acetone and acetonitrile can be recovered through distillation. The recovery scheme is shown Figure 22. As can be seen, one distillation suffices to recover both solvents. The analysis performed to reach this conclusion is detailed in Chapter 4.

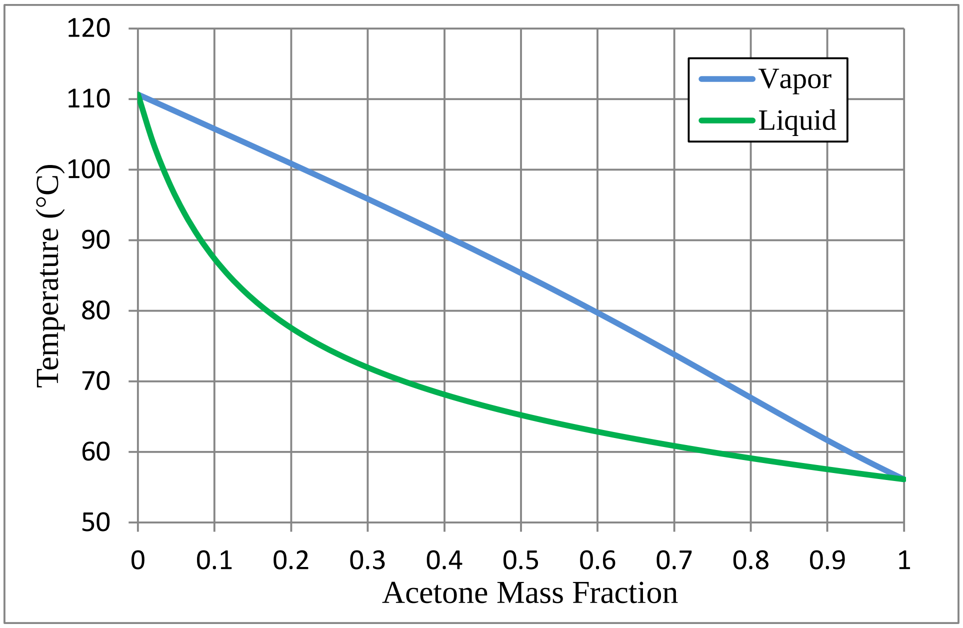


Figure 20. Vapor-liquid equilibrium *T*-*x*-*y* diagram for acetone and toluene at P = 1 atm. Generated in Aspen Plus® with thermodynamic property method UNIQUAC.

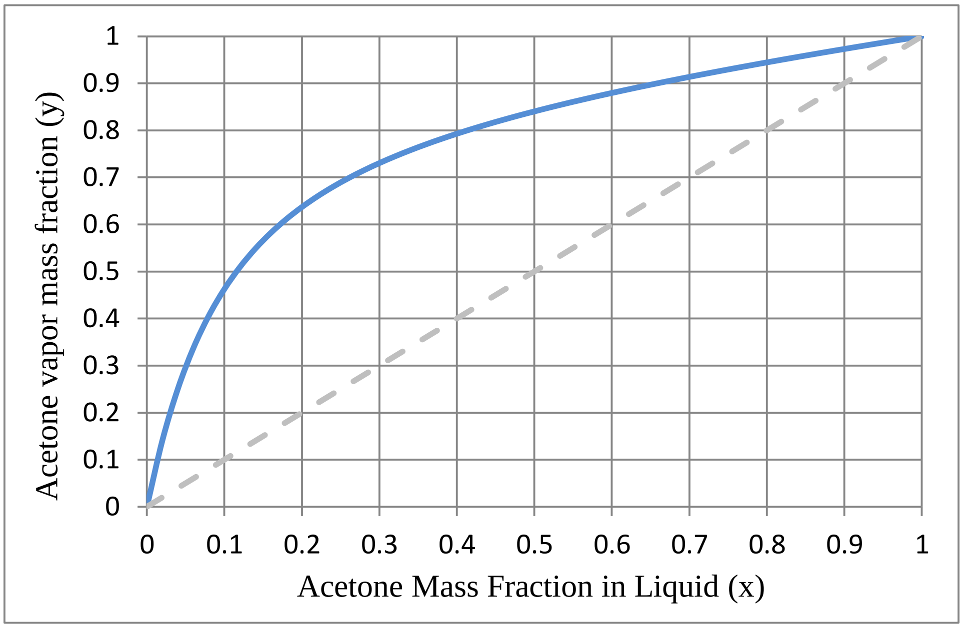


Figure 21. Vapor-liquid equilibrium *x*-*y* diagram for acetone and toluene at P = 1 atm. Generated in Aspen Plus® with thermodynamic property method UNIQUAC.

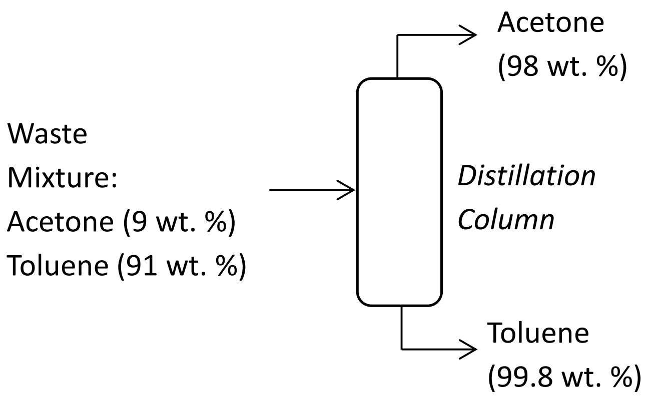


Figure 22: Toluene and acetone recovery scheme in the hydrocortisone case.

Life Cycle Inventory. The detailed LCIs for toluene and acetone are included in Appendix F. The total emissions to the environment are 1.21 kg per 1 kg of toluene manufactured. Air emissions make up almost all of the total emissions, with 1.19 kg of emissions from CO_2. Toluene manufacture requires 61.9 MJ-Eq of energy per kg. The majority of this energy is supplied by fossil fuels as seen in Appendix G. The LCA for the base process can be seen in Appendix H.

Celecoxib Case: IPA and Water

Overview. A solvent waste stream composed of isopropanol (IPA) and water is produced from the manufacture of the Celecoxib, the API of the drug Celebrex®. This API is made at Puerto Rico and Singapore plants. In 2007, the Barceloneta plant in Puerto Rico generated 5.5 kilotons of waste per year, containing mainly IPA, at 46.8 wt. %, and water.

This solvent waste is generated from multiple waste streams, with varying compositions of isopropanol, ethanol, methanol, water and dissolved solids. Because the presence of lower alcohols was in small concentrations, for the purpose of this study, the waste was simplified to an IPA and water binary system.

Thermodynamic Analysis and Recovery Process Design. Conventional distillation is limited in obtaining pure IPA from the waste, since water forms an azeotrope with IPA at 87.8 % wt. The azeotrope is not pressure sensitive, which limits the use of pressure-swing distillation. The T-x-y and x-y vapor liquid equilibrium diagram for IPA and water is provided in Figure 23 and Figure 24.

In 2008, a design case study has been performed by Rowan University with Pfizer through a prior EPA grant, "Advancing P2 in Pharmaceutical Manufacturing"[77]. The manufacturing operation at their plant in Barceloneta, Puerto Rico, was evaluated and several green engineering alternatives for the purification and recovery of isopropanol from waste streams proposed. A conceptual study of distillation, extraction, reactive distillation, adsorption, and membrane-based processes was performed. Several green design approaches were evaluated using distillation combined with either molecular sieve adsorption or membrane pervaporation. These process schemes appear to have the most promise to effectively purify and recover isopropanol. In addition, the dehydration of isopropanol has been extensively covered in scientific literature and a combination of distillation and pervaporation units has been suggested for solvent recovery.[35,54,78,]

Distillation to the azeotrope was proposed as the first step in a sequential separations train followed with a more advanced separation operation. Pervaporation is one of several unit operations that can be used in combination with distillation in the separation of azeotropic solvent mixtures. The recovery of isopropanol using distillation followed by pervaporation was simulated and optimized using R.SWEET. The distillation column was set to obtain a distillate with an IPA mass purity of 85 % wt., which was sent to a pervaporation unit, set to obtain a mass purity of 99 % wt. The feed to the pervaporation unit was heated from the distillate temperature of around 80 °C to 95 °C, in order to increase mass transfer through the membrane. The inter-module heaters outlet temperature was 95 °C as well. The flow rate to the pervaporation unit was determined as the distillate flow rate in the celecoxib case, to ensure a continuous operation (the IPA and water azeotrope is obtained in the distillate while water is obtained in the bottoms). The recovery scheme of the celecoxib case is provided in Figure 25. A distillate containing a composition of IPA 85 % wt. was obtained in the distillation column and sent to the pervaporation unit to dehydrate the stream and achieve a 99.5 % wt. purity.

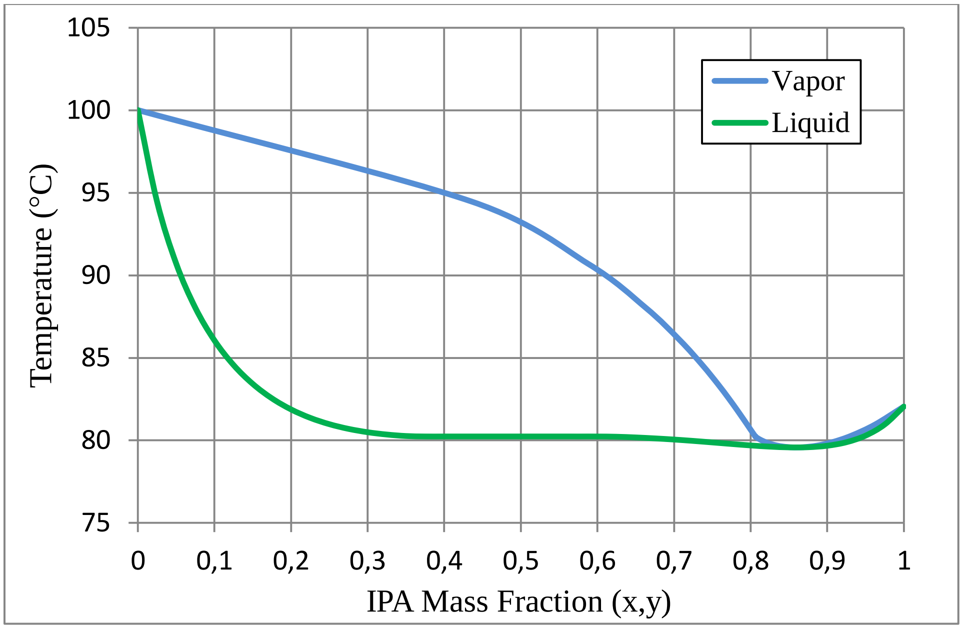


Figure 23. Vapor-Liquid Equilibrium *T-x-y* diagram for IPA and water at P = 1 atm Generated in Aspen Plus® with UNIQUAC

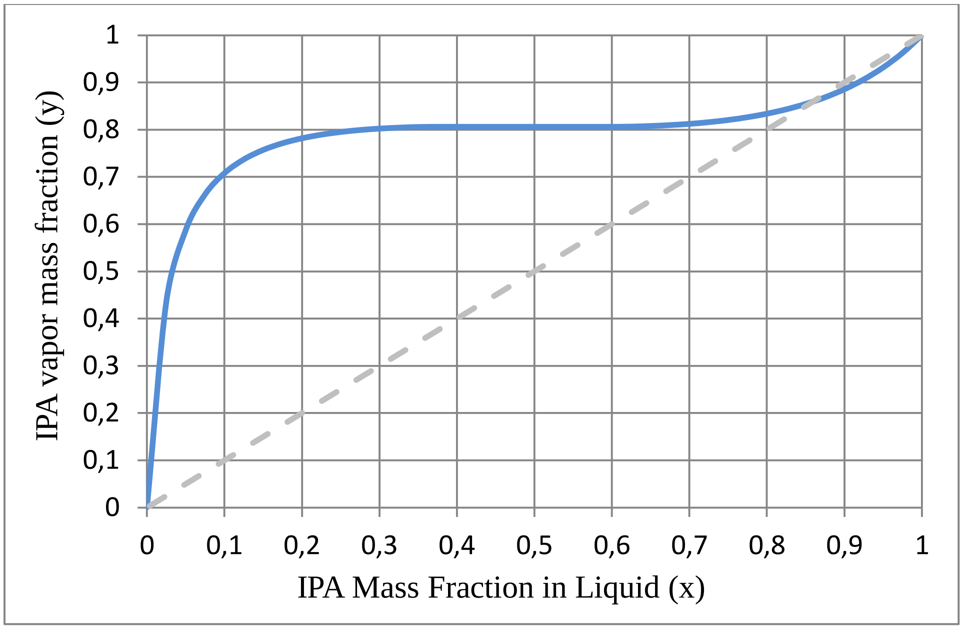


Figure 24. Vapor-Liquid Equilibrium *x-y* diagram for IPA and water at P = 1 atm. Generated in Aspen Plus® with thermodynamic property method UNIQUAC.

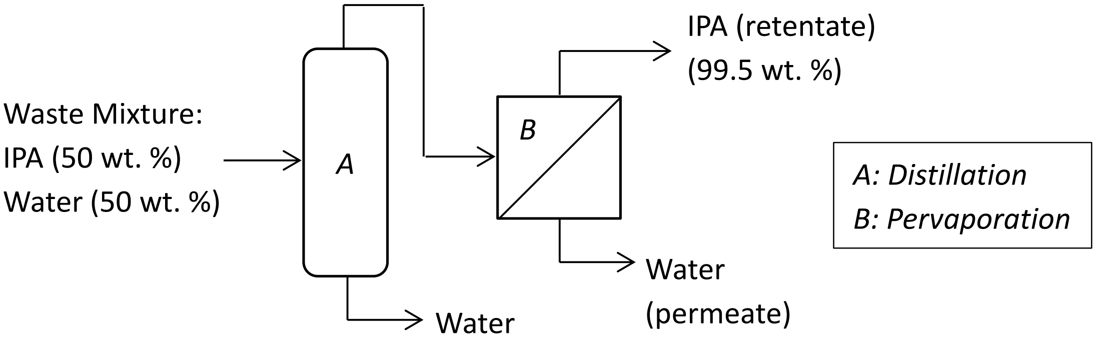


Figure 25. IPA recovery scheme in the celecoxib case.

Life Cycle Analysis. The manufacture and incineration LCIs of isopropanol and ultrapure water are presented in Appendix F. The emissions due to the production of isopropanol were estimated through the direct and indirect hydration of propylene.

The LCI of steam and electricity used at the Puerto Rico plant has already been developed in the document “Advancing P2 in Pharmaceutical Manufacturing”. The LCI of saturated steam at 125 psig and Puerto Rico’s electricity production, used at the plant, is presented in Appendix G.

A LCA comparison between the base and the recovery process is shown in Appendix H. The breakdown of the operating cost in the base case and the recovery case are displayed in Appendix J.

Chapter 4

Results and Discussion

The environmental and economic results of the case studies are summarized in Table 15. Life cycle emissions avoided are calculated as the difference between the base case and the recovery case life cycle emissions. Detailed results of the base case and recovery case life cycle emissions and operating cost savings can be seen in Appendix H and I, respectively. The graphical results of the distillation reflux ratio sensitivity analyses (RRSA) are shown in Figure 26 to Figure 35, while the feed stage sensitivity analyses are presented in Figure 27 to Figure 36. For the purpose of this study, a reflux ratio increment of 1 was used in the RRSA, but shorter increments can be used in R.SWEET to further refine the optimization.

In the selamectin case, the first distillation RRSA for the acetonitrile recovery (Figure 26) shows a maximum LCE avoided (LCEA) at a reflux ratio of 9 and a maximum operating cost savings (OCS) at a reflux ratio of 28. Albeit this difference, at the maximum LCEA, the OCS are 95.1 % of the maximum OCS. In Table 15, the optimum reflux ratio for all the cases corresponds to the one that maximizes LCEA. However, both LCEA and OCS are positive at either maximum; therefore, the recovery system can be operated between these reflux ratio ranges according to the pharmaceutical company's priorities. The meaning of the LCEA maximum is that as the reflux ratio increases up to the maximum, the manufacture and waste incineration LCEA increase at a higher rate than the recovery process emissions. After the maximum, the contrary occurs, which is the reason of the maximum occurrence. This can be seen in Figure 28, in which the slope of the manufacture and incineration LCEA curve is higher than the slope of the recovery process emissions curve at a reflux ratio lower than 9, and lower at a reflux ratio higher than 9. This means that the difference between the manufacture and incineration LCEA and the recovery process emissions generated (Equation 3) are higher at a reflux ratio of 9. The manufacture and incineration LCEA are directly proportional to the recovery, since as more solvent is recovered, more LCE are avoided. This is the reason why in Figure 28 the slope of the recovery curve and the manufacture and incineration LCEA curve are the same. On the other hand, the steam and electricity use are directly proportional to the reflux ratio, which is depicted in the linear increase of the recovery process emissions as the reflux ratio increases.

Using the LCEA optimum reflux ratio, an 84.1 % recovery of acetonitrile is accomplished, which means that, in the recovery case, 9,671 kg of virgin acetonitrile needs to be purchased for the production of selamectin, reduced from 60,840 kg. It should be noted that at the LCEA optimum reflux ratio, the recovery is not maximum, since the ultimate objective is not to recover the highest amount of solvent, but to minimize the environmental impact. The feed stage sensitivity analysis (Figure 27) shows that the optimum feed stage is 4 for both the LCEA and the OCS.

Table 15. Environmental and economic case studies results

<table>
<tr><th colspan="2">Case Study</th><th colspan="2">Selamectin</th><th>Nelfinavir</th><th>Hydrocortisone</th><th>Celecoxib</th></tr>
<tr><td rowspan="5">Emissions Avoided (kg/yr)</td><td>Total[a]</td><td colspan="2">253,600</td><td>63,900</td><td>1,145,000</td><td>11,769,000</td></tr>
<tr><td>to air</td><td colspan="2">246,200</td><td>52,760</td><td>1,144,000</td><td>10,291,000</td></tr>
<tr><td>CO_2[b]</td><td colspan="2">243,900</td><td>52,400</td><td>1,140,000</td><td>10,205,000</td></tr>
<tr><td>to water</td><td colspan="2">7,450</td><td>11,160</td><td>1,200</td><td>1,476,000</td></tr>
<tr><td>to soil</td><td colspan="2">19</td><td>-3</td><td>-6</td><td>728</td></tr>
<tr><td colspan="2">Carbon footprint reduction ($kgCO_2eq$/yr)</td><td colspan="2">253,300</td><td>253,259</td><td>1,145,000</td><td>10,755,000</td></tr>
<tr><td colspan="2">Operating Cost Savings (US$/yr)</td><td colspan="2">236,800</td><td>98,500</td><td>293,300</td><td>4,235,000</td></tr>
<tr><td colspan="2" rowspan="3">IRR (%)</td><td colspan="2">2.3</td><td>-10.2</td><td>6.2</td><td>80.9</td></tr>
<tr><td colspan="4"><i>Combined: 25.3</i></td><td></td></tr>
<tr><td colspan="5"><i>All cases combined: 94.2</i></td></tr>
<tr><td colspan="2" rowspan="3">Payback Period (yr)</td><td colspan="2">8,9</td><td>-</td><td>7.3</td><td>1.2</td></tr>
<tr><td colspan="4"><i>Combined: 3.5</i></td><td></td></tr>
<tr><td colspan="5"><i>All cases combined: 1.1</i></td></tr>
<tr><td colspan="2">Optimum Distillation Parameters</td><td>Acetonitrile recovery
FS[c]: 4
RR[d]: 9</td><td>Acetone recovery
FS[c]: 5
RR[d]: 6</td><td>FS[c]: 3
RR[d]: 4</td><td>FS[c]: 5
RR[d]: 5</td><td>FS[c]: 6
RR[d]: 2</td></tr>
<tr><td colspan="2">Minimum Reflux Ratio (R_m)[e]</td><td>0.99</td><td>0.94</td><td>-</td><td>1.07</td><td>-</td></tr>
<tr><td colspan="2">RR[d]/R_m</td><td>9.1</td><td>9.6</td><td>-</td><td>4.7</td><td>-</td></tr>
<tr><td colspan="2">Mass flow rate (kg/h)[f]</td><td>454</td><td>509</td><td>511</td><td>1,748</td><td>1,112</td></tr>
<tr><td colspan="2">Total operating time (days)</td><td>7.8</td><td>2.7</td><td>6.4</td><td>6.1</td><td>205</td></tr>
</table>

[a] Total emissions is the sum of emissions to air, water and soil. [b] CO_2 emissions are included in the air emissions [c] FS: Feed Stage. [d] RR: Reflux Ratio. [e] Calculated with the Underwood equation. [f] This mass flow rate is the highest allowable to prevent flooding in the distillation column using the optimum distillation parameters

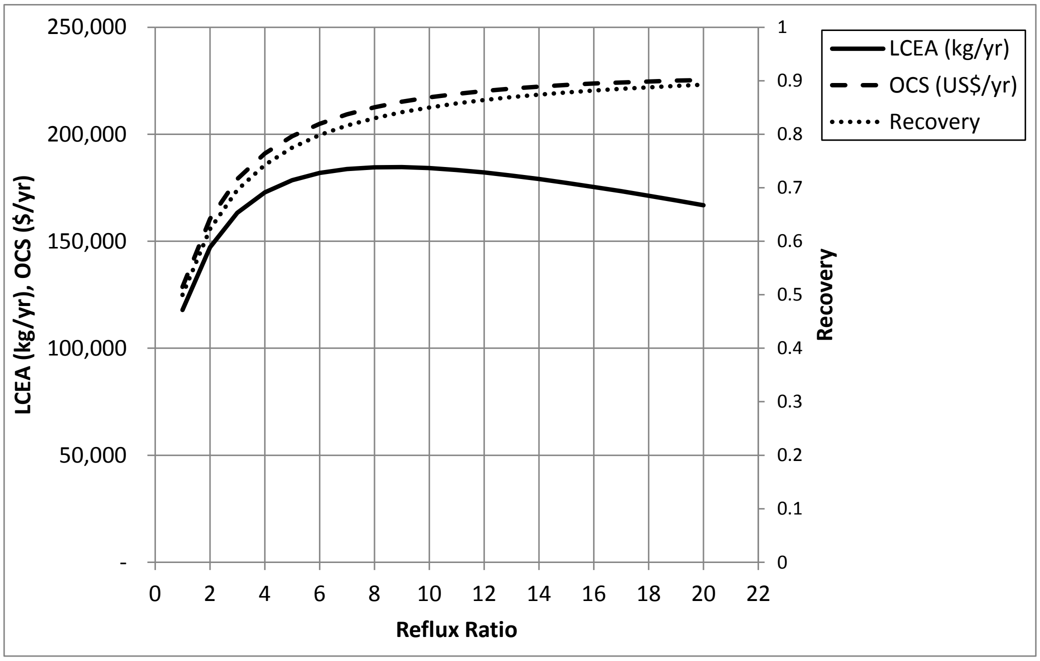


Figure 26. Sensitivity analysis of the LCEA, OCS and recovery with the reflux ratio as the independent variable, for the acetonitrile recovery (first distillation) in the selamectin case study. The feed stage remains constant at the optimum value of 4.

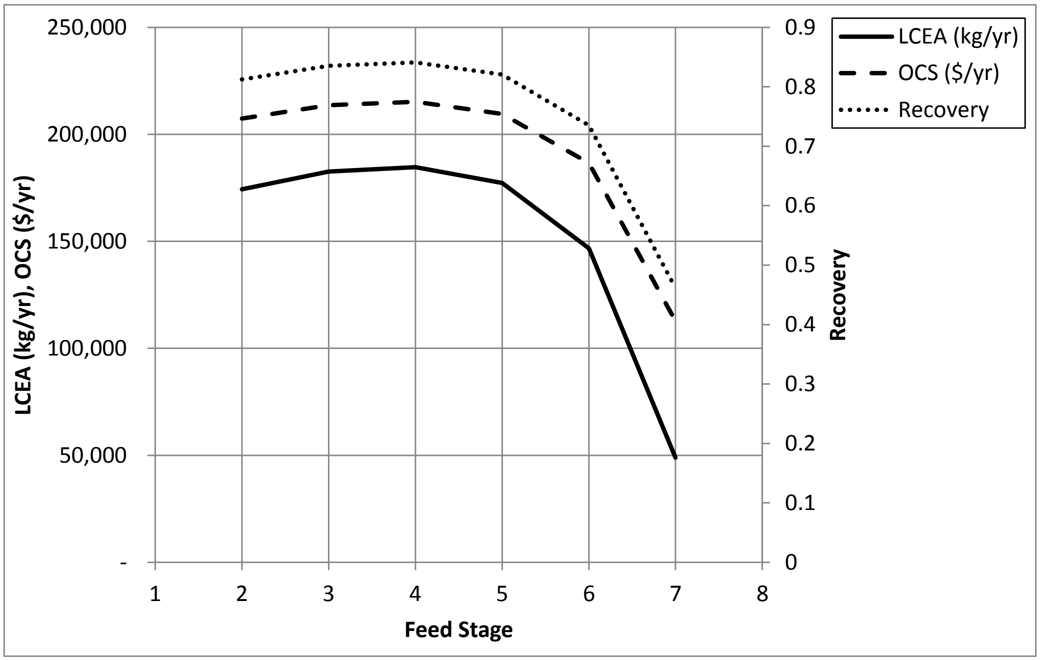


Figure 27. Sensitivity analysis of the LCEA, OCS and recovery with the feed stage as the independent variable, for acetonitrile recovery (first distillation) in the selamectin case study. The reflux ratio remains constant at the optimum value of 9.

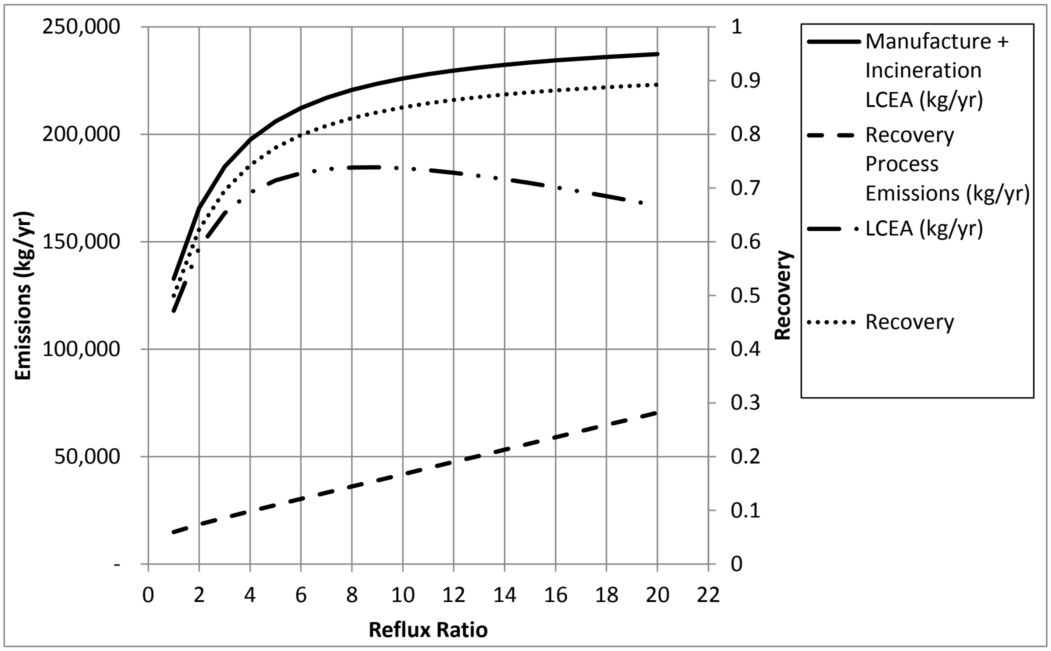


Figure 28. Sensitivity analysis of the manufacture and incineration LCEA, recovery process emissions generated, and recovery with the reflux ratio as the independent variable, for the selamectin case study. The feed stage remains constant at the optimum value of 4.

The second distillation RRSA for the acetone recovery in the selamectin case (Figure 29) shows a maximum LCEA at a reflux ratio of 5 and a maximum operating cost savings (OCS) at a reflux ratio of 8. At the maximum LCEA, the OCS are 98.2 % of the maximum OCS. Again, both LCEA and OCS are positive at either maximum. The feed stage sensitivity analysis (Figure 27) shows that the optimum feed stage is 6 for both the LCEA and the OCS. Using the LCEA optimum reflux ratio, an 85.0 % recovery of acetone is achieved, resulting in the need to purchase 3,385 kg of virgin acetone from an original mass of 23,660 kg.

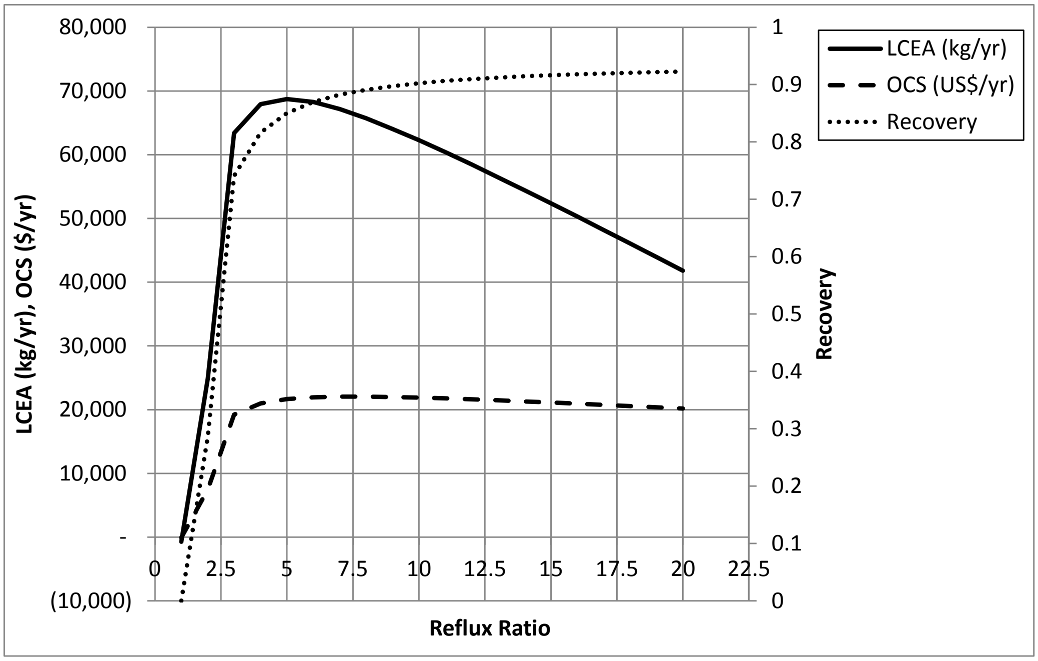


Figure 29. Sensitivity analysis of the LCEA, OCS and recovery with the reflux ratio as the independent variable, for the acetone recovery (second distillation) in the selamectin case study. The feed stage remains constant at the optimum value of 6.

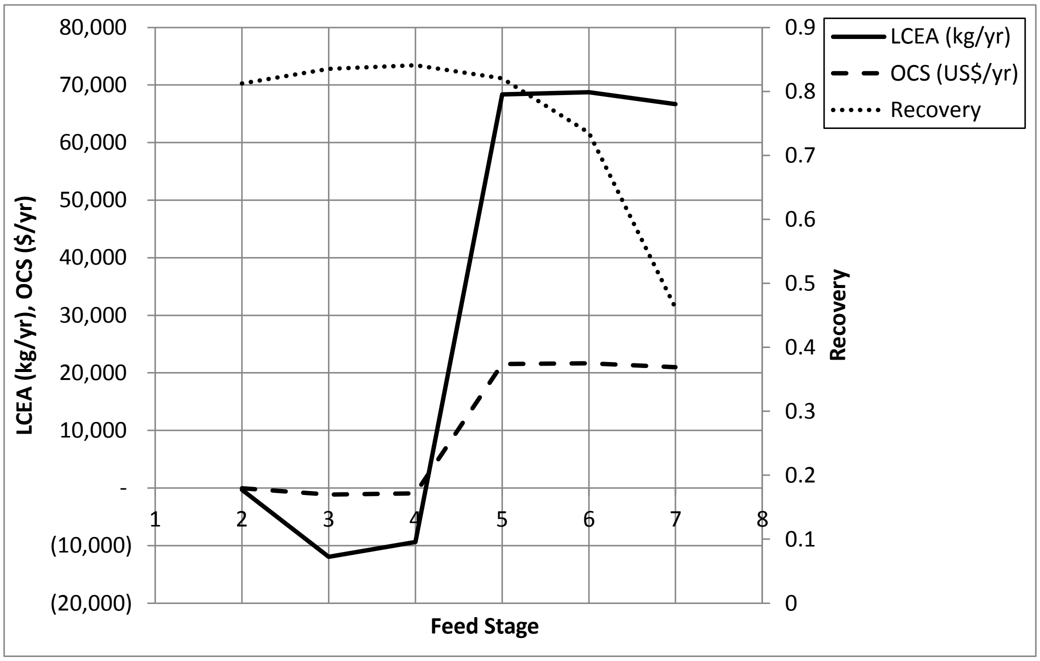


Figure 30. LCEA, OCS and recovery sensitivity analysis with the feed stage as the independent variable, for the acetone recovery (second distillation) in the selamectin case study. The reflux ratio remains constant at the optimum value of 9.

The nelfinavir case RRSA (Figure 31) shows a maximum LCEA at a reflux ratio of 14 and a maximum OCS at a reflux ratio of 28. As in the selamectin case, both LCEA and OCS are positive at either maximum. At the LCEA optimum reflux ratio, the OCS are 98.8 % that of the maximum OCS. The optimum feed stage, for both OCS and LCEA, as 5. At the LCEA optimum reflux ratio, the purchase of virgin IPA for the process is reduced from 67,700 kg/yr to 6,400 kg/yr, being the IPA recovery 90.5 %.

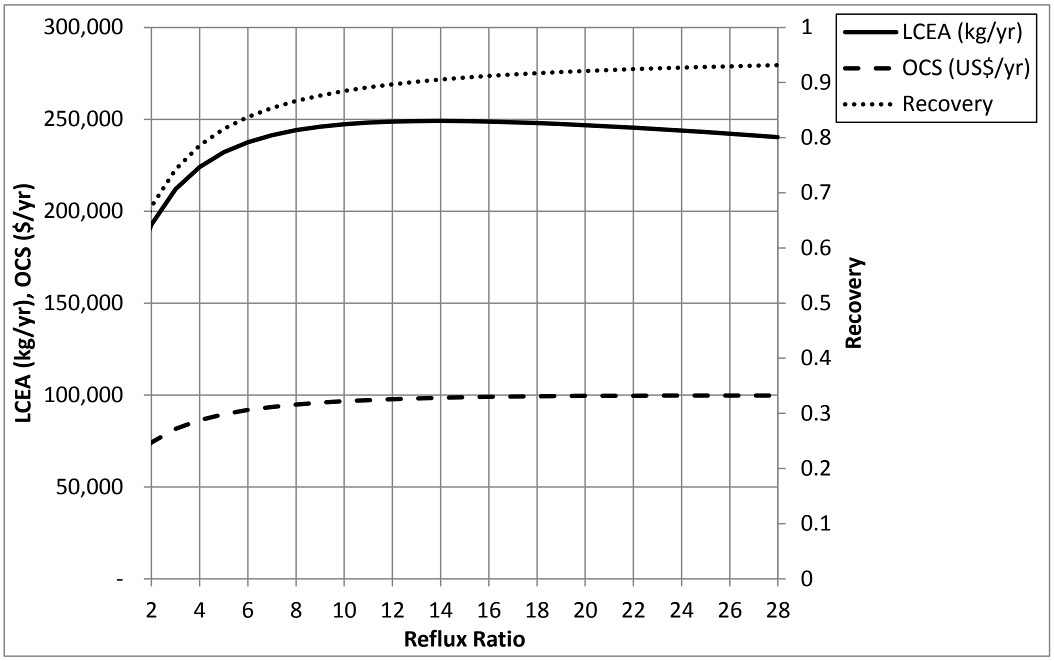


Figure 31. LCEA, OCS and recovery sensitivity analysis with the reflux ratio as the independent variable, for the nelfinavir case study. The feed stage remains constant at the optimum value of 5.

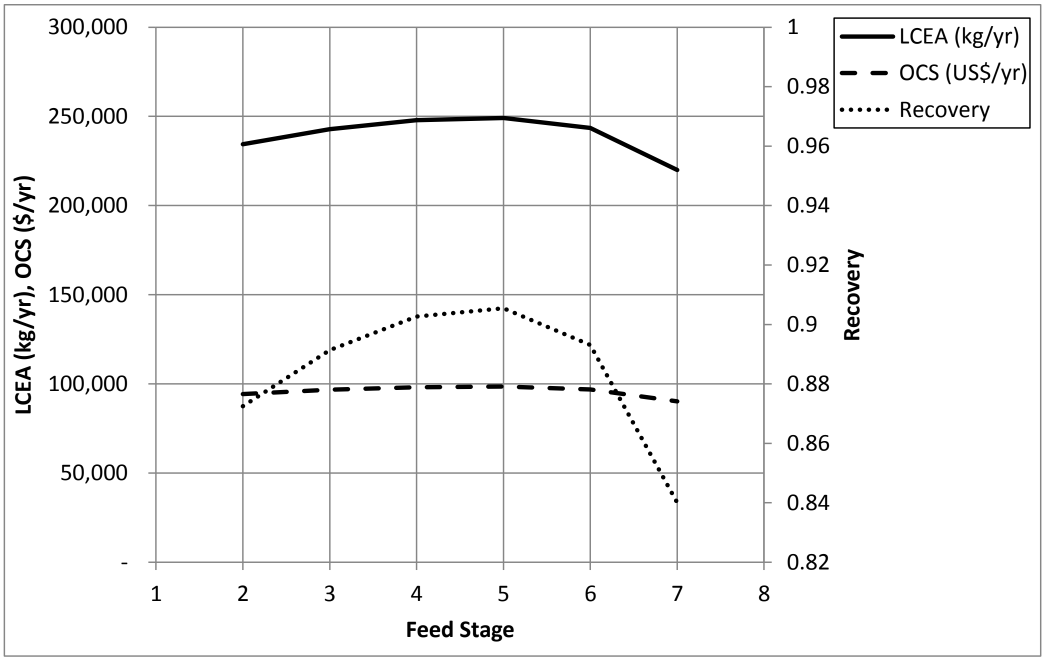


Figure 32. Sensitivity analysis of the LCEA, OCS and recovery with the feed stage as the independent variable, for the nelfinavir case study. The reflux ratio remains constant at the optimum value of 14.

The hydrocortisone case RRSA is shown in Figure 33. This graph shows that both LCEA and OCS curves have a spike at a reflux ratio of 5. The spike occurs because secondary component, acetone, is also being recovered. Below a reflux ratio of 5, the system only targets toluene recovery, but at a reflux ratio of 5 and above, the mass composition of acetone in the distillate is equal or higher than the acetone required purity, justifying its recovery as well. The feed stage sensitivity analysis of this case (Figure 34) shows also a spike, for the same reason, at a feed stage of 5. Although in both sensitivity analyses, the OCS spike looks smaller than the LCEA one, it represents a 24,500 US$/yr increase. In this case, a 100 % recovery is achieved, since both the distillate (acetone) and the bottoms (toluene) streams are recovered. The feed stage sensitivity analysis also shows a spike at a feed stage of 6. From feed stages 2 to 5, only toluene is recovered, while at a feed stage of 6 and 7, acetone can be recovered as well. In this case the emissions in the recovery process are only the ones from the steam and electricity needed to run the distillation column, since both solvents are recovered and their manufacture and incineration avoided.

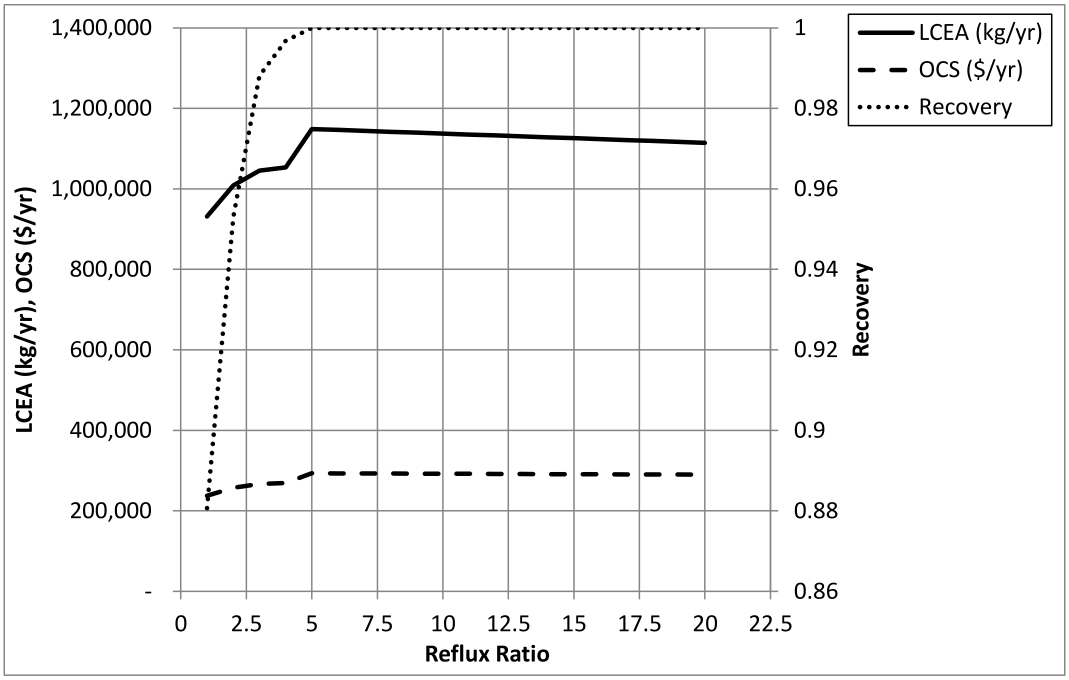


Figure 33. Sensitivity analysis of the LCEA, OCS and recovery with the reflux ratio as the independent variable, for the hydrocortisone case study. The feed stage remains constant at the optimum value of 6.

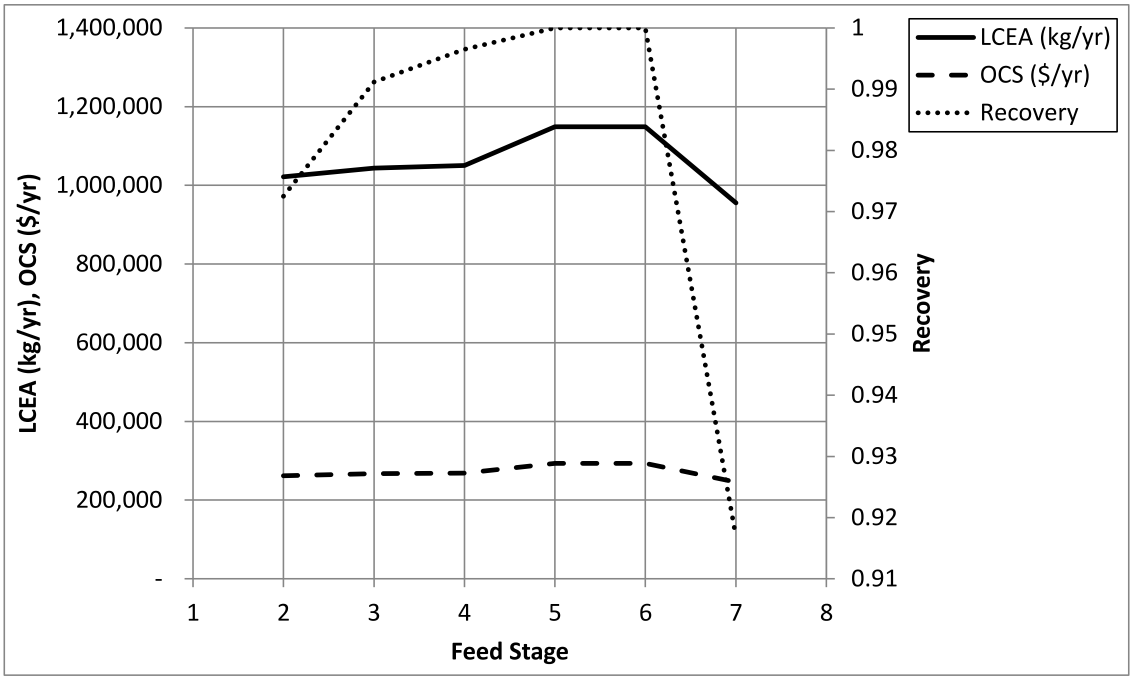


Figure 34. LCEA, OCS and recovery sensitivity analysis with the feed stage as the independent variable, for the hydrocortisone case study. The reflux ratio remains constant at the optimum value of 5.

In the nelfinavir and hydrocortisone recovery scenarios, soil emissions increase, although negligibly compared to the total emissions avoided.

The celecoxib case RRSA is shown in Figure 35. The operating cost savings in this figure are only for the distillation unit and do not consider the pervaporation operating costs. Also, distillation does not produce LCEA since the IPA waste streams needs to be further purified in the pervaporation unit, but they were nevertheless calculated as if 85 % wt. was the required purity, in order to perform the sensitivity analysis. In this case study, the distillate stream cannot achieve the IPA desired purity of 85 % wt. for reflux ratios lower than 2; therefore, IPA cannot be recovered. At a reflux ratio of 1, the LCEA and the OCS are negative because energy is used to run the separation process but no solvent is recovered. At a reflux ratio higher than 2, the system is able to recover IPA at a mass composition equal to its required purity. The optimum reflux ratio in this case study is approximately 2 for both the LCEA and OCS. The feed stage sensitivity analysis of this case (Figure 36) shows the same behavior: at a feed stage lower than 6, the LCEA and OCS are negative because IPA is not recovered, while energy is utilized.

In the celecoxib case, 2,548,407 kg/yr of IPA are avoided to manufacture, representing a recovery rate of 99.5%. This case study demonstrates that the recovery of solvents from more difficult to separate azeotropic mixtures can still achieve carbon footprint reductions and operating cost savings.

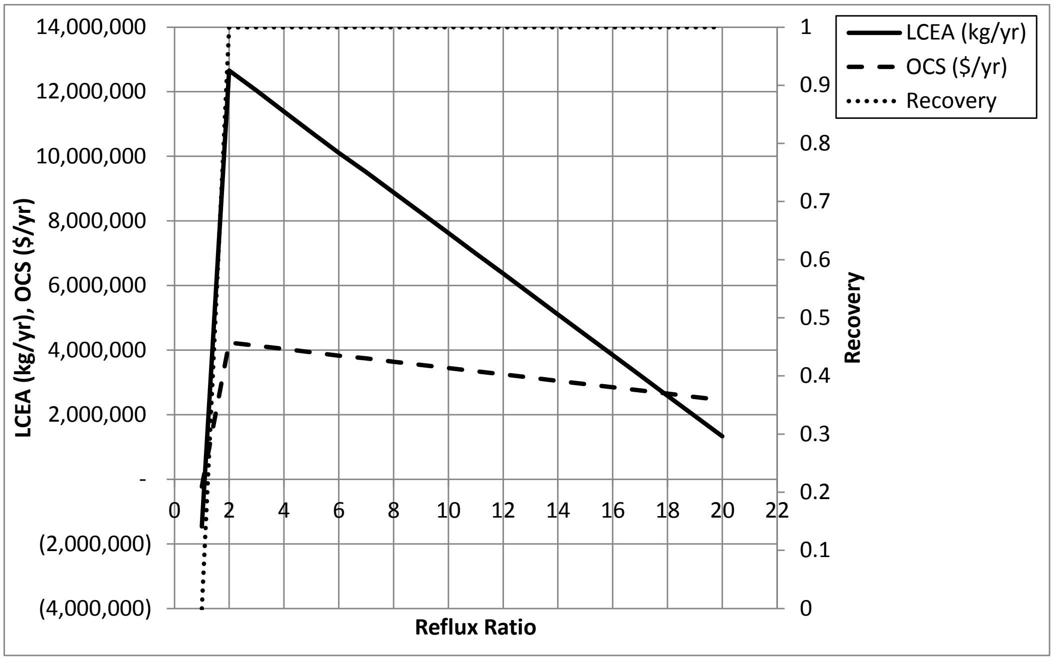


Figure 35. Sensitivity analysis of the LCEA, OCS and recovery with the reflux ratio as the independent variable, for the celecoxib case study. The feed stage remains constant at the optimum value of 6.

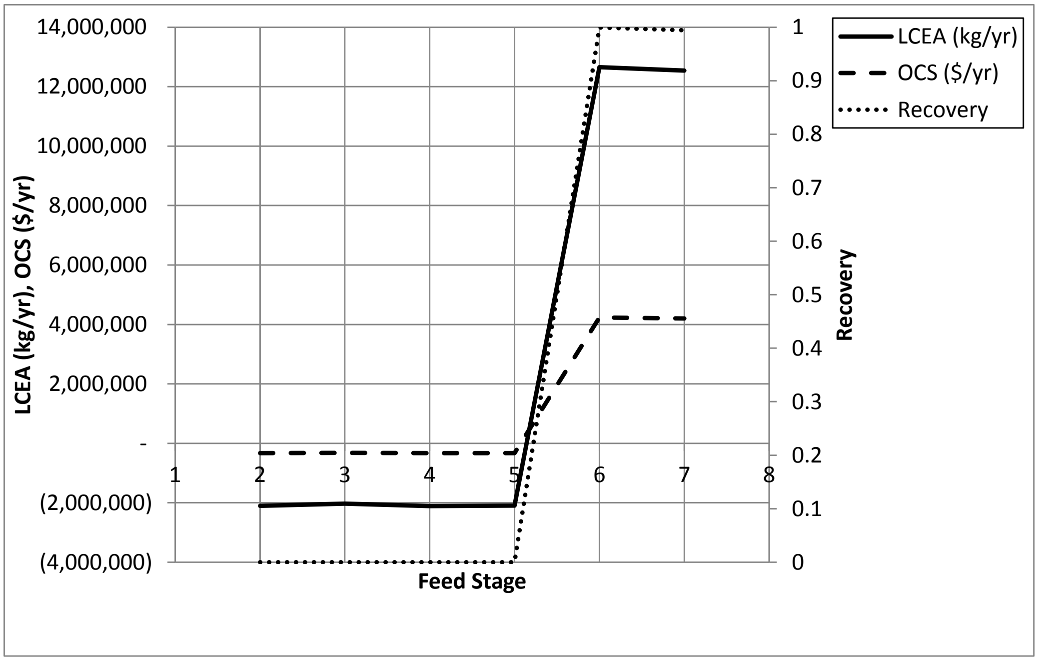


Figure 36. Sensitivity analysis of the LCEA, OCS and recovery with the feed stage as the independent variable, for the celecoxib case study. The reflux ratio remains constant at the optimum value of 2.

The selection of the optimum feed stage determined by our tool can also provide significant emissions and cost savings, as seen in Figure 27, Figure 32, Figure 34, and Figure 36. The feed stage sensitivity analysis would not be useful when rating an existing column that already has a feed plate that cannot be rearranged. In this case, the feed stage sensitivity analysis should be run with the existing feed stage as a constant. It may occur, however, that a distillation column has more than one feed location from which to choose. In this case, our tool can run sensitivity analyses with these existing feed locations as the independent variables to obtain the optimum available feed location. In our recovery skid, we have imagined that the distillation column has multiple feed stages and that the internals can be rearranged to modify the feed stage.

A comparison between the life cycle emissions of the base case and the recovery case, for each case study is shown from Figure 37 to Figure 40. A small increase in the recovery process emissions generates significant life cycle emissions reduction. Conversely, small recovery process costs generate significant monetary savings in the purchase of virgin solvents and waste treatment (i.e.: incineration) of solvent waste, as shown in Figure 41 through Figure 44. In the hydrocortisone case study, life cycle emissions and operating costs in the recovery case are zero because both solvents (acetone and toluene) are recovered. In the celecoxib case study, the raw materials life cycle emissions and operating costs in the recovery case are negligible because the remaining component in the solvent waste is water, which has very little cost and low life cycle emissions.

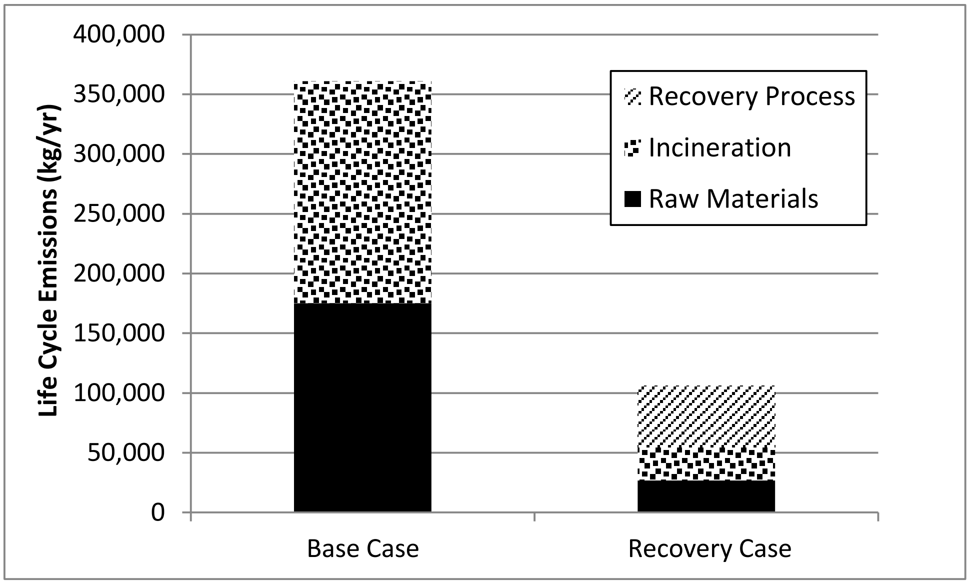


Figure 37. Life cycle emissions comparison between base case and recovery case in the selamectin case study.

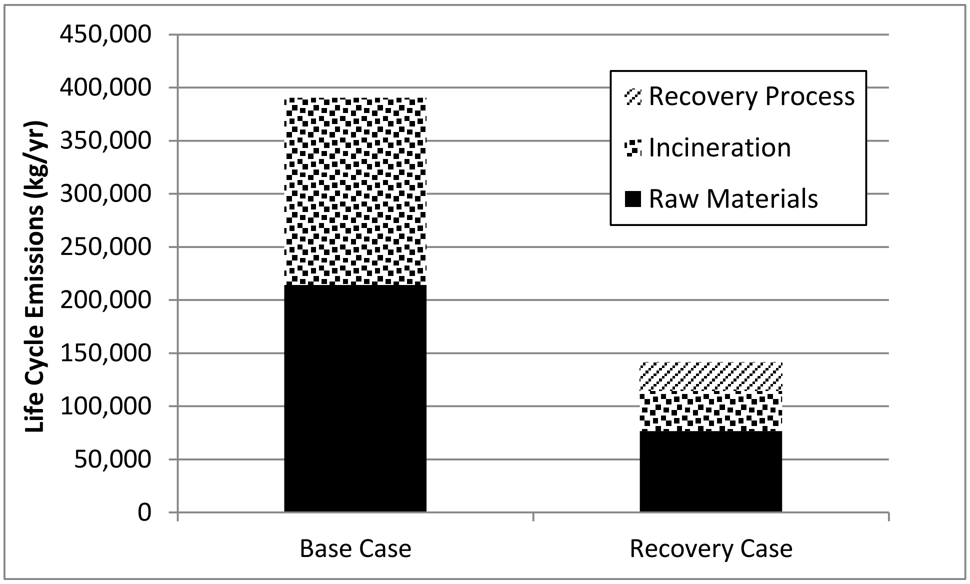


Figure 38. Life cycle emissions comparison between base case and recovery case in the nelfinavir case study.

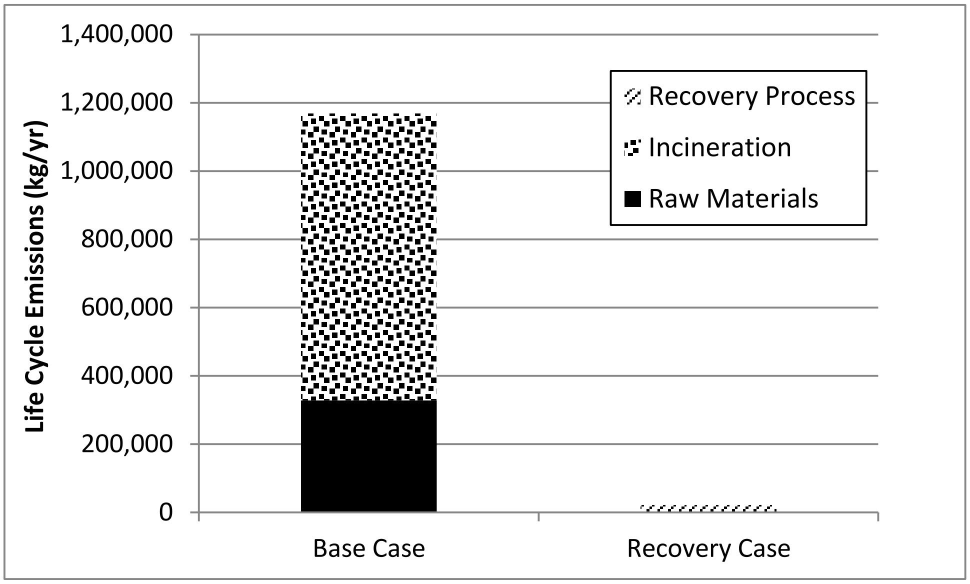


Figure 39. Life cycle emissions comparison between base case and recovery case in the hydrocortisone case study.

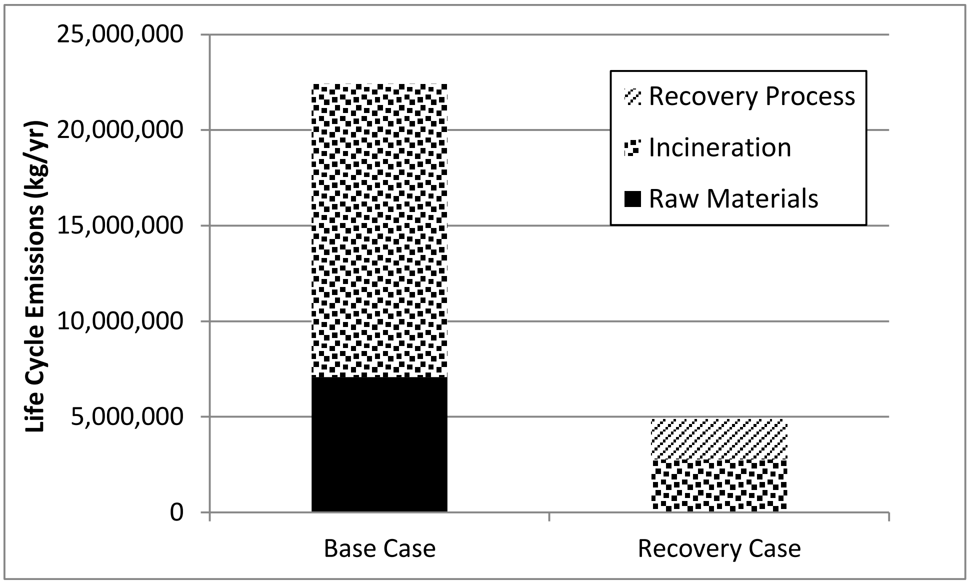


Figure 40. Life cycle emissions comparison between base case and recovery case in the celecoxib case study.

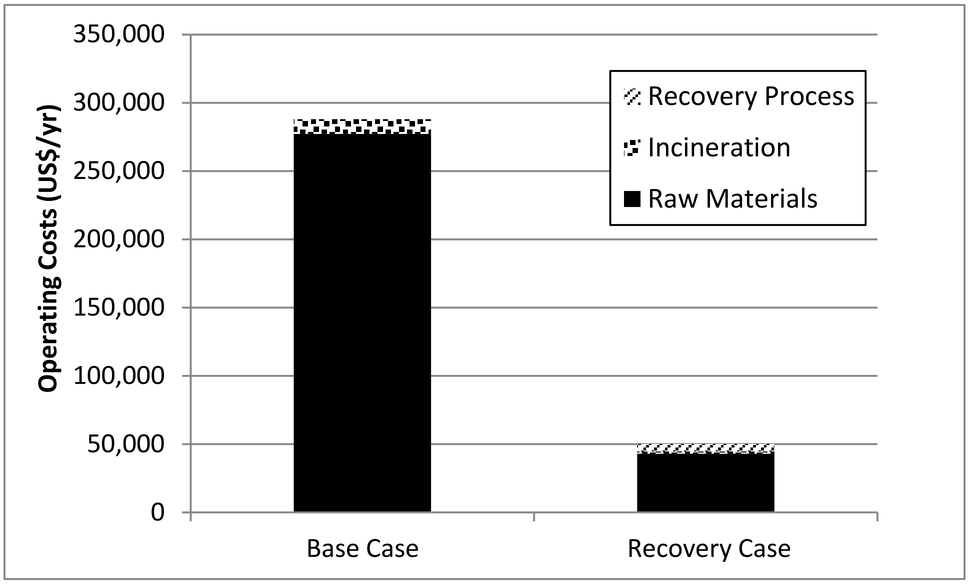


Figure 41. Operating costs comparison between base case and recovery case in the selamectin case study.

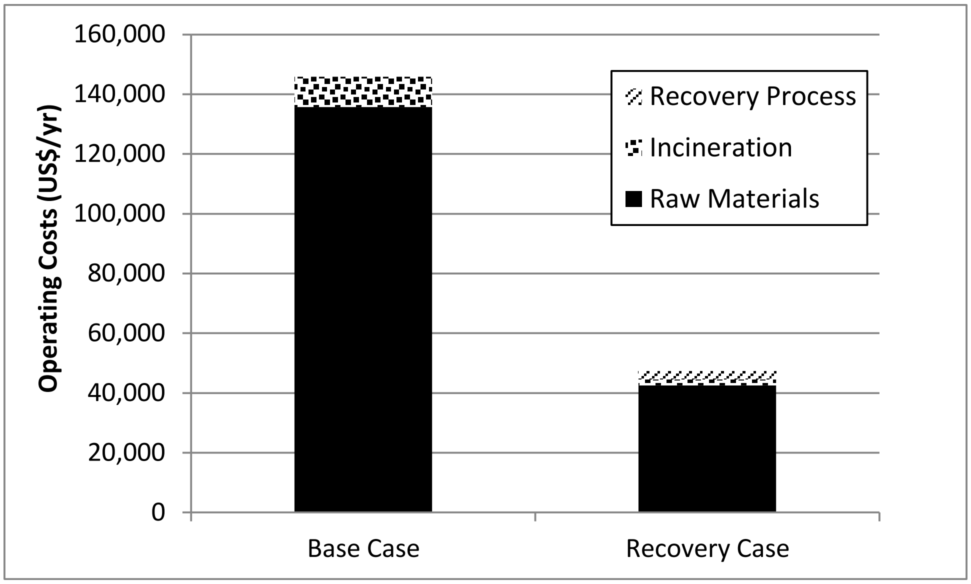


Figure 42. Operating costs comparison between base case and recovery case in the nelfinavir case study.

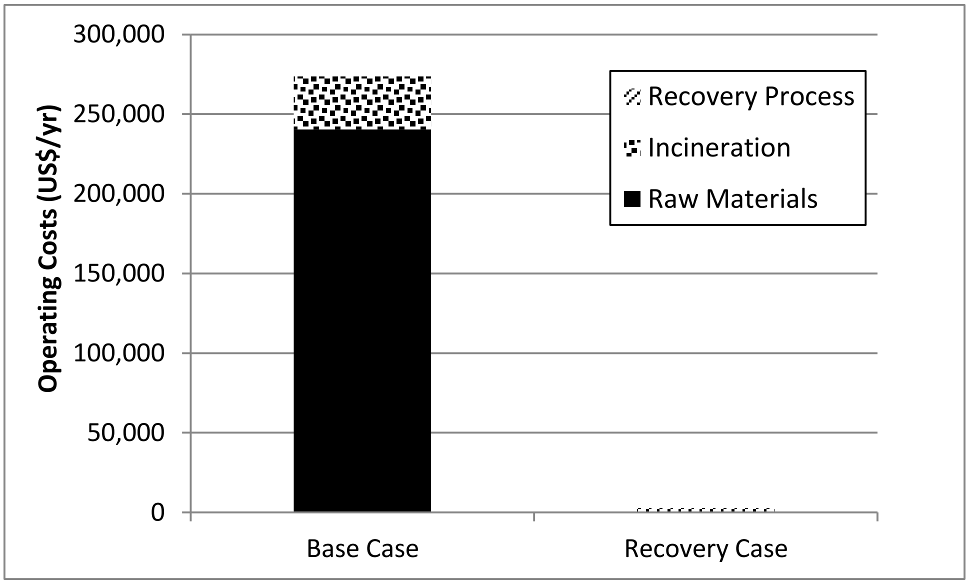


Figure 43. Operating costs comparison between base case and recovery case in the hydrocortisone case study.

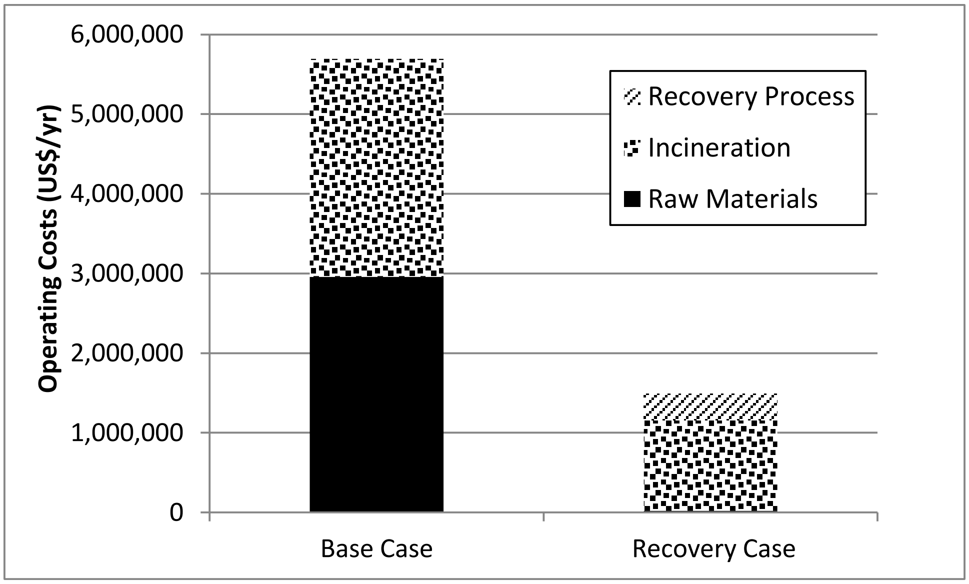


Figure 44. Operating costs comparison between base case and recovery case in the celecoxib case study.

The IRR for all case studies but nelfinavir's are positive. The skid could be used to recover all four solvent waste streams provided proper scheduling, since the summation of the recoveries operating time, shown in Table 15, is 228 days, i.e., less than one year. A cash flow analysis for this situation includes the cost savings of the four recovery projects and the investment cost of one skid, making the economic analysis results even more attractive. In cases where separation equipment already exist and remains idle during certain period of time, the investment cost could be smaller or zero, making the recovery projects more profitable. The selamectin, nelfinavir, and hydrocortisone processes occur at the same manufacturing plant; therefore, a cash flow analysis considering the investment cost of one distillation system skid and the savings of the three cases yielded a higher profitability than the individual cases.

Solvent mixture volatilities are also analyzed as they have a direct impact in utility consumption. Greenness scoring methods for organic solvents exist that use the vapor pressure to determine how easily a solvent mixture can be separated[2]. However, relative volatility information alone does not suffice to analyze the complexity of a mixture separation. Therefore, the Recovery Process Selection Guide can be used as a screening tool to select solvents for API manufacturing that are easier to separate, making the process greener. As an example, the company PennAKem® proposes 2-MeTHF as a green replacement for THF since it is more easily separated from water because it forms a heterogeneous mixture, as opposed to the homogeneous and azeotropic mixture formed by THF and water[79]. An evaluation of 2-MeTHF as a green solvent is further presented in Chapter 6. Equation 3 shows that the higher the LCI of the organic solvent being recovered, the higher the environmental positive impact of the recovery will be. Therefore, solvents with high LCI should be prioritized to recover or to be replaced with green solvents with low LCI.

Conventional vs. R.SWEET's Optimum Reflux Ratio

Chemical engineering handbooks recommend an economic optimum reflux ratio between 1.1 and 1.5 times the minimum reflux ratio (R_m). At this range, the combined capital cost and operating cost is minimized[80,81], as seen in Figure 45. R.SWEET's optimum reflux ratios of the selamectin and hydrocortisone cases are significantly higher than what these conventional values recommend. In more agreement with R.SWEET's results, McCormick et al.[82] suggest that the minimum reflux ratio multiplier may be 10 or more, depending on the system and equipment. Very small refluxes, close to the minimum reflux ratio, may prevent packed towers from being thoroughly wetted; an undesired situation. McCabe et al.[83] explains that most plants are operated at reflux ratios somewhat above the conventional optimum, because the total costs (fixed costs + operating costs) are not very sensitive to the reflux ratio at a range close to the optimum (although the upper limit of this range are not specified) and better operating flexibility can be obtained with reflux ratios greater than the optimum.

The minimum reflux ratio concept is used when the separation between two components is specified and the number of stages is not specified, since the reflux ratio defines the number of stages. As the reflux ratio increases, the operating costs increase due to higher heat duties in the reboiler and condenser, but the number of required theoretical stages decreases, lowering the height if the column and consequently the fixed costs. A compromise situation must be met, as shown in Figure 45. The fixed costs reach a minimum until higher reflux ratios demand for higher column diameters, and they increase again.

In our situation, the number of stages (or packing height) and column diameter is already defined. A change in the reflux ratio does not modify the column dimensions. The minimum reflux design approach is not useful in our case because the recovery skid has to be flexible to deal with different solvent waste streams, as opposed to a specific stream. However, to operate the distillation column of the skid one might be tempted to select the conventional optimum reflux ratio and bypass a deeper analysis, since this may be time consuming. The minimum reflux ratio could be calculated with the desired separation specifications. In our case, where the column dimensions are defined, when the reflux ratio is modified the feed flow could be adjusted to avoid flooding point and ensure proper mass transfer. Therefore, it is important to highlight that R.SWEET's optimum reflux ratios do not follow conventional rules of thumb, but an optimum operation can be achieved without compromising hydraulics performance.

However, R.SWEET model has its limitations, which are explained next. In R.SWEET's model, increasing the reflux ratio increases the cost of steam and electricity (to pump more cooling media), but not the cost of the skid. Therefore, it is assumed that the size of the reboiler and condenser is fixed and can handle the variations in heat duties that increasing the reflux ratio demands; or that the reboiler and condenser size does not affect significantly the skid cost. In other words, the cost of the skid doesn't change with the reflux ratio variation. In R.SWEET model, the demand for greater heat duties when increasing the reflux ratio is satisfied with an increase in the cooling media and steam flow rates in the condenser and reboiler, respectively. This higher flow rates increase the cost of steam and electricity, used for pumping the cooling media. In reality, a heat duty increase may require an increase in the condenser or reboiler size, increasing the skid cost, or by using a higher pressure steam or cooling media with lower inlet temperature.

Therefore, R.SWEET assumes that:

- The skid cost increase demanded by the condenser or reboiler size increase is not significant, and/or
- The cost increase of using a different heat transfer medium is not significant.

Note that, in R.SWEET’s model, the distillation column itself does not change its dimensions, since the feed flow rate is adjusted at R.SWEET's optimum reflux ratio to avoid flooding.

With these assumptions, solvent recovery analyses can be enriched with an environmental life cycle and economic approach to provide not only green engineering, but smart engineering as well. R.SWEET analysis can be applied to existing distillation columns or to the design of flexible solvent recovery skids. In R.SWEET, the results of a RRSA include the reboiler heat duty, which can be used to limit the reflux ratio increase. The reflux ratio cannot be higher than that which results in a reboiler and/or condenser heat duty that exceeds its maximum allowable, whether the reboiler and/or condenser already exists or are in the design phase.

As shown in Table 16, when using R.SWEET's optimum reflux ratio, the emissions and cost savings are as much as 49.7 % and 59.9 % higher, respectively, than if the traditional optimal values for reflux ratio were used. In the acetonitrile recovery of the selamectin case, the reflux ratio that maximized the LCEA was considered the optimum, because the reflux ratio that maximized the OCS was 28, which seems impractical, and because the reflux ratio that maximizes LCEA generates OCS that are 95.1% the maximum OCS. The conventional optimum reflux ratio for the acetone recovery in the selamectin case study did not achieve the desired purity of acetone, and therefore it was not considered in this analysis.

The ability to determine an optimum reflux ratio is a key advantage to operators and engineers that use R.SWEET. In the nelfinavir and celecoxib cases, the Underwood minimum reflux ratio was not calculated because both IPA and THF, and IPA and water mixture are strongly non ideal, in which the Underwood equation is not applied. The IPA and THF mixture shows a tangent pinch, as shown in Figure 18, while the IPA and water mixture contains an azeotrope. On the contrary, the acetone and acetonitrile mixture (selamectin case), and toluene and acetone mixture (hydrocortisone case), show ideal thermodynamic behavior, as seen in Figure 15 and Figure 21, respectively. A detailed calculation of the Underwood minimum reflux ratio is provided in Appendix K.

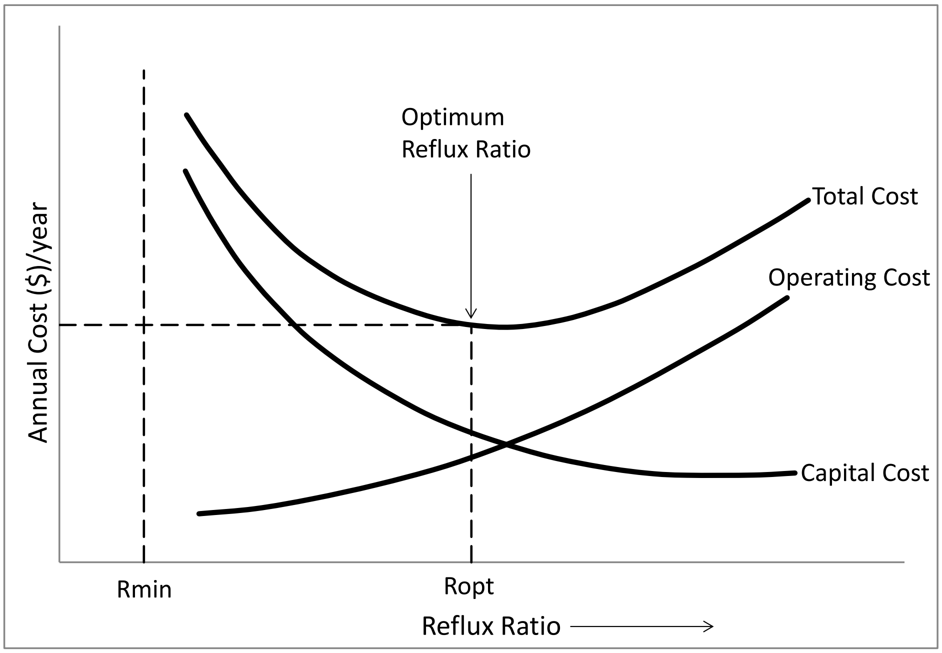


Figure 45. Conventional optimum reflux ratio analysis. Adapted from Seader et al (1997)[80].

Table 16. LCEA and OCS obtained with our tools optimum reflux ratio and with conventional optimum reflux ratio

Case Study		Selamectin - Acetonitrile Recovery	Hydrocortisone
LCEA (kg/yr)	with conventional optimum reflux ratio	123,301	946,587
	with R.SWEET's OCS optimum reflux ratio	184,635	1,148,713
	Improvement (%)	49.7	21.4
OCS (US$/yr)	with conventional optimum reflux ratio	134,529	241,598
	with R.SWEET's OCS optimum reflux ratio	215,139	293,286
	Improvement (%)	59.9	21.4

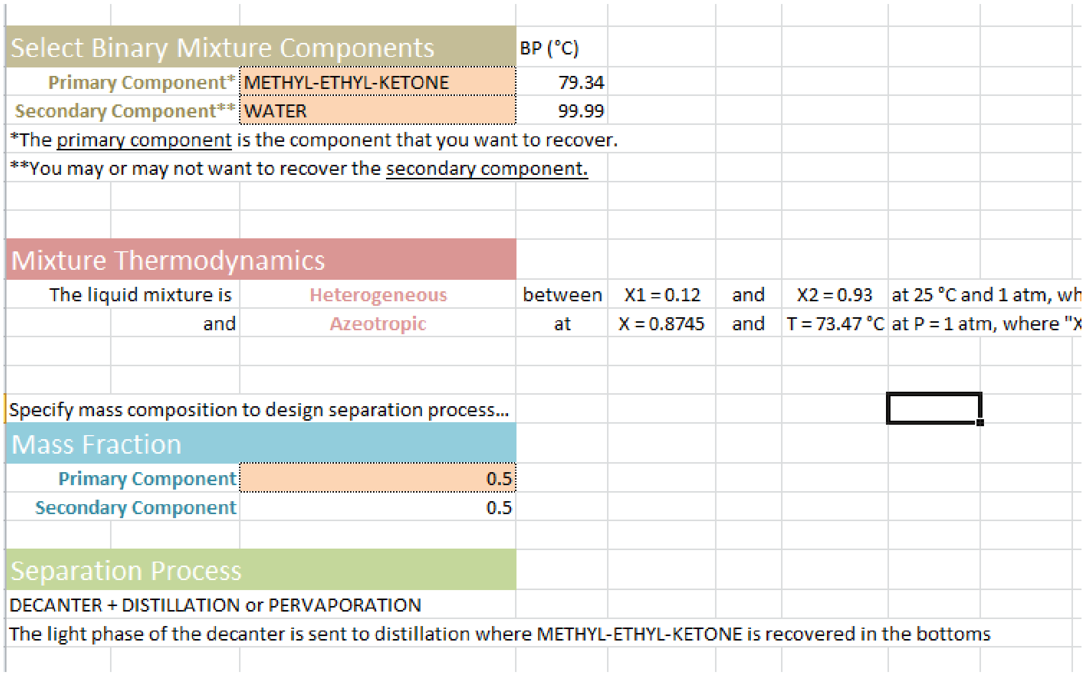
Pervaporation Membranes Comparison with R.SWEET

In the celecoxib case, the performance of two polymeric membranes, PERVAP® 2510 and PERVAP® 2201 from Sulzer Chemtech, and a ceramic membrane from Mitsui & Co. were compared using the PV Simulator. The results show that membrane PERVAP® 2201 could not be used for the celecoxib case, since its minimum required area (245 m^2) is higher than the available area (210 m^2). The Mitsui membrane showed very promising results, requiring the lowest membrane area of 50 m^2. However, the pervaporation unit design was based on Sulzer's flat sheet membranes, so Mitsui tubular membranes would have been incompatible with the skid; therefore, only Sulzer's membranes were considered. The PERVAP® 2510 showed that it can achieve the desired recovery in the celecoxib case in a continuous mode combined with distillation. Furthermore, its feed and inter-module heater outlet temperature could be reduced to 84 °C, from the original estimate of 95 °C, while still using the available membrane area of 210 m^2 and achieving the desired separation, which would reduce the heat requirements by 10.6 %. These results aided in the pervaporation membrane selection for the skid. This analysis shows that the PV simulator can be used to easily assess the performance of different type of membranes for a given recovery project. The experimental data to model these membranes were obtained from Qiao et al.[54] and Van Hoof, et al.[35].

Chapter 5

A Heterogeneous Case

To show how R.SWEET is used to separate heterogeneous mixtures, a hypothetical case study was analyzed. The selected waste was a mixture of methyl ethyl ketone (MEK) and water, with equal mass composition. The target solvent was MEK at a mass composition of 99 wt. %. A waste mass of 100,000 kg per year was assumed. The RPSG tells us that this mixture is heterogeneous at this composition and at 25 °C. The MEK composition in the heavy phase is 12 wt. %, while the light phase contains 93 wt. %. Furthermore, an azeotrope is present at a composition of 87.5 wt. %, with a boiling point of 73.5 °C. Figure 46, shows how this information is presented by the RPSG. At the bottom of Figure 46, the recommended process can also be seen.



Select Binary Mixture Components | BP (°C)

Primary Component*	METHYL-ETHYL-KETONE	79.34
Secondary Component**	WATER	99.99

*The primary component is the component that you want to recover.
**You may or may not want to recover the secondary component.

Mixture Thermodynamics

The liquid mixture is	Heterogeneous	between	X1 = 0.12	and	X2 = 0.93	at 25 °C and 1 atm, wh
and	Azeotropic	at	X = 0.8745	and	T = 73.47 °C	at P = 1 atm, where "X

Specify mass composition to design separation process...

Mass Fraction

Primary Component	0.5
Secondary Component	0.5

Separation Process

DECANTER + DISTILLATION or PERVAPORATION
The light phase of the decanter is sent to distillation where METHYL-ETHYL-KETONE is recovered in the bottoms

Figure 46. Information output of the RPSG for the hypothetical case study of MEK and water.

R.SWEET uses this information to simulate the distillation of the light phase, in which MEK is recovered in the bottoms at 99 wt. %, since its boiling point is higher than the azeotrope's boiling point. The separation process is depicted in Figure 47. To solve the decanter mass balance, R.SWEET uses the lever rule. A distillation column with the characteristics of the skid described in Chapter 3 was used.

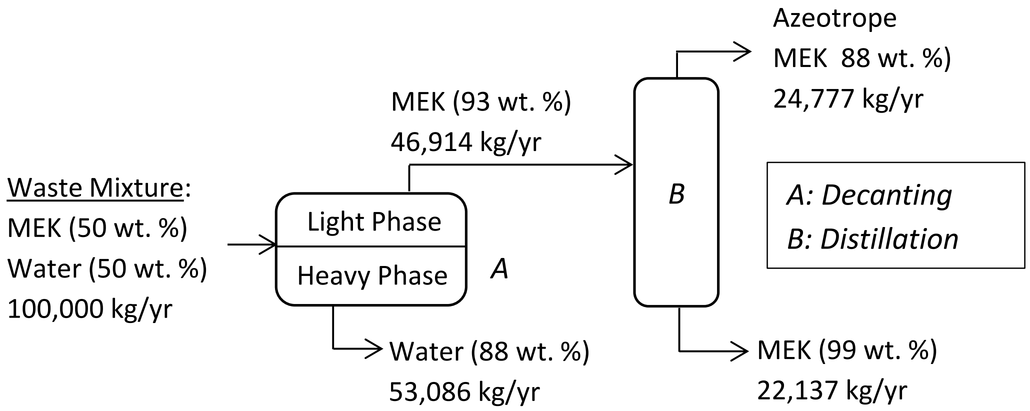


Figure 47. MEK dehydration process for the heterogeneous case study.

The recovery of the decanter was 87.3 %, and in the distillation 50.2 %, resulting in an overall recovery of 43.8 %. Even at this relatively low recovery, LCEA and OCS are obtained. The distillation RRSA (Figure 48) and feed stage sensitivity analysis (Figure 49) shows that both LCEA and OCS are maximized at a reflux ratio of 2 and feed stage of 5.

These results could be improved by increasing the recovery. The problem with this separation is that two streams that contain MEK are not being recovered: the heavy phase of the decanter, containing 12 wt. % of MEK and the distillate of the distillation, with 88 wt. %, which is almost the azeotropic composition. To increase the recovery, there are two possibilities:

1) to design a process such as shown in Figure 50, or
2) to sequentially use the process in Figure 47 to separate MEK from the both streams previously mentioned, i.e., to re-introduce the azeotrope from the distillate to the decanter.

Nevertheless, these options may not always be possible to implement due to equipment availability. It is interesting to note, however, that a simple scheme (Figure 47) showed promising results.

Currently, R.SWEET does not contain the degree of process ramification required to recommend a wide variety of separation process from which to select, which could result, for example, in the Figure 50 process. Further programming would be required.

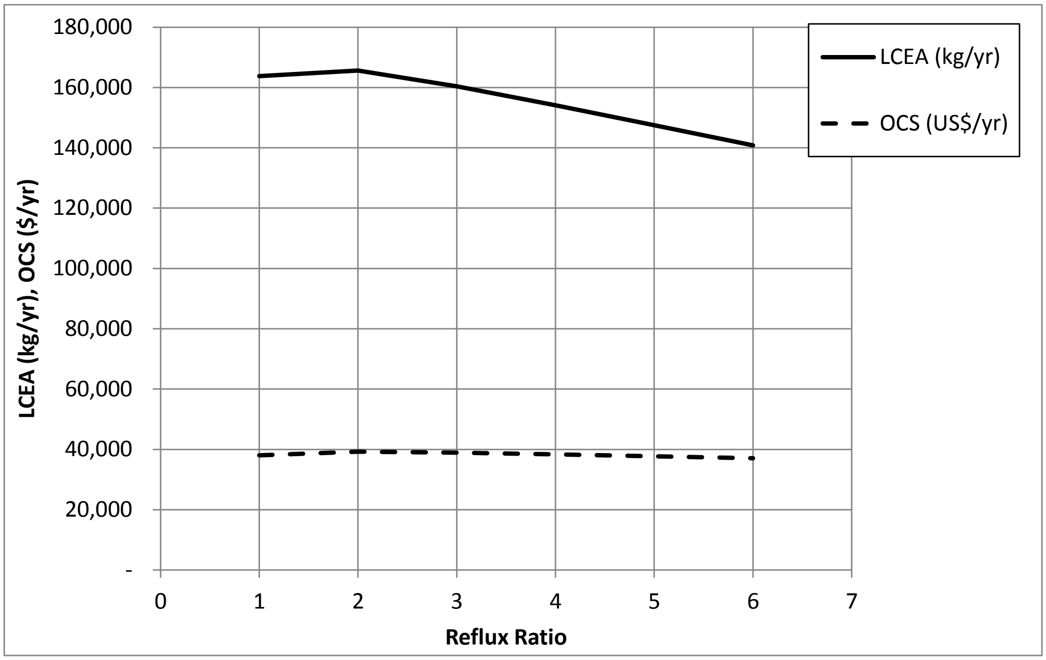


Figure 48. Sensitivity analysis of the LCEA, OCS with the reflux ratio as the independent variable, for the heterogeneous case study. The feed stage remains constant at the optimum value of 5.

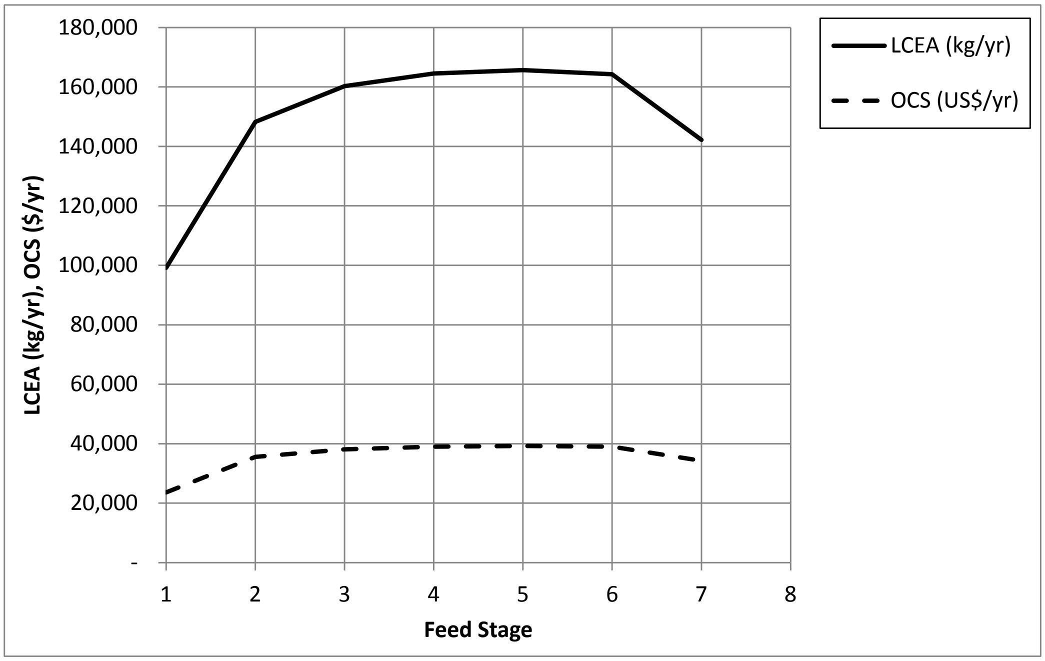


Figure 49. Sensitivity analysis of the LCEA, OCS with the feed stage as the independent variable, for the heterogeneous case study. The reflux ratio remains constant at the optimum value of 2.

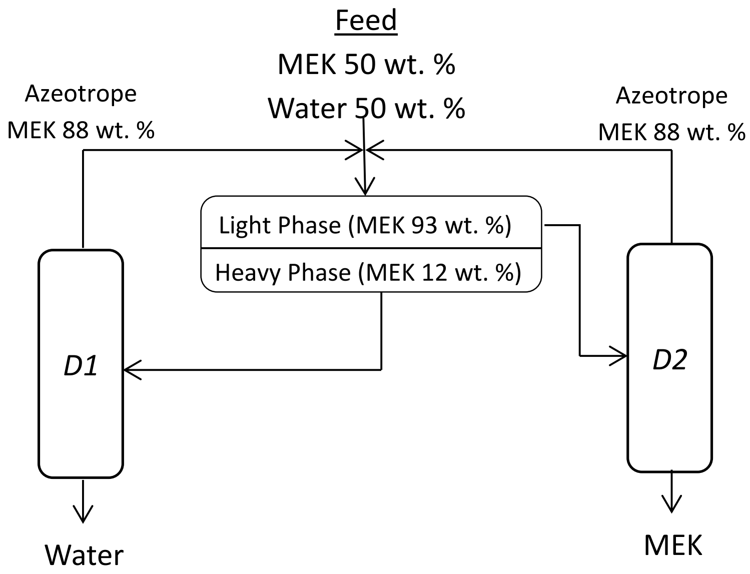


Figure 50. Alternative process to dehydrate MEK and increase its recovery. *D1* and *D2*: distillation columns.

Chapter 6

Green Solvents

Another way of reducing the environmental impact of organic solvent use in the pharmaceutical industry is by using green solvents. Green solvent may have one or more of these characteristics, as compared to conventional solvent: 1) lower LCI, 2) lower toxicity and 3) easily recovered for recycle. Organic solvents with lower LCI are usually derived from renewable sources such as bio-waste or agricultural by-products. The second characteristic is usually associated with low volatility, resulting in a less probability to be inhaled by humans, creating thus a safer work environment, or to be released to the environment due to fugitive emissions. The ability to form biphasic systems is an attractive property of organic solvents because it allows for less energy intensive and more efficient separation and recovery[10]. These characteristics are present in 2-methyl tetrahydrofuran (MeTHF), produced by PennAKem and marketed as *eco*MeTHF™.

MeTHF is produced by PennAKem and sold as a potential replacement for THF, which is widely used in pharmaceutical syntheses. The use of MeTHF as a solvent in the pharmaceutical industry has increased steadily from 2005 to 2008 and is expected to keep increasing. In 2010, the global demand of THF was 525 million kg per year[84] and it is expected to exceed 800 million kg per year in 2017[85]. PennAKem markets MeTHF as one of their carbon neutral solvents. This is claimed because the starting material, furfural, is produced from agricultural by-products. Therefore, PennAKem calls its product *eco*MeTHF™. This method of furfural production does not impact the world's food supply and also keeps PennAKem's material supply and prices from fluctuating as highly as they would with a petroleum based chemical. PennAKem claims that *eco*MeTHF^{TM} is a better solvent choice than THF because it can be recovered from water more easily, leading to lower costs in both utility and solvent purchasing for the consumer. Several pharmaceutical companies have already expressed interest in pursuing this chemical as an alternative to THF.

MeTHF has some unique properties that make it a green solvent. In solvent polarity and Lewis base strength, MeTHF is between THF and diethyl ether. It is also useful as a solvent in low-temperature lithiation, lithium aluminum hydride reductions, metal catalyzed coupling reaction, and the Reformatsky reaction. It can also replace dichloromethane in biphasic reaction. Due to its low solubility in water at high temperatures, 6.6% at 60°C, it is easier to separate it from water, as compared to THF.[86] THF is miscible in water and forms an azeotrope at atmospheric pressure at a mole fraction of 0.78. MeTHF forms an azeotrope at atmospheric pressure at a mole fraction of 0.88. A *Txy* vapor-liquid-liquid and *xy* vapor-liquid equilibrium curve of MeTHF and water is shown in Figure 52. NRTL binary interaction coefficients for MeTHF and water were provided by PennAKem, in order to obtain in Aspen Plus® the previously mentioned curves.

Aycock proposes that MeTHF can be dehydrated by a decanter followed by batch distillation with an overhead liquid-liquid phase separator operated at 60°C. The MeTHF from the separator is refluxed into the column to increase the mass fraction beyond that of the azeotrope. Dry MeTHF is recovered from the reboiler. The overhead separator is operated at 60°C because MeTHF is 6.6% soluble in water, but water is only 4.6%

soluble in MeTHF[86]. This recovery process can serve as the basis for a continuous distillation solvent recovery simulation. The process scheme used to recover MeTHF and THF from aqueous waste mixtures was analyzed to evaluate the "greenness" of MeTHF.

The objective of this section is to analyze the environmental impact of *eco*MeTHF™ versus THF in the production and use in the pharmaceutical industry. In order to do this, the LCI of *eco*MeTHF™ and THF were generated and the recovery process for both solvents was modeled. The "chemical" route (conversion of 1,4-butanediol to THF) and the "biomass" route (conversion of corn to furfural to THF) were analyzed for the production of THF. In the latter case, the product will be called *eco*THF™. The biogenic carbon approach (BCA) was used when calculating the LCI of MeTHF and *eco*THF™. This approach considers that CO_2 emissions are zero when they are generated from biomass (e.g., incineration of biomass) because the released CO_2 originally came from the atmosphere.

MeTHF has the potential to be substituted for THF in organometallic reaction steps in various API syntheses. Companies Pfizer and Johnson & Johnson has indicated that they would likely use MeTHF in a replacement ratio of 1:1[87,88]. This means that for every kg of THF used, 1 kg of MeTHF could be potentially used as substitute.

The base case corresponds to a waste stream containing a 50-50 % wt. mixture of chemical THF and water, and the incineration of this waste for energy recovery. This base case was compared with more environmentally favorable cases involving THF replacement and waste recovery techniques:

1) the substitution of chemical THF with *eco*THF™ and the recovery and re-use of *eco*THF™ with extractive distillation, using glycol as entrainer;

2) the substitution of chemical THF with *eco*THF^{TM} and the recovery and re-use of *eco*THF^{TM} with continuous distillation followed by pervaporation; and

3) the substitution of chemical THF with *eco*MeTHF^{TM}, and the recovery of the *eco*MeTHF^{TM} waste with a decanter-distillation system.

The comparison of the two *eco*THF^{TM} recovery processes had the additional objective of analyzing the greenness of pervaporation[89].

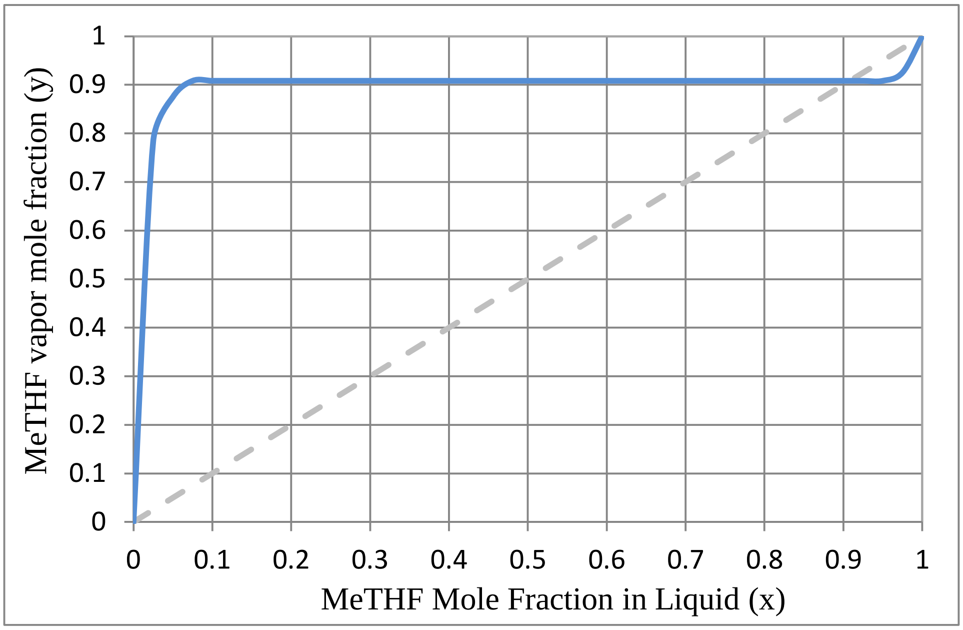


Figure 51. MeTHF and water vapor-liquid equilibrium. An azeotrope occurs at a mole fraction of 0.88 at atmospheric pressure.

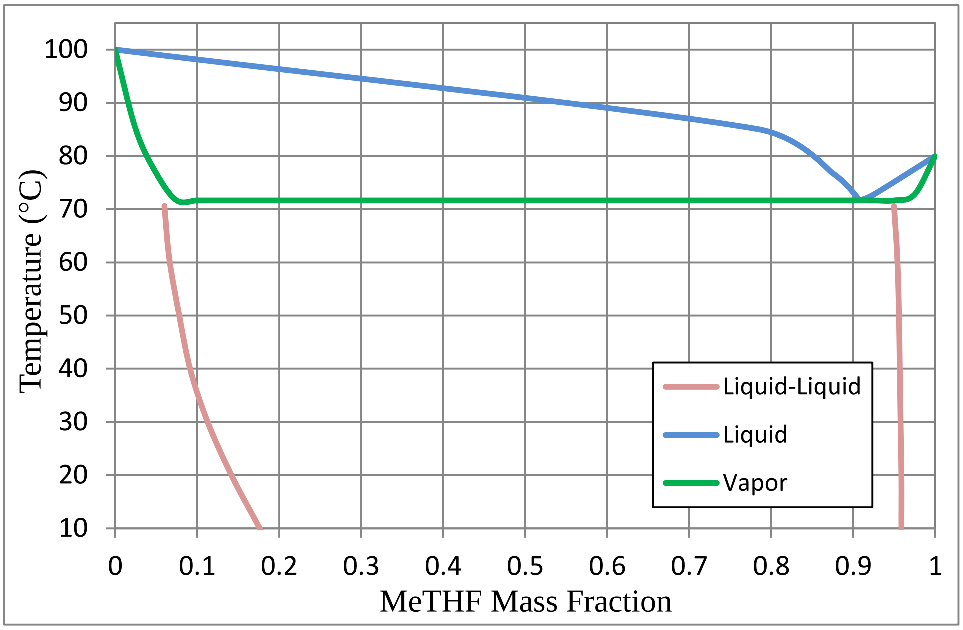


Figure 52. MeTHF and water *T*-*x*-*y* equilibrium diagram, including liquid-liquid equilibrium. Liquid 1 is rich in water, and Liquid 2 is rich in MeTHF.

The LCI of both glycerol and chemical THF (from 1,4-butanediol) was taken from SimaPro®. The LCI of glycerol was required to analyze the first more environmentally favorable case. The LCI of *eco*THF™ and *eco*MeTHF™ are not included in SimaPro®'s database. To calculate their LCIs, their manufacture was modeled in SimaPro® with information provided by PennAKem. This calculation was performed in a previous project called "PennAKem Pharma Solvent Life Cycle Analysis & Process Modeling" by the Chemical Department of Rowan University, and it will not be detailed here. The LCIs of glycerol, chemical THF, *eco*THF™, and *eco*MeTHF™ are shown in Table 17. The total emissions associated with 1 kg of glycerol are 2.33 kg, 1.76 kg of which are CO_2, 5.58 kg of raw materials are used, and the CED is 70.8 MJ. The total emissions associated with 1 kg of chemical THF are 5.65 kg, 5.46 kg of which are CO_2, 4.01 kg of raw materials are used, and the CED is 132 MJ. In the production of *eco*THF™ and *eco*MeTHF™, spent corn cobs (corn cobs residue after harvesting) are used to make furfural, which is then used to create furan to produce *eco*THF^{TM}, and methyl furan to produce *eco*MeTHF^{TM}.

Table 17. LCI from SimaPro® for 1kg of Glycerol, 1 kg of chemical THF, 1 kg of *eco*THF^{TM} and 1 kg of *eco*MeTHF^{TM}

	THF Manufacture	Glycerol Manufacture	*eco*THF^{TM}	*eco*MeTHF^{TM}
Total Raw Materials Used, kg	4.01E+00	5.58E+00	5.33E+02	1.21E+02
Total CED, MJ-Eq	1.28E+02	7.08E+01	6.15E+00	-2.00E+01
Total Air Emissions, kg	5.52E+00	1.79E+00	1.45E+00	1.62E-01
CO_2, kg	5.46E+00	1.76E+00	1.39E+00	1.50E-01
CO, kg	4.82E-03	1.14E-02	7.32E-03	6.63E-03
Methane, kg	1.45E-02	4.46E-03	2.72E-03	-9.38E-04
NO_X, kg	8.67E-03	4.79E-03	3.26E-02	1.38E-02
NMVOC, kg	3.25E-03	8.03E-04	2.94E-03	2.46E-03
Particulates, kg	3.57E-03	2.36E-03	9.74E-04	1.26E-03
SO_2, kg	1.15E-02	3.91E-03	1.77E-02	-4.55E-03
Total Water Emissions, kg	1.26E-01	5.34E-01	3.41E-02	2.73E-02
VOCs, kg	7.93E-06	2.73E-06	5.82E-06	5.56E-06
Total Soil Emissions, kg	2.31E-03	1.77E-03	2.08E-03	1.94E-03
Total Emissions, kg	5.65E+00	2.33E+00	1.49E+00	1.91E-01

The production of 1 kg of ecoTHFTM generates 1.49 kg of emissions, most of which are released to the air. The CO_2 emissions are 1.39 kg, and the CED is 6.15 MJ-Eq/kg. The production of *eco*MeTHF^{TM} generates 0.191 kg of total life cycle emissions per kg of *eco*MeTHF^{TM} produced. A total of 0.162 kg of air emissions, including 0.150 kg of CO_2, are created in the production of *eco*MeTHF^{TM}. The process also avoids 20 MJ-Eq/kg of CED. The production of *eco*MeTHF^{TM} is greener than both chemical THF and *eco*THF^{TM}. Manufacturing 1 kg of *eco*MeTHF^{TM} instead of 1 kg of THF would reduce

5.46 kg of emissions (97 % reduction), while the manufacture of *eco*THF^{TM} would avoid 4.16 kg of emissions (74 % reduction). This information is useful to the pharmaceutical sector in guiding decision makers with solvent substitution strategies for greener API syntheses. Therefore, *eco*MeTHF^{TM} has the potential to make a significant impact on the sustainability of the pharmaceutical and fine chemical sector. However, this provides only a cradle to gate analysis because the disposal of the solvent is not being considered.

In a cradle to grave LCA, the LC emissions of the recovery need to be calculated as well. The boundaries for this analysis include solvent cradle to solvent grave and therefore solvent waste recovery is evaluated. The objective is to answer: *which is a better alternative to chemical THF: ecoTHF*^{TM} *or ecoMeTHF*^{TM}*?* The recovery of *eco*THF^{TM} and *eco*MeTHF^{TM} from water has an impact in the answer of this question, as less energetic recoveries are environmentally friendlier. Note that chemical THF and *eco*THF^{TM} are the same chemical, but the *eco*THF^{TM} manufacture process is more environmentally friendly as *eco*THF^{TM} is produced from furfural (a bio-based raw material, manufactured from corn cobs), which is reflected in the LCI difference.

The recovery of *eco*THF^{TM} from a 50-50 % wt. mixture was modeled as an extractive distillation process and as a distillation followed by a pervaporation unit. The dehydration of MeTHF using the same composition was performed with a decantation followed by two subsequent distillations. The purity specification for both solvents was assumed to be 99.5 %wt. Aspen Plus$^{\circledR}$ was utilized to model the separation of the *eco*THF^{TM} and water mixture by extractive distillation. Our software tool was used to simulate the decanting, distillation and pervaporation processes, and to calculate the life cycle emissions, operating cost savings and cash-flow.

The chemical THF incineration LCI is presented in Appendix F. It was assumed that the fraction of *eco*THF^{TM} not recovered in both the extractive distillation process and the distillation and pervaporation process is incinerated. However, its incineration CO_2 emissions are zero because *eco*THF^{TM} is composed of biogenic carbon. The *eco*THF^{TM} incineration LCI is available in Appendix F. The steam and electricity LCIs used in all the recovery cases were steam from an average chemical plant and electricity from United States' production mix, respectively, obtained from SimaPro$^{®}$ and included in Appendix G. The reason for this selection is that the facility where the recoveries take place cannot be specified.

The selection of an entrainer for the dehydration of THF was based upon the selectivity of the entrainer, the relative volatility change between THF and water, the miscibility of water and THF, the distillate and residue products, and the azeotrope formation with the azeotropic THF and water feed. These criteria were studied for five potential entrainers and the ideal entrainer selected was glycerol. The effect of the five entrainers of the relative volatility of the mixture can be seen in Figure 53. From this graph it can be seen that the addition of glycerol increases the relative volatility of THF and water to the point where the azeotrope no longer exists.

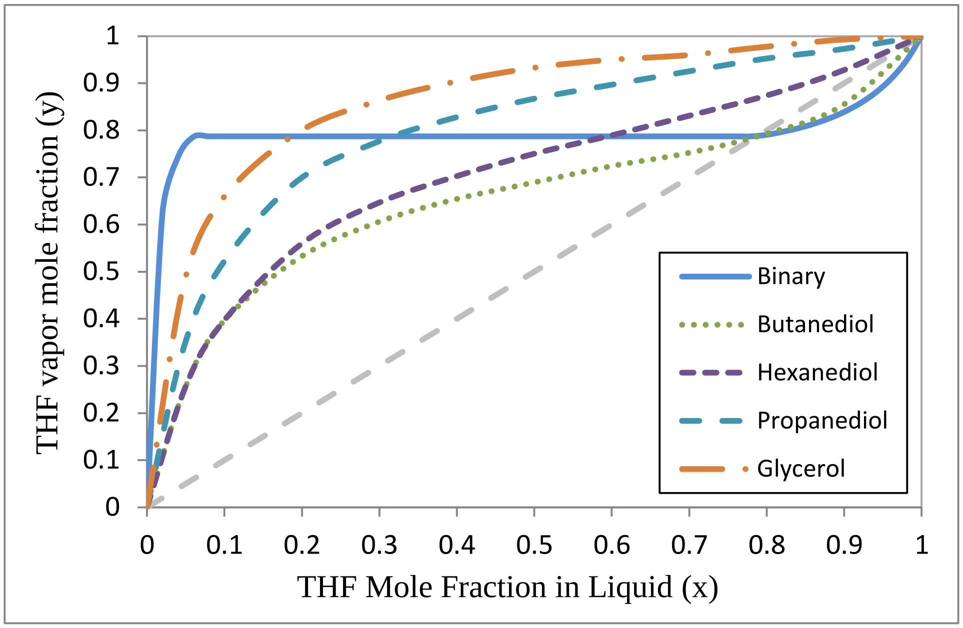


Figure 53. Pseudobinary diagram at 30 % entrainer to feed ratio (P = 1 atm), adapted from Gomez et al.[29]

An additional consideration is the cost of the entrainer selected. Of the five potential entrainers, ethylene glycol is cheapest, followed by glycerol. Even though ethylene glycol has the lowest price and is a suitable candidate, glycerol was chosen because of the lower toxicity and smaller volumes required[29].

The simulation of the recovery of *eco*THF™ with glycerol as an entrainer yielded an *eco*THF™ recovery of 99.53%. This means that if a pharmaceutical manufacturing process uses this recovery process, it would need to make up 0.0047 kg of *eco*THF™ per kg of *eco*THF™ used in the process. A mass ratio of 1:1 of glycerol and solvent waste was used, and the recovery of the glycerol to recycle was 99.95%. Therefore, 0.0010116 kg of glycerol was used per kg of THF fed to the recovery process. The extractive distillation recovery process diagram can be seen in Figure 54. The steam and electricity used per kg of *eco*THF^{TM} fed to the recovery system was 3.5 kg and 0.52 kWh, respectively.

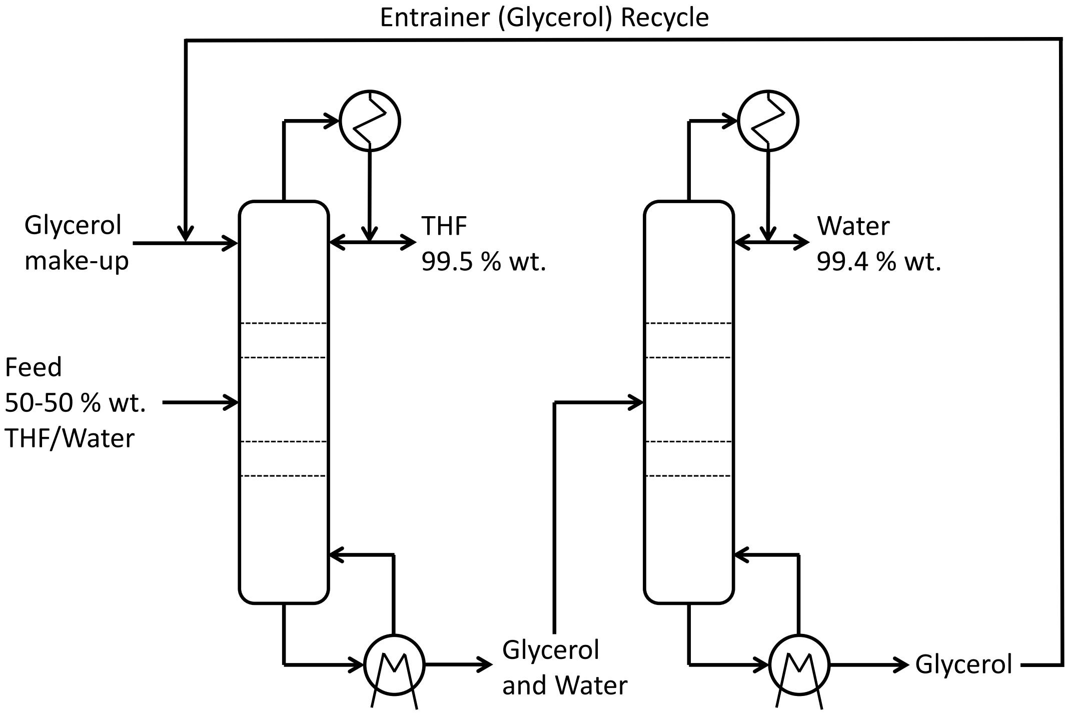


Figure 54. Block flow diagram for the extractive distillation of THF from water using glycerol as an entrainer.

The *eco*THF^{TM} extractive distillation recovery case life cycle emissions are shown in Appendix H. A sensitivity analysis was performed to determine the optimal feed stage and reflux ratio for the two distillation columns given that each column was composed of 8 theoretical trays.

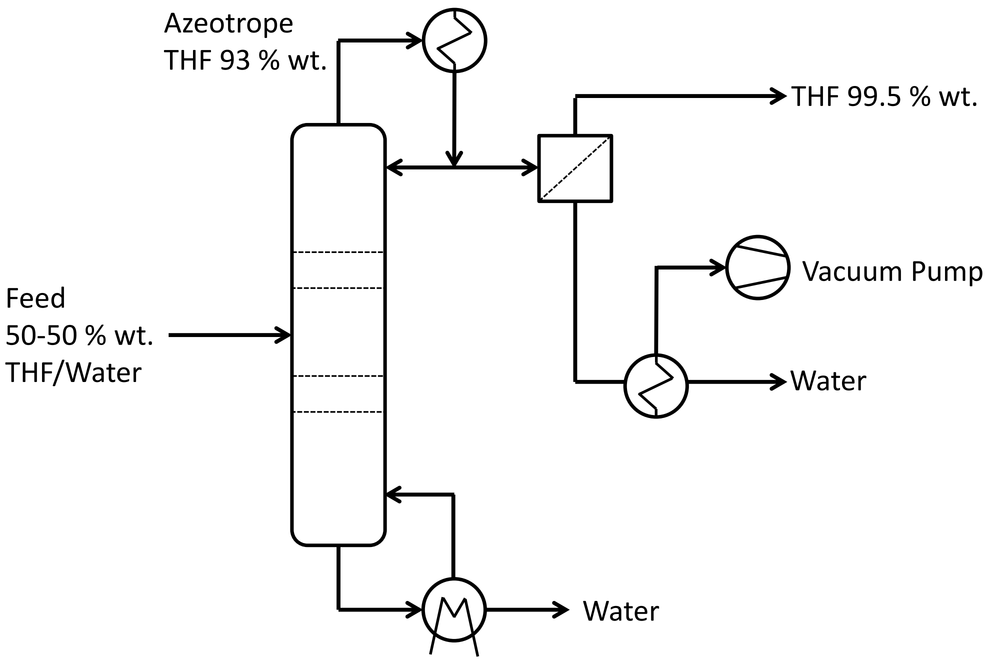


Figure 55. Dehydration of THF integrating distillation and pervaporation.

The simulation of the recovery of *eco*THF^{TM} using distillation and pervaporation yielded a recovery of 99.25%. The process diagram is shown in Figure 55. The steam and electricity used per kg of THF used was 0.66 kg and 0.094 kWh, respectively. This recovery case life cycle emissions are shown in Appendix H. A sensitivity analysis was used to select the optimum reflux ratio and feed stage for the distillation column, using R.SWEET. As with the previous cases, a column with 8 theoretical stages was used.

The recovery of *eco*MeTHF^{TM} process diagram is shown Figure 56. The recovery achieved was 99 %. The reflux ratio and feed stage that maximized the emissions avoided were selected for both columns. In this case, the theoretical stages for columns # 1 and # 2 were 4 and 5 respectively. The steam and electricity used per kg of *eco*MeTHF^{TM} used was 0.49 kg and 0.058 kWh, respectively. Comparing these values with those of the THF recovery, we can see that the energy requirement for the *eco*MeTHF^{TM} recovery is lower.

It was assumed that the fraction of *eco*MeTHF^{TM} not recovered is incinerated. As with *eco*THF^{TM}, *eco*MeTHF^{TM} incineration CO_2 emissions are zero because it is composed of biogenic carbon. Since *eco*MeTHF^{TM} is not available in Ecosolvent®, it was assumed that the incineration LCI is the same as *eco*THF^{TM} because both solvents are chemically similar. The *eco*MeTHF^{TM} recovery case LC emissions are presented in Appendix H. A comparison between the environmentally favorable cases shows that the *eco*MeTHF^{TM} case is the greenest alternative. corresponding reductions.

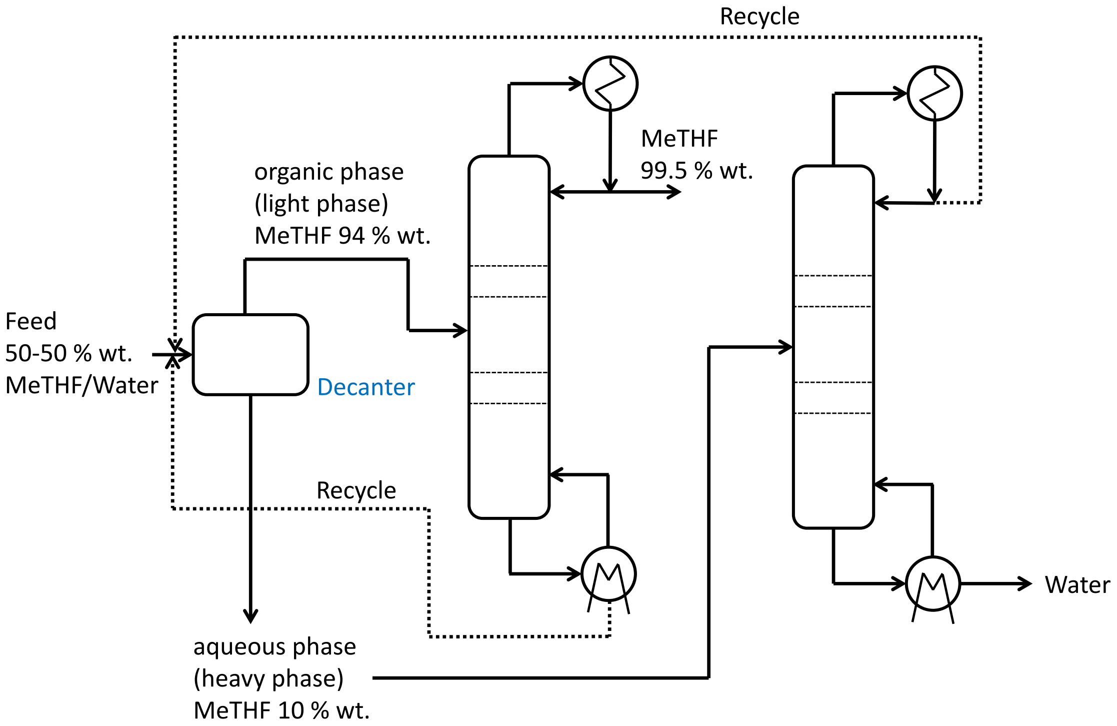


Figure 56. MeTHF recovery process. LS: Light Phase Stream (high concentrations of MeTHF), HS: Heavy Phase Stream (high concentrations of water)

The emissions in the recovery cases are lower than in the base case because less solvent is manufactured and incinerated; therefore, the LC emissions associated to this processes are lower as well. In the *eco*MeTHF^{TM} recovery case, the reduction of both total and CO_2 emissions is 98 %. The results of the total emissions produced in the three recovery cases analyzed are shown in Figure 57. It can be seen that the emissions are lower in the *eco*MeTHF^{TM} recovery case. This study verifies that *eco*MeTHF^{TM} is a green solvent replacement for THF, as suggested by PennAKem. Note that the raw material emissions are negligible when compared to the recovery process emissions, which correspond to the steam and electricity emissions. Therefore, this analysis shows that the steam and electricity use in the *eco*MeTHF^{TM} recovery case is the lowest, which means it is easier to recover MeTHF than THF, as claimed by PennAKem. This result indicates that when the recovery is included in the LCA, the higher ease of recovery of MeTHF as compared to THF has a significant impact in the "greenness" of the API manufacturing.

The total life cycle emissions of the THF use when recovering THF with distillation followed by pervaporation are 81% lower than when recovering THF with extractive distillation. This result fulfills the second objective of this chapter, which was to prove that pervaporation is a greener recovery process than extractive distillation.

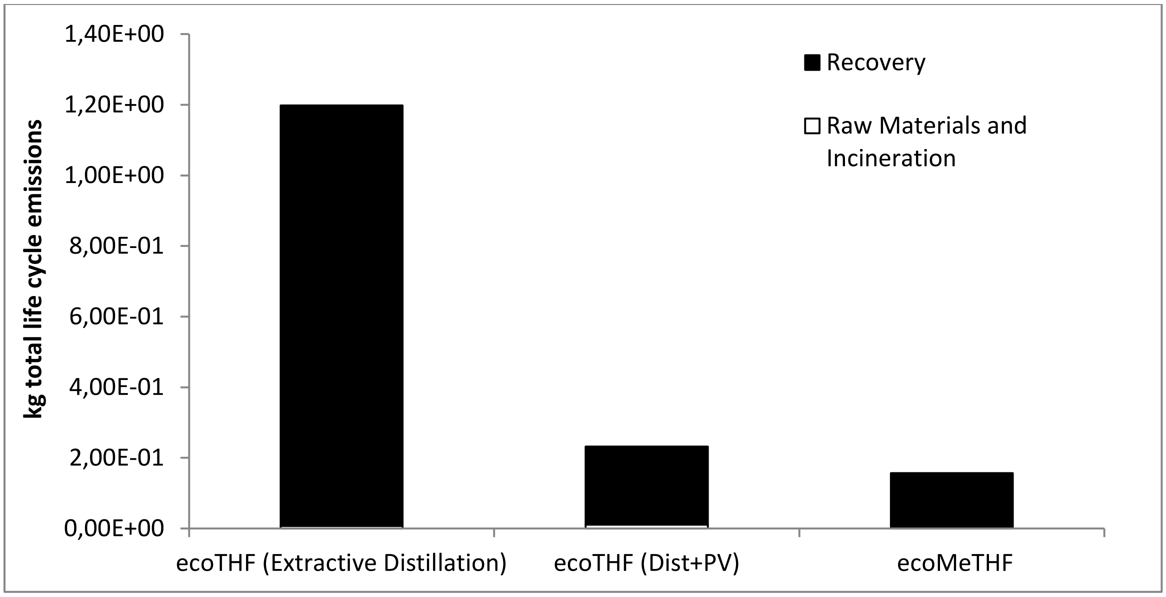


Figure 57. Total emission generated in the recovery cases

The cost of THF, US$3.28/kg, was obtained through ICIS Pricing[21]. The cost of MeTHF was neither provided nor available at ICIS Pricing. Its bulk price was, however, estimated with the price of smaller volumes of the same chemical available at the laboratory providers Spectrum[90] and Sigma-Aldrich[91] websites. A MeTHF to THF price ratio (using a price for the same container volume, for comparison consistency) from the two providers was calculated and averaged. The averaged ratio was then multiplied by the known THF bulk price. The algebraic expression is as follows:

$$MeTHF_{bulk\ price} = 0.5 \cdot \left(\frac{MeTHF_{Spectrum}}{THF_{Spectrum}} + \frac{MeTHF_{Sigma-Aldrich}}{THF_{Sigma-Aldrich}} \right) \cdot THF_{ICIS\ bulk\ price}$$

The resulting MeTHF price was determined to be US$8.71/kg. The cost of steam, electricity and waste management was assumed to be the same as in the Kalamazoo plant in Michigan (Selamectin case), since it is reasonable that this plant is representative of a typical pharmaceutical plant in the United States. The cost of glycerol, US$2.28/kg, for the extractive distillation recovery case was also obtained from ICIS Pricing[21]. The incineration cost was assumed to be the same as in the Kalamazoo plant.

The economic analysis of the base case and of the THF and MeTHF recovery cases is shown in Table 18, Table 19, Table 20 and Table 21. The savings are calculated as the base case cost minus the recovery case cost.

Table 18. Base case economic analysis

	Quantity (kg/kg THF use)	Unitary Price (US$/kg)	Cost (US$/year)
THF	1	3.28	3.28
Waste Management	1	0.129	0.129
		Total =	3.41

Table 19. THF extractive distillation recovery case economic analysis

	Quantity (kg/kg THF use, *kWh/kg THF use)	Unitary Price (US$/kg, *US$/kWh)	Cost (US$/kg THF use)
THF	0.0047	3.28	0.0154
Glycerol	0.00102	2.28	0.00232
Waste Management	0.0047	0.129	0.000131
Steam	3.46	0.02	0.0692
Electricity*	0.521	0.1	0.0521
		Total =	0.124
		Savings =	3.29

Table 20. THF distillation + pervaporation recovery case economic analysis

	Quantity (kg/kg THF use, *kWh/kg THF use)	Unitary Price (US$/kg, *US$/kWh)	Cost (US$/kg THF use)
THF	0.00748	3.28	0.0245
Waste Management	0.00748	0.129	0.000964
Steam	0.660	0.02	0.0132
Electricity*	0.0941	0.1	0.00941
		Total =	0.0481
		Savings =	3.36

Table 21. MeTHF recovery case economic analysis

	Quantity (kg/kg MeTHF use, *kWh/kg MeTHF use)	Unitary Price (US$/kg, *US$/kWh)	Cost (US$/kg MeTHF use)
*eco*MeTHF™ Purchase	0.0100	8.71	0.0873
Waste Management	0.0100	0.129	0.00129
Steam	0.49	0.02	0.00974
Electricity*	0.058	0.1	0.00577
		Total =	0.104
		Savings =	3.31

The economic analysis results show that, even though MeTHF costs more than twice than THF, the operating costs in the MeTHF recovery case are lower than in the THF extractive distillation recovery case. This occurs mostly because the quantity of steam and electricity used in the extractive distillation process are 7 and 9 times, respectively, the quantities used in the MeTHF case, which reflects the ease of separation of MeTHF. The THF distillation followed by pervaporation recovery case cost is the lowest, however, the operating cost savings are almost the same as those of the MeTHF recovery case, being 98.5 % and 97.1 % of the base case costs, respectively.

Chapter 7

Conclusions

An environmental and economic analysis of solvent recovery in the manufacture of API's was performed. A software toolbox that combines process simulation with environmental and economic impact determination was developed. The results of using our tool in four different solvent waste case studies show that the environmental impact and the operating cost of API manufacturing can be reduced with solvent recovery.

Our tool was used to determine the near optimum distillation operating parameters that maximized LCEA and OCS. The reflux ratio sensitivity analysis performed with the tool showed that conventional heuristics for selecting the optimum reflux ratio do not always apply to solvent recovery. The tool was also used to aid in the selection of pervaporation dehydration membranes.

The feasibility of using the same process skid to recover binary solvent mixtures from LVWS's and HVWS's, and with different thermodynamic properties was evaluated with the R.SWEET tool. All the cases showed positive environmental and economic results. It was shown that using a single recovery skid to purify solvent waste streams with different thermodynamic behavior increases the profitability of the recovery project. The design of a skid flexible enough to treat different waste streams is a key factor to achieve this profitability.

A "green technology" such as pervaporation was included in the skid to evaluate its performances and "greenness". The simulation and economic evaluation results were satisfactory.

The majority of the emissions avoided correspond to the solvent manufacture and incineration LCE that occur outside the boundaries of the pharmaceutical plant, which is consistent with results obtained in previous studies and shows the importance of the LCA. Therefore, green solvents with low LCI should also be used when possible to reduce the manufacture life cycle emissions. Furthermore, green solvent with easy recoverability reduce the incineration life cycle emissions.

Currently, the R.SWEET tool has the flexibility to simulate the recovery of homogeneous azeotropic and non-homogeneous solvent waste mixtures. Future work will expand the tool capabilities to include

- decanting simulation and design;
- three-component separation simulation; and
- handling of solids.

Although our initial efforts have been focused on the pharmaceutical industry, this tool has the potential to be applied to other commercial sectors.

Acknowledgments

Support for this project was provided by the United States Environmental Protection Agency through grant 97212311-0. Special thanks to Rowan students Molly Russell and Stephen Montgomery, and Pfizer staff Frank Urbanski, Carlos Junco, and Peter Dunn for their invaluable collaboration.

List of References

1 Sheldon, R.A. (1997). Catalysis and pollution prevention. *Chem. Ind.,1*, 12-15.

2 Slater, C. S., Savelski, M. J., Carole, W. & Constable D. (2010), Solvent Use and Waste Issues. In P. Dunn, A. Wells, M. Williams (Eds). Green Chemistry in the Pharmaceutical Industry (pp. 2,4, 42-54). Germany: Wiley-VCH.

3 Jimenez-Gonzalez, C., Ponder, C.S., Broxterman, Q.B. & Manley, J.B. (2011). Using the Right Green Yardstick: Why Process Mass Intensity is Used in the Pharmaceutical Industry to Drive More Sustainable Processes. *Org. Process Res. Dev.,15*, 912–917.

4 Butters, M., Catterick, D., Craig, A., Curzons, A., Dale, D. , Gillmore, A., … White, W. (2006). Critical Assessment of Pharmaceutical Processes-A Rationale for Changing the Synthetic Route. *Chemical Reviews, 106*(7), 3002-27.

5 United States Environmental Protection Agency, Office of Environmental Information, Toxic Release Inventory Program, TRI-NET (2010) [Database Software]. Retrieved from: http://www2.epa.gov/toxics-release-inventory-tri-program/download-trinet

6 Slater, C. S. & Savelski, M. J. (2007). A method to characterize the greenness of solvents used in pharmaceutical industry. *Journal in Environmental Science and Health Part A*, *42*, 1595-1605.

7 United States Environmental Protection Agency (2013, June). *Priority Pollutants*. Retrieved from http://water.epa.gov/scitech/methods/cwa/pollutants.cfm/.

8 Verschueren, K. (2001). *Handbook of Environmental Data on Organic Chemicals*. John Wiley & Sons, Inc.

9 Montgomery, J.H. (2000). *Groundwater Chemicals. Desk Reference* (third ed.). Boca Raton, FL, USA: CRC Press LLC.

10 Clark, J.H. & Tavener, S.J. (2007). Alternative Solvents: Shades of Green. *Organic Process Research & Development*, *11*, 149-155

11 Boring, A. (2012). Offshoring Production and Intra-industry Trade. *ETSG 2012 Leuven, Fourteenth Annual Conference, 13-15 September 2012*. Retrieved from the European Trade Study Group website: http://www.etsg.org/ETSG2012/Programme/Papers/471.pdf.

12 United States Environmental Protection Agency (2013, September). Solid Waste Management Hierarchy. Retrieved from the United States Environmental Protection Agency website: http://www.epa.gov/wastes/nonhaz/municipal/hierarchy.htm

13 Michigan Department of Environmental Quality. Environmental Assistance Division (1998). *Considerations in Selecting a Commercial (Off-Site) Solvent Recycling Service. Fact Sheet.*

14 Anastas, P. T. & Zimmerman, J. B. (2003). Design through the Twelve Principles of Green Engineering. *Env. Sci. and Tech.*, *37*(5), 94A-101A.

15 Jimenez-Gonzalez, C., Poechlauer, P., Broxterman, Q. B., Yang, B., Ende, D., Baird, J.,…, Manley, J. (2011). Key Green Engineering Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers. *Organic Process Research & Development*, *15*, 900-911.

16 United States Environmental Protection Agency (2008). *2009-2014 EPA Strategic Plan Change Document***,** Goal 5, Strategic Measure 5.2.1 "Prevent Pollution and Promote Environmental Stewardship", Washington, DC.

17 Slater, C.S. & Savelski, M.J. (2009). Towards a Greener Manufacturing Environment. *Innovations in Pharmaceutical Technology, 29*, 78-83.

18 Raymond, M. J., Slater, C. S. & Savelski, M. J. (2010). LCA approach to the analysis of solvent waste issues in the pharmaceutical industry. *Green Chem., 12*, 1826-1834.

19 ETH Zurich, Safety & Environmental Technology Group (2006). *The Ecosolvent Tool (Version 1.0.1)* [Computer Software]. Retrieved from ETH Zurich website: http://www.sust-chem.ethz.ch/tools/ecosolvent/

20 Pre Consultants (2012). SimaPro [Computer LCA Software]. Retrieved from Pre Consultants website: http://www.pre.nl/simapro/

21 ICIS Pricing (2013, February). Indicative Chemical Prices A-Z. (Editor: Joseph Chang) Retrieved from ICIS Pricing website http://www.icis.com/chemicals/channel-info-chemicals-a-z/

22 Institute for 21st Century Energy. An Affiliate of the U.S. Chamber of Commerce (2012, May). *Crude oil price volatility. Metric of the month. A deeper look into interesting trends in energy security data.* Retrieved from the Institute for 21st Century Energy website: http://www.energyxxi.org/sites/default/files/file-tool/MetricoftheMonth-MAY12CrudeOilPriceVolatility.pdf

23 Rosseau, R. W. (1987). *Handbook of Separation Process Technology*. Wiley and Sons.

24 The University of Edinburgh, *Data Source for Azeotropes*. Retrieved from University of Edinburgh website: http://www.chemeng.ed.ac.uk/people/jack/azeotrope/access.html

25 Felder, R. M. & Rousseau, R. W. (2005), *Elementary principles of chemical processes 3rd edition*, Hoboken, NJ: John Wiley & Sons, Inc.

26 Smallwood, I. (2002). *Solvent Recovery Handbook* (2nd ed., pp. 112). Boca Raton, FL, USA: Blackwell Science.

27 Geankoplis, C. J. (2003), *Transport processes and separation process principles* (4th ed.). Upper Saddle River, NJ, USA: Prentice Hall.

28 Seader, J. D., Henley, E. J. (2006). *Separation Process Principles* (2nd ed., pp. 12). John Wiley & Sons.

29 Gomez, P. & Gil, I. (2009). Simulation of the Tetrahydrofuran Dehydration Process by Extractive Distillation in Aspen Plus. *Latin American Applied Research*, *39*, 275-284.

30 Pierotti, G. J. (1948). Extractive Distillation Process. *United States Patent 2,455,803.*

31 Van Winkle, M. (1968). *Distillation.* USA: McGraw Hill.

32 Seader, J. D. (2006). *Separation Process Principles* (2nd. ed., pp 756). NY: John Wiley and Sons.

33 Pham, H. & Doherty, M. (1990). Design and Synthesis of Heterogeneous Azeotropic Distillation II – Residue Curve Maps. *Chemical Engineering Science, 45*(7), 1837-1843.

34 Bieker, T. & Simmrock, K. H. (1994). Knowledge integrating system for the selection of solvents for extractive and azeotropic distillation. *Computers & Chemical Engineering, 18*(Supplement 1), S25-S29.

35 Van Hoof, V., Van den Abeele, L., Buekenhoudt, A., Dotremont, C. & Leysen, R. (2004). Economic comparison between azeotropic distillation and different hybrid systems combining distillation with pervaporation for the dehydration of isopropanol. *Separation and Purification Technology, 37*, 33-49.

36 Slater, C. S., Savelski, M. J., Moroz, T. M. & Raymond, M. J. (2012). Pervaporation as a green drying process for tetrahydrofuran recovery in pharmaceutical synthesis. *Green Chemistry Letters and Reviews,5*(1), 55-64

37 Wynn, N. (2001, October). *Pervaporation Comes of Age* (October Issue, pp. 66-72). CEP Magazine, AIChE.

38 Baker, R. W. (2004). *Membrane Technology and Applications*. West Sussex, UK: John Wiley & Sons Ltd.

39 Seader, J. D. & Henley, E. J. (1998). *Separation Process Principles*. John Wiley and Sons, Inc.

40 Mulder, M. (1997). *Basic Principles of Membrane Technology*. Dordecht: Kluwer Academic Publishers.

41 Carlson, E. (1996). *Don't Gamble with Physical Properties For Simulations* (October Issue, pp. 35-46). CEP Magazine, AIChE.

42 Csefalvay, E., Szitkai, Z., Mizsey, P. & Fonyo Z. (2008). Experimental data based modeling and simulation of isopropanol dehydration by pervaporation. *Desalination, 229*, 94-108.

43 Verhoef, A., Degreve, J., Huybrechs, B., Veen, H. V., Pex, P. & Van der Bruggen, B. (2008). Simulation of a hybrid pervaporation-distillation process. *Computers & Chemical Engineering, 32*, 1135-1146.

44 Vane, L. (personal communication, July 1, 2013)

45 Lipnizki, F. & Field, R. W. (1999). Simulation and process design of pervaporation plate-and-frame modules to recover organic compounds from waste water. *Trans IChemE, 77*, 231-240.

46 Lipnizki, F., Olsson, J., & Tragardh, G. (2002). Scale-up pervaporation for the recovery of natural aroma compounds in the food industry. Part 1: simulation and performance. *Journal of Food Engineering, 54*, 183-195.

47 Lovasz, A., Farkas, T. & Mizsey, P. (2009). Methodology for modeling of pervaporation: step from binary to ternary mixtures. *Desalination, 241*, 188-196.

48 Naidu, Y. & Malik, R. K. (2011). A generalized methodology for optimal configurations of hybrid distillation-pervaporation processes. *Chemical Engineering Research and Design, 89*, 1348-1361.

49 Feng, X. & Huang R. Y. M. (1996). Estimation of activation energy for permeation in pervaporation processes. *J. Membrane. Sci., 118*, 127-131.

50 Nath, K. (2008). *Membrane Separation Processes*. New Delhi: Prentice Hall of India Private Limited.

51 Schweitzer, P.A. (1996). *Handbook of Separation Techniques for Chemical Processes* (third ed.). New York: McGraw-Hill.

52 Ho, W. S. & Sirkar, K. K. (1992). *Membrane Handbook*. New York, USA: Chapman & Hall.

53 Noble, R.D. & Stern, S.A. (1995). *Membrane separations technology. Principles and applications*. Amsterdam: Elsevier Science B.V.

54 Qiao, X., Chung, T. S., Fen Guo, W., Matsuura, T. & Teoh, M. M. (2005). Dehydration of isopropanol and its comparison with dehydration of butanol isomers from thermodynamic and molecular aspects. *Journal of Membrane Science, 252,* 37–49.

55 Ramzan, N., Degenkolbe, S. & Witt, W. (2008). Evaluating and improving environmental performance of HC's recovery system. *Chem Eng J., 140*, 201–213

56 FIZ CHEMIE Berlin (2013). *Entrainer Selection software. Calculation of Additives and Separation Methods.* Retrieved from FIZ CHEMIE Berlin website: http://www.chemistry.de/

57 McCabe, W. L., Smith, J. C. & Harriot P. (1993). *Unit Operations of Chemical Engineering* (fifth ed.). McGraw-Hill.

58 Pilling, M. & Holden, B. S. (2009, September). *Choosing Trays and Packings for Distillation* (September Issue, pp. 44-50). CEP Magazine, AIChE.

59 Trading Economics (2013, June). *United States Inflation Rate*. Retrieved from the Trending Economics website: http://www.tradingeconomics.com/united-states/inflation-cpi/

60 Revolution; MSDS (2004, May). Retrieved from Pfizer Inc. website: http://www.pfizerah.com/PAHimages/msds_us/RV.pdf

61 Client Information About Revolution, Pfizer Animal Health (2005). Retrieved from Pfizer Inc. website: http://www.pfizerfrank.com/PDF/PfizerFrank/revolution_en_co_ois.pdf

62 Selamectin. CAS Registry Number 220119-17-5. Retrieved from SciFinder Scholar website: https://scifinder.cas.org/scifinder/view/substance/substanceList

63 Walshe, N. D. & Cambers, S. J. (2005). *Patent No. 6906184.* US.

64 Rojas, E., Guerrero- Pérez, M. O. & Bañares, M. A. (2009). Direct ammoxidation of ethane: An approach to tackle the worldwide shortage of acetonitrile. *Catalysis Communications*, *10*(11), 1555-1557.

65 Majors, R. E. The continuing acetonitrile shortage: how to combat it or live with it. *LCGC North America 2009, 27, 6.*

66 New Jersey Department of Environmental Protection (2011). Ground Water Quality Standard for Acetonitrile".. www.nj.gov/dep/wms/bwqsa.

67 Acetone: Health Information Summary. New Hampshire Department of Environmental Services. Concord, NH. Retrieved from www.des.nh.gov

68 Aspen Plus$^{®}$ (2011) [Computer Chemical Processes Simulator Software]. AspenTech.

69 Wilkinsin, G. R. (1976) The Manufacture and Use of Selected Inorganic Cyanides. Kansas

City: Midwest Research Institute (for the U.S.EPA).

---

70 Nelfinavir, MSDS (2009, September). Retrieved from website: http://www.viivhealthcare.com/en/products/~/media/Files/G/GlaxoSmithKline-Plc/Attachments/pdfs/products/Viracept-Tablets-EN.pdf

71 Nelfinavir (2011). CAS Registry Number 159989-64-7. Retrieved from SciFinder Scholar website: https://scifinder.cas.org/scifinder/view/substance/substanceList.

72 Logsdon, J. E. & Loke R. A. (2000). Isopropyl Alcohol. *Kirk-Othmer Encyclopedia of Chemical Technology*. John Wiley & Sons, Inc. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/0471238961.0919151612150719.a01/abstract

73 Isopropyl Alcohol. MSDS (2011). Retrieved from ScienceLab website: www.sciencelab.com.

74 Tetrahydrofuran. MSDS (2011). Retrieved from ScienceLab website: www.sciencelab.com.

75 Hydrocortisone Acetate (2011). Cas Registry Number 50-03-3. Retrieved from SciFinder Scholar website: https://ezproxy.rowan.edu:2360/scifinder/view/scifinder/scifinderExplore.jsf.

76 TriOptic-S, MSDS (2011). Retrieved from Pfizer Inc. website: http://www.pfizerah.com/PAHimages/compliance_pdfs/US_EN_TS_compliance.pdf..

77 Slater, C. S., Savelski, M., Hounsell, G., Pilipauskas, D. & Urbanski , F. (2008). Analysis of Separation Methods for Isopropanol Recovery in the Celecoxib Process. *Proceedings of the 2008 Meeting of the American Institute of Chemical Engineers*, Philadelphia, PA.

78 Urtiaga, A, Casado, C., Asaeda, M. & Da Ortiz, I. (2006). Comparison of SiO2-ZrO2-50% and commercial SiO2 membranes on the pervaporative dehydration of organic solvents. *Desalination, 193*, 97–102.

79 Aul, R., Comanita, B. (2007). A green alternative to THF. Manufacturing chemist, May 2007, 33-34.

80 Seader, J. D., Siirola, J. J. & Barnicki, S. D. (1997). Section 13: Distillation. In R. Perry, D. Green, J. Maloney (Eds.), *Perry's Chemical Engineers Handbook* (7th edition, pp. 13-32,13-34).

81 Fair, J. R., (1997). Distillation. In D. Ruthven (Ed.), *Encyclopedia of Separation Technology* (Volume 1, pp. 603). New York: John Wiley & Sons, Inc.

82 McCormick, J. E., & Roche E. C. (1997). Section 1.1. Continuous Distillation: Separation of Binary Mixtures. In P. Schweitzer (Ed.), *Handbook of Separation Techniques for Chemical Engineers* (3rd edition, pp. 1-38). New York: McGraw-Hill.

83 McCabe, W. L., Smith J. C., Harriott, P. (2005). *Unit Operations of Chemical Engineering* (7th Edition, pp. 692). New York: McGraw-Hill.

84 Campos, D., Knopf, J., Majumdar, S. & Nemser, S (2011, June). THF Dehydration by Pervaporation with Perflurinated Composite Membrane. *NAMS 2011, June 4-8*, Las Vegas, NV, USA.

85 Global Industry Analysts, Inc. (2011, April). Global Tetrahydrofuran Market to Exceed 800 Thousand Tons by 2017, According to a New Report by Global Industry Analysts, Inc.. Retrieved from PRWeb website: http://www.prweb.com/releases/tetrahydrofuran/PTMEG_solvents/prweb8281771.htm..

86 Aycock, D. F. (2007). Solvent application of 2-methyltetrahydrofuran in organometallic and biphasic reaction. *Organic Process Research & Development,11*, 156-159

---

87 Dunn, P. (2012). Personal Communication.

88 Lee-Jeffs, A (2012). Personal Communication.

89 Chapman, P. D., Tan, X., Livingston A. G., Li, K. & Oliveira, T. (2006). Dehydration of tetrahydrofuran by pervaporation using a composite membrane. *Journal of Membrane Sciences, 268,* 13-19.

90 Spectrum Laboratory Products, Inc. (2013, March). Retrieved from Spectrum Laboratory Products, Inc website: https://www.spectrumchemical.com/OA_HTML/index.jsp?minisite=10020&respid=22372&language=US

91 Sigma-Aldrich® (2013, March). Retrieved from Sigma-Aldrich® website: http://www.sigmaaldrich.com/united-states.html

Appendix A

Organic Solvents available in R.SWEET

Table A 1. List of solvents included in R.SWEET

methyl tert butyl ether (MTBE)	formic acid	1,2-dimethoxyethane
n,n-dimethylformamide	isobutyl acetate	1-propanol
n-butanol	isopentyl acetate	2-butanol
n-butyl acetate	isopropyl acetate	acetic acid
n-heptane	isopropyl alcohol (IPA)	acetone
n-hexane	Methanol	acetonitrile
n-methyl 2-pyrrolidone	methyl acetate	chlorobenzene
tetrahydrofuran (THF)	methylcyclohexane	cyclohexane
toluene	methyl ethyl ketone (MEK)	dichloromethane (DCM)
water	methyl isobutyl ketone (MIK)	ethanol
ethyl acetate		

Appendix B

Detailed Recovery Process Selection Guide Functioning

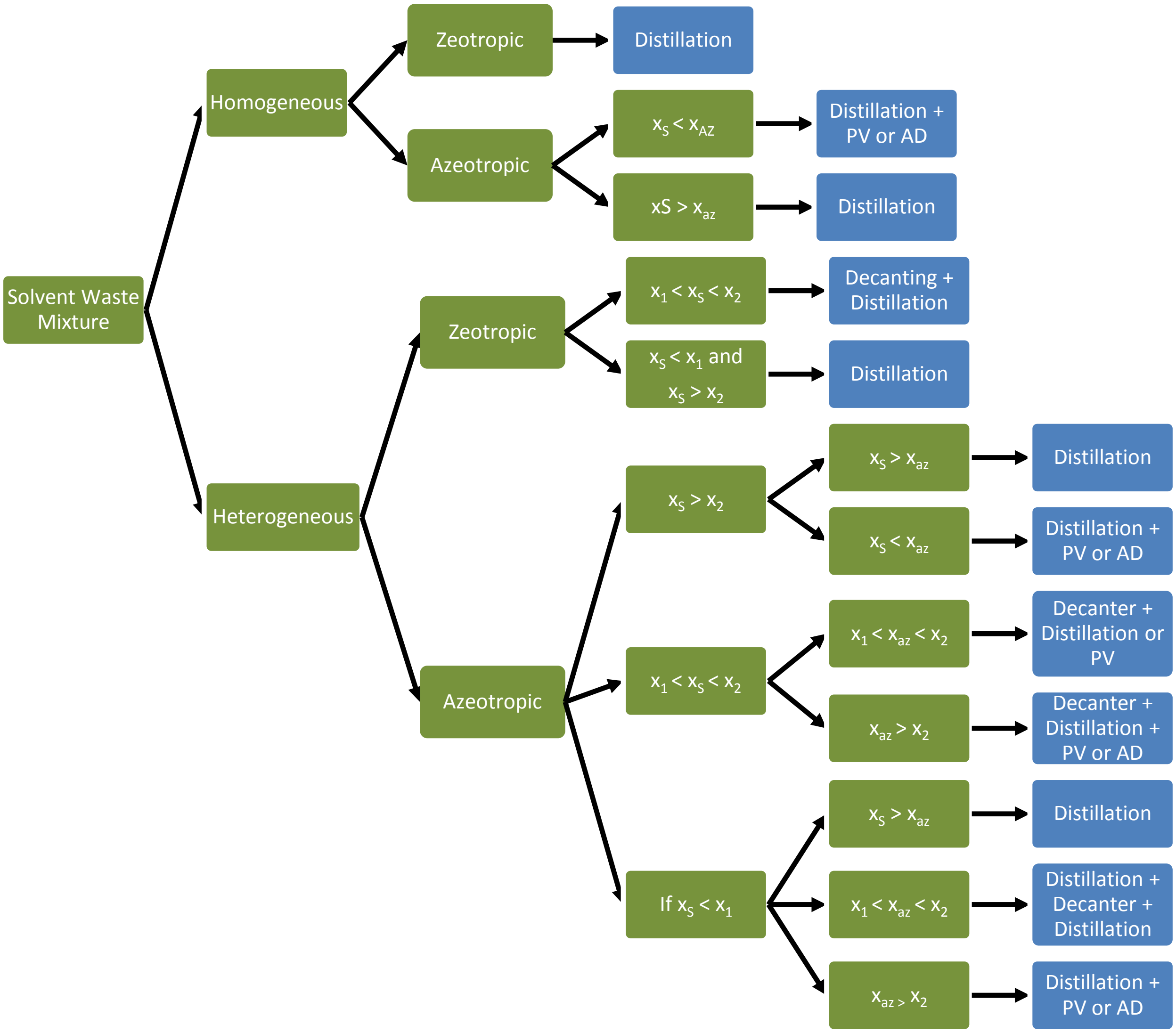


Figure A 1. Recovery Process Selection Guide decision tree. x_S: Mass fraction of the solvent to recover; x_1: Solvent mass fraction in the liquid phase with low concentration of the desired solvent, in the heterogeneous mixture; x_2: Solvent mass fraction in the liquid phase with high concentration of the desired solvent, in the heterogeneous mixture; x_{az}: Mass fraction in the azeotrope; PV: Pervaporation; AD: Azeotropic Distillation.

To demonstrate how the Recovery Process Selection Guide works, five binary solvent mixtures were selected to show the 5 different possible separation techniques that can be suggested by the tool:

- distillation,
- distillation, then pervaporation (PV) or azeotropic distillation (AD),
- decanting, then distillation,
- decanting, then distillation, then PV or AD, and lastly,
- distillation then decanting then distillation.

A binary mixture of methanol and water is homogeneous and zeotropic as shown by the vapor-liquid equilibrium diagram in Figure A 2, created using Aspen Plus® Binary Analysis.

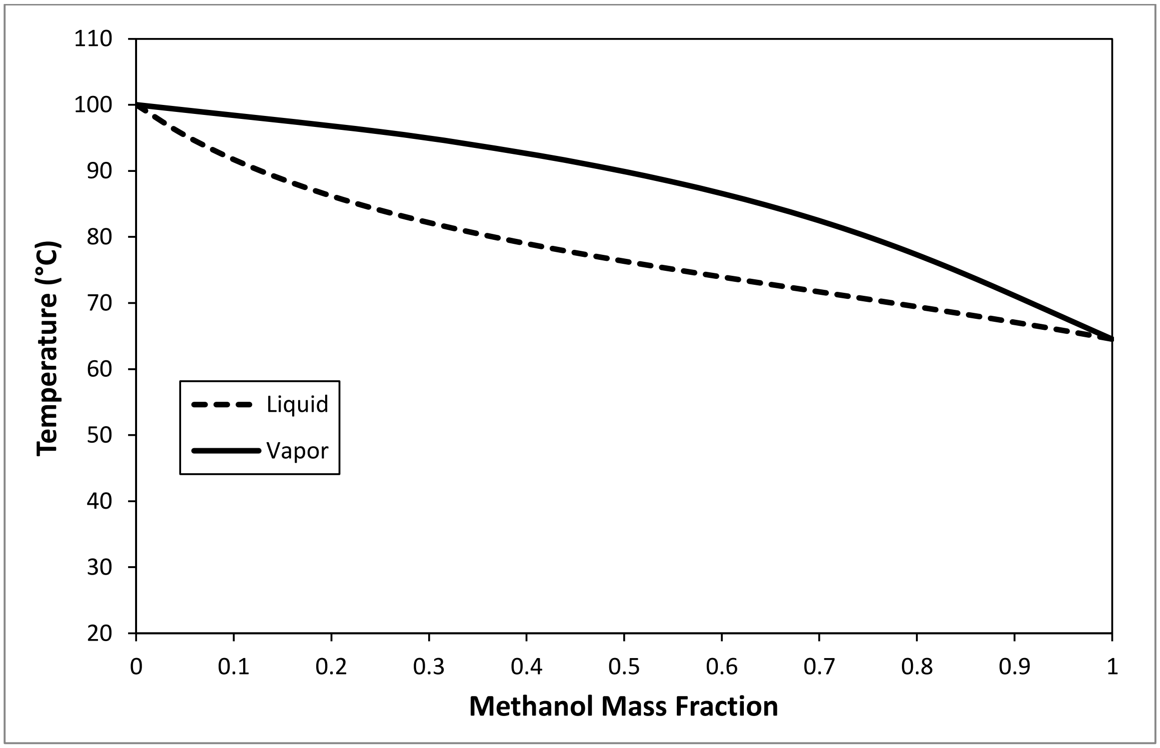
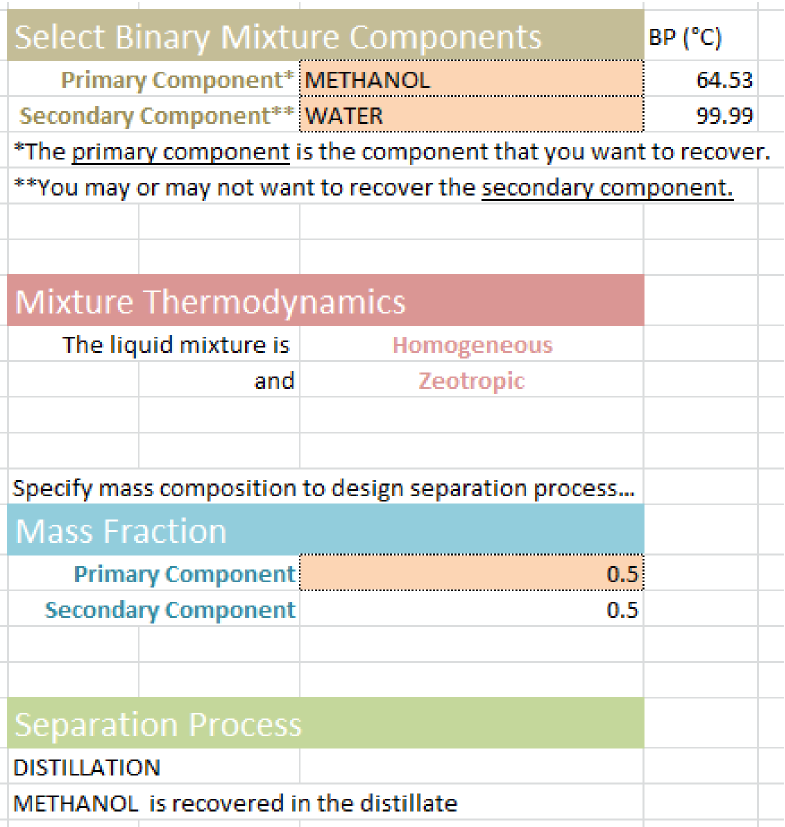


Figure A 2. Vapor-liquid equilibrium diagram for a binary mixture of methanol and water at 1 atm created using Aspen Plus® Binary Analysis.

Simple distillation would effectively separate and recover methanol for re-use in a plant. Based on the thermodynamic behavior of this system, it is apparent that for all possible feed compositions, a single distillation column would effective. For the 50-50 % wt. methanol and water mixture, a screenshot from the tool can be seen in Figure A 3, which shows that distillation is the suggested separation process and methanol would be recovered in the distillate, which agrees with the conclusion reached from observing the system thermodynamics.



Select Binary Mixture Components		BP (°C)
Primary Component*	METHANOL	64.53
Secondary Component**	WATER	99.99

*The primary component is the component that you want to recover.

**You may or may not want to recover the secondary component.

Mixture Thermodynamics

The liquid mixture is Homogeneous

and Zeotropic

Specify mass composition to design separation process...

Mass Fraction	
Primary Component	0.5
Secondary Component	0.5

Separation Process

DISTILLATION

METHANOL is recovered in the distillate

Figure A 3. Screenshot of the solvent process selection guide tool for a 50-50 % wt. mixture of methanol and water.

Not all mixtures that require only simple distillation as the separation process have the same thermodynamic behavior. In the 1,2-dimethoxyethane/water system in Figure A 5, the n-hexane/n-methyl-2-pyrrolidone systems in Figure A 6 and Figure A 7, the desired solvent can effectively be purified with distillation, even though these mixtures have different thermodynamic behavior.

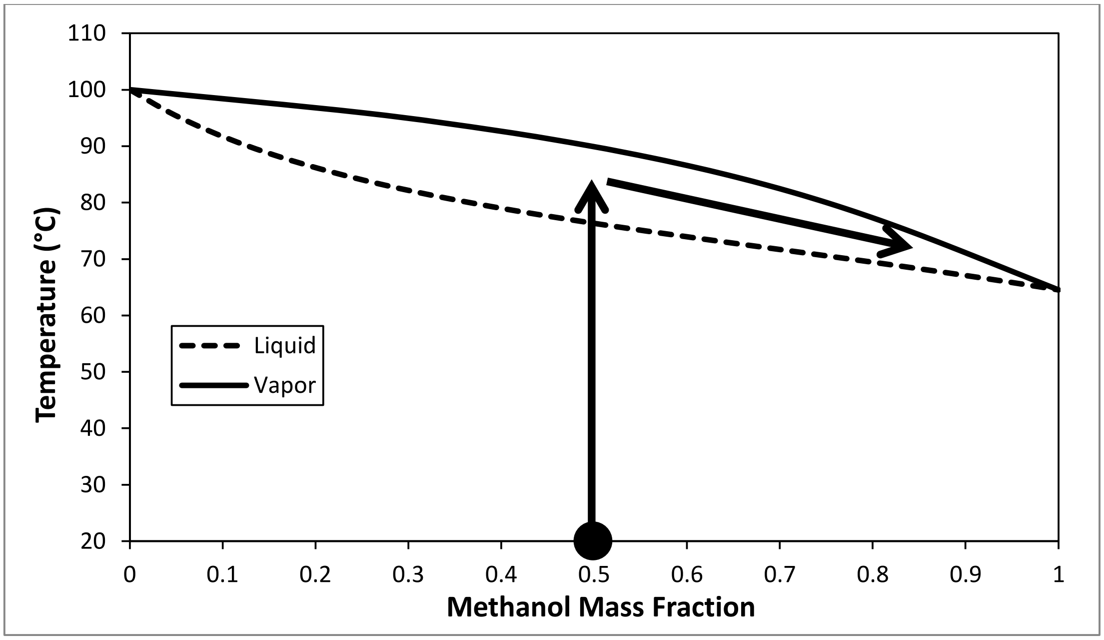


Figure A 4. Illustration of a purification process for a 50-50% mixture of water and methanol to obtain methanol by distillation.

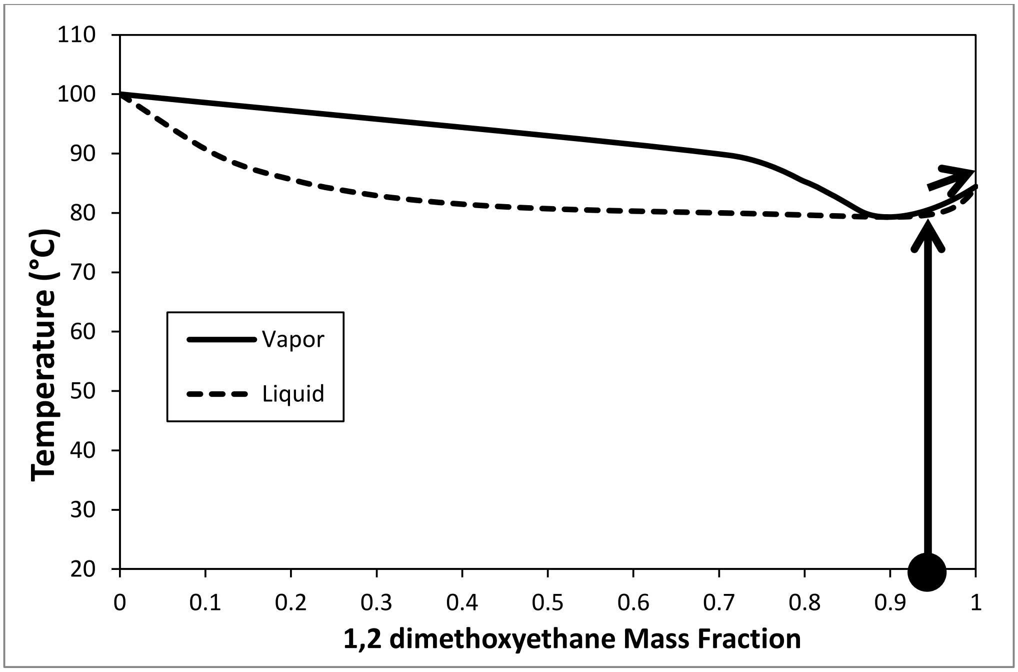


Figure A 5. Illustration of a purification process for a 95 % wt. mixture of 1,2-dimethoxyethane in water to obtain 1,2-dimethoxyethane by distillation.

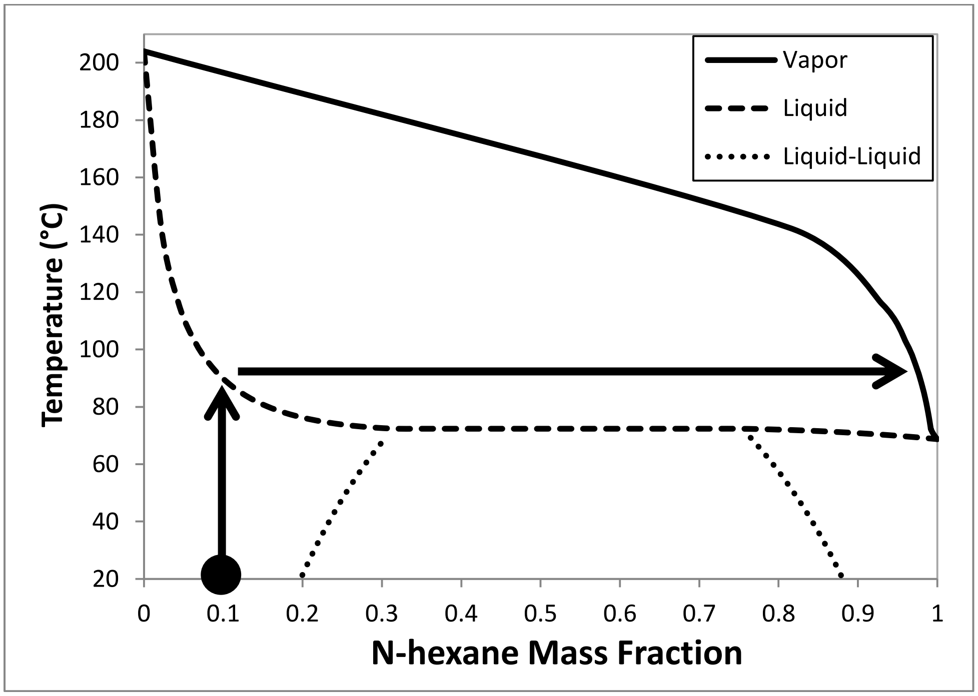


Figure A 6. Illustration of a purification process for a 10 % wt. mixture of n-hexane in n-methyl-2-pyrrolidone to obtain n-hexane by distillation.

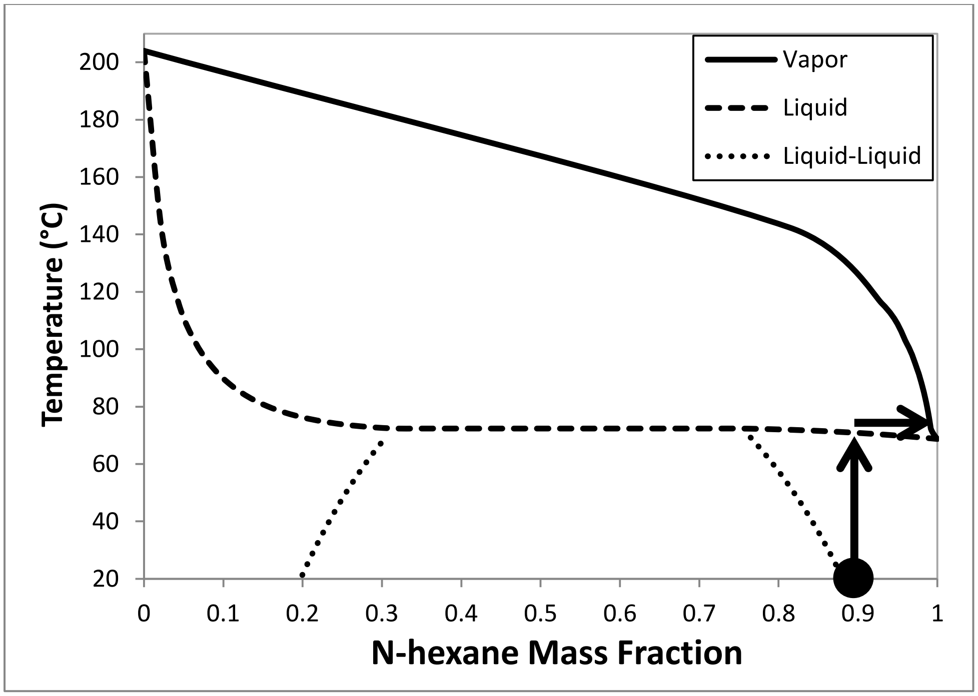


Figure A 7. Illustration of a purification process for a 90 % wt. mixture of n-hexane in n-methyl-2-pyrrolidone to obtain n-hexane by distillation.

The second separation process that can be suggested by the tool is distillation followed by either a pervaporation or azeotropic distillation. Such is the case of a 25 % wt. mixture of 1,2-dimethoxyethane in water as seen in the vapor-liquid equilibrium diagram of Figure A 8.

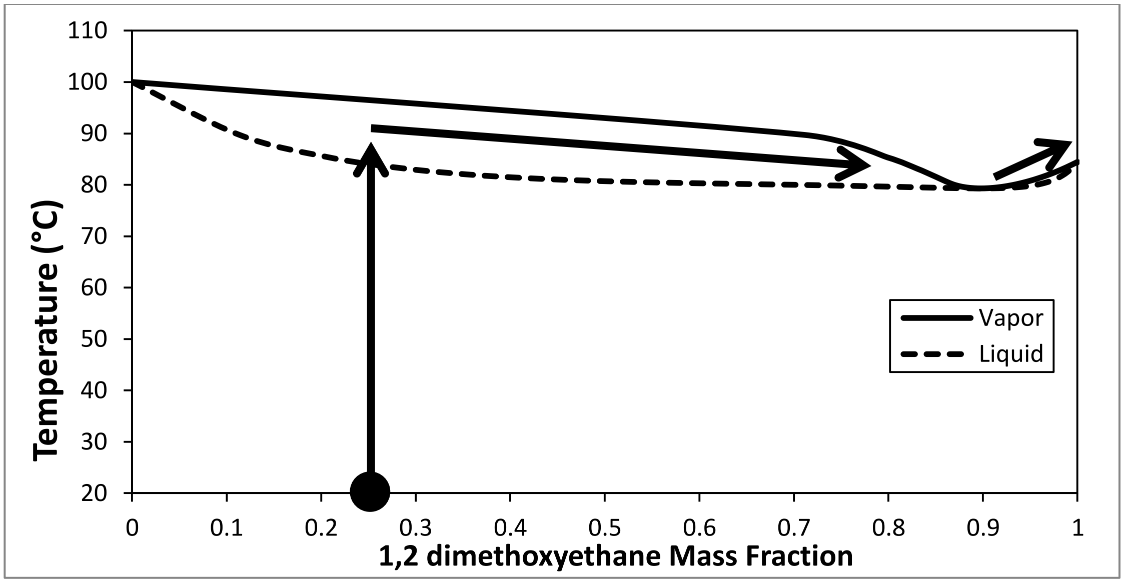


Figure A 8. Illustration of a purification process for a 25 % wt. mixture of 1,2-dimethoxyethane in water to obtain 1,2-dimethoxyethane by distillation to the azeotrope and then either pervaporation or azeotropic distillation to the purity desired.

A representative block flow diagram for the purification process of the 25 % wt. mixture of 1,2-dimethoxyethane can be seen in Figure A 9. The case assumes a 25 % wt. mixture of 1,2-dimethoxyethane is fed to a distillation column, which produces a water bottoms product and an approximately 90 % wt. azeotropic mixture of 1,2-dimethoxyethane. This azeotropic mixture can then be fed either to a pervaporation system or an azeotropic distillation process to dehydrate the mixture and obtain 1,2-dimethoxyethane product to be recycled back to the pharmaceutical process.

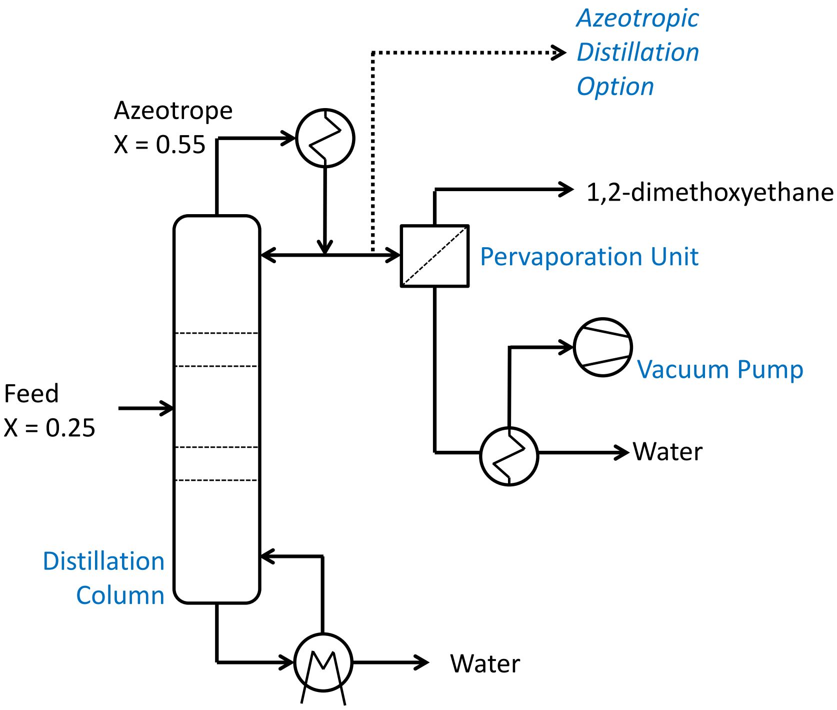
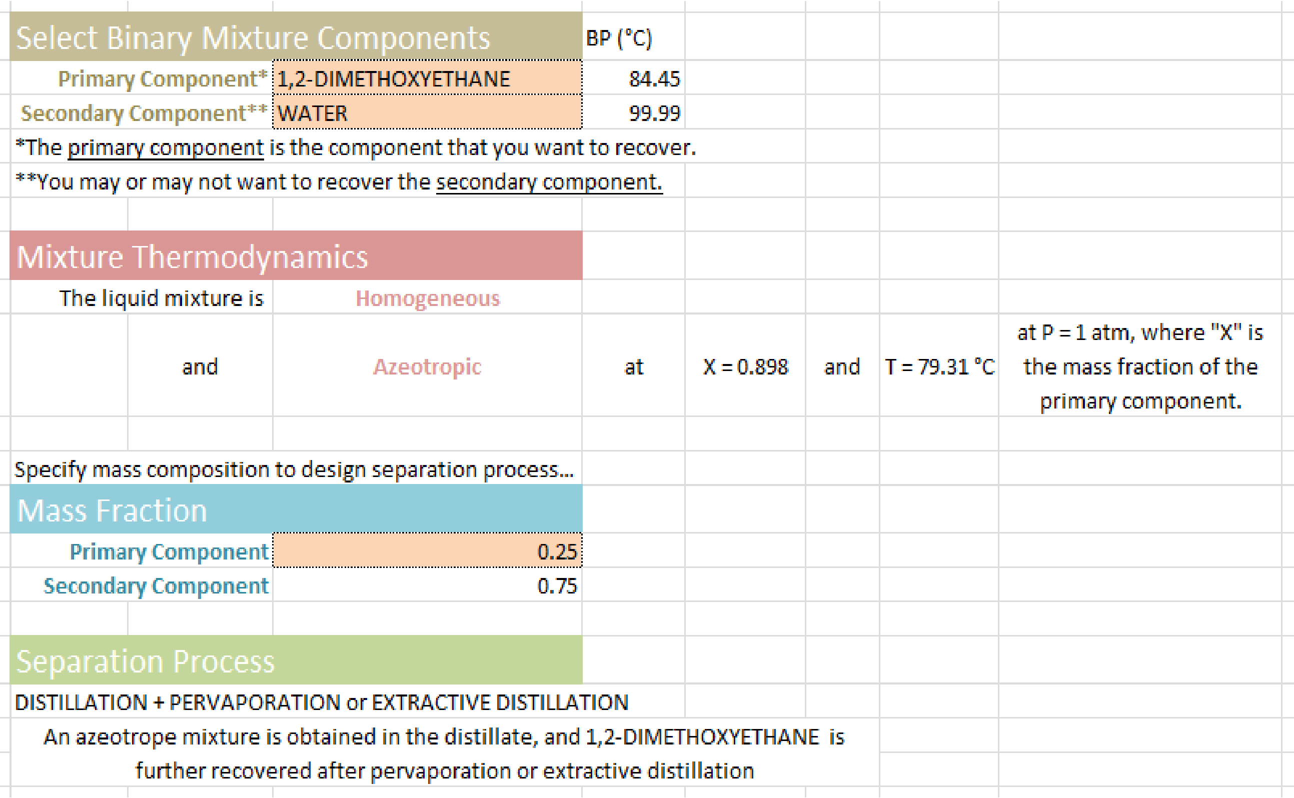


Figure A 9. Process flow diagram for a 25 % wt. mixture of 1,2-dimethoxyethane in water. Mass fractions shown are mass fractions of 1,2-dimethoxyethane in the mixture. Concentrations shown are for illustrative purposes.

When using the solvent recovery selection guide tool, the user will input the two solvents, 1,2-dimethoxyethane and water, and a mass fraction of 0.25 for 1,2-dimethoxyethane. This results in the screenshot seen in Figure A 10. The suggested separation process from the solvent recovery selection guide matches the process determined by studying the system thermodynamics (Figure A 8).



Select Binary Mixture Components		BP (°C)
Primary Component*	1,2-DIMETHOXYETHANE	84.45
Secondary Component**	WATER	99.99

*The primary component is the component that you want to recover.

**You may or may not want to recover the secondary component.

Mixture Thermodynamics

The liquid mixture is Homogeneous

and Azeotropic at X = 0.898 and T = 79.31 °C at P = 1 atm, where "X" is the mass fraction of the primary component.

Specify mass composition to design separation process...

Mass Fraction	
Primary Component	0.25
Secondary Component	0.75

Separation Process

DISTILLATION + PERVAPORATION or EXTRACTIVE DISTILLATION

An azeotrope mixture is obtained in the distillate, and 1,2-DIMETHOXYETHANE is further recovered after pervaporation or extractive distillation

Figure A 10. Screenshot of the recovery process selection guide for a 25 % wt. mixture of 1,2-dimethoxyethane in water. Cells that require user input are highlighter in orange.

A binary mixture of 2-methyltetrahydrofuran (2-MeTHF) and water, is heterogeneous between 10 to 94 % wt. of 2-MeTHF at 25 °C (Figure A 11). If the feed mixture is within this heterogeneous range, the first step in the separation process would use a decanter to separate the two liquid phases.

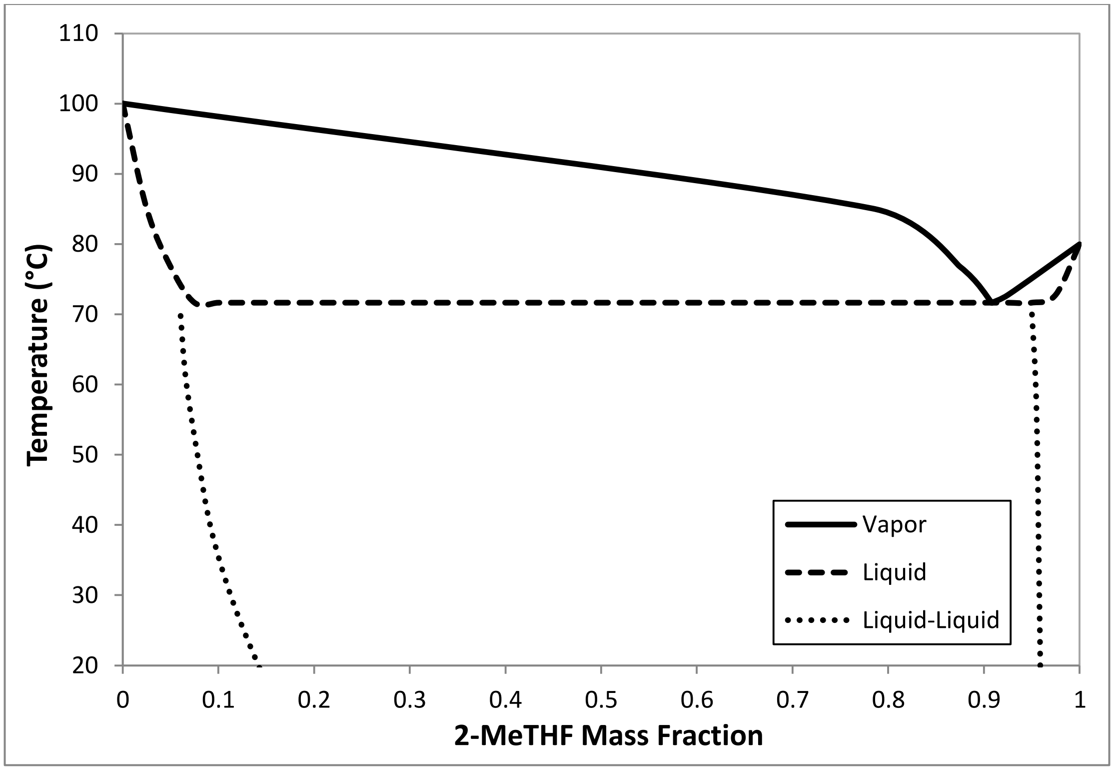


Figure A 11. A vapor-liquid equilibrium diagram for the water and n-butanol binary mixture at 1 atm created using Aspen Plus® Binary Analysis.

For a 50-50% mixture of 2-MeTHF and water, it can be seen from Figure A 12 that the mixture is heterogeneous which is indicated by the fact that the liquid equilibrium line is horizontal from approximately 10-94 % wt. 2-MeTHF. From this, the ideal first step in the separation process would use a decanter to separate the two liquid phases. Exiting the decanter will be an aqueous stream containing approximately 10 % wt. 2-MeTHF and an organic stream containing approximately 94 % wt. 2-MeTHF. The organic stream would then need to be further purified with distillation in order to be recycled. A representative block diagram for this process can be seen in Figure A 13.

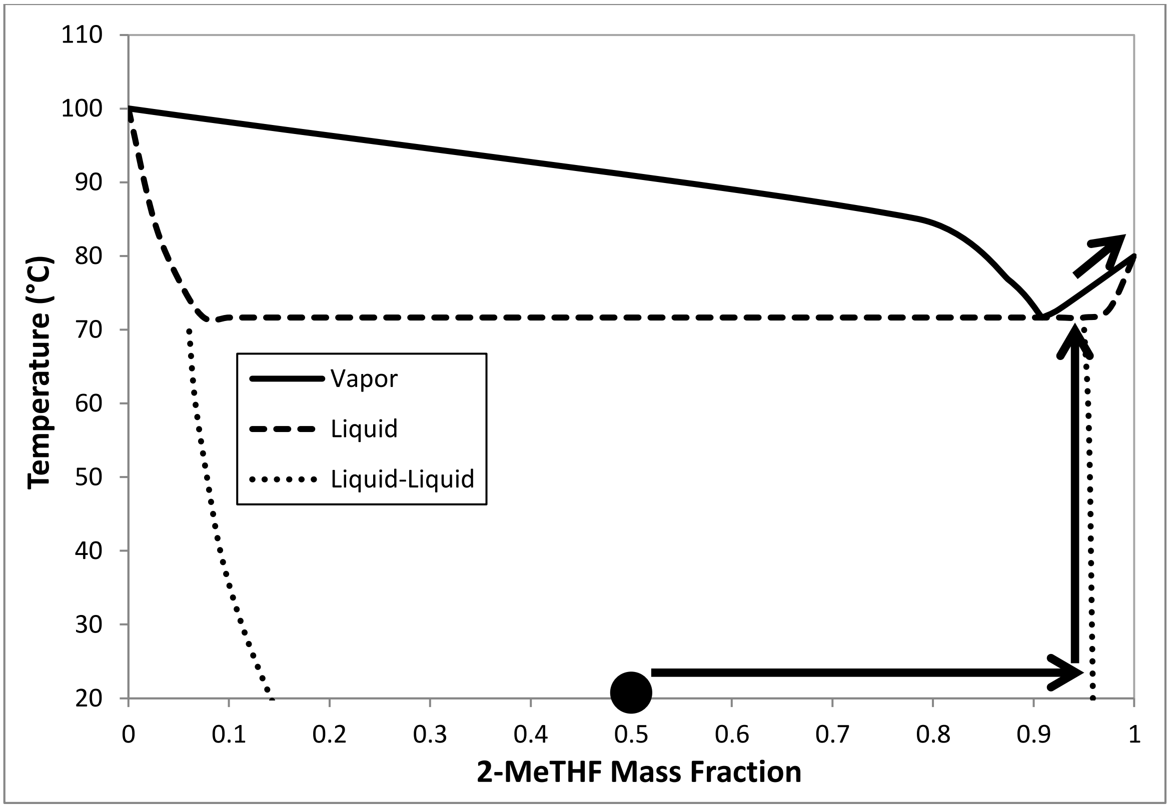


Figure A 12. Illustration of a purification process for a 50-50 % wt. mixture of water and 2-MeTHF to obtain 2-MeTHF by decanting and then distillation.

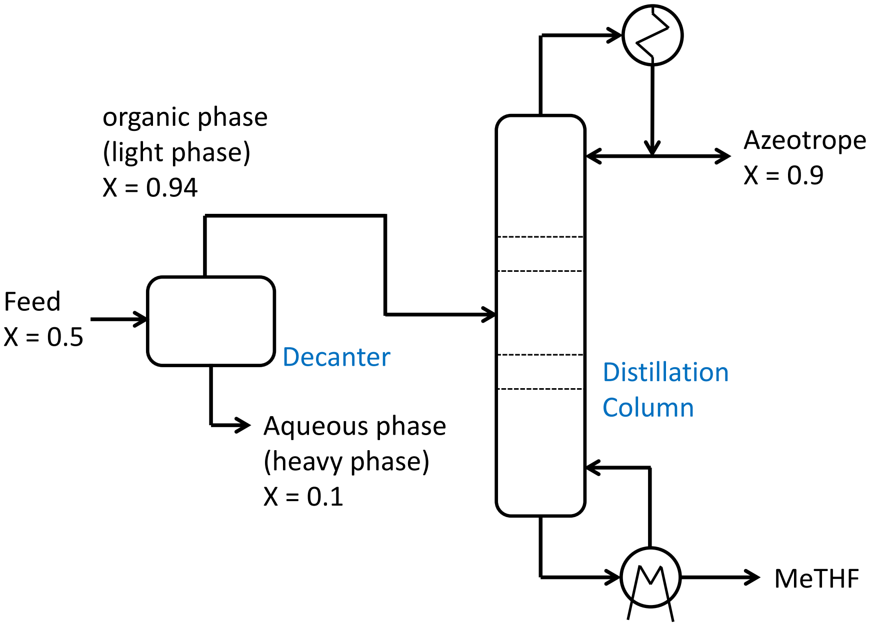
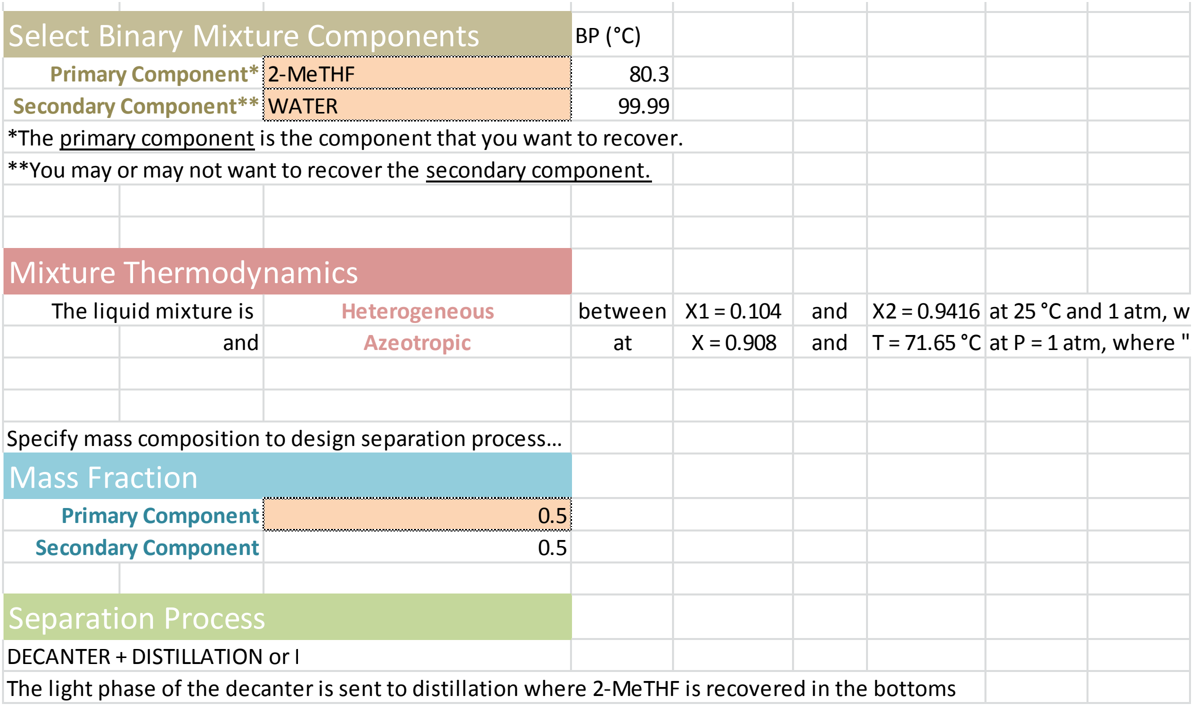


Figure A 13. Separation Process for a 50-50 % wt. mixture of 2-MeTHF and water. Mass fractions (X) shown are the mass fractions of 2-MeTHF in the mixture. Concentrations shown are for illustrative purposes.



Select Binary Mixture Components		BP (°C)
Primary Component*	2-MeTHF	80.3
Secondary Component**	WATER	99.99

*The primary component is the component that you want to recover.
**You may or may not want to recover the secondary component.

Mixture Thermodynamics

The liquid mixture is	Heterogeneous	between	X1 = 0.104	and	X2 = 0.9416 at 25 °C and 1 atm, w
and	Azeotropic	at	X = 0.908	and	T = 71.65 °C at P = 1 atm, where "

Specify mass composition to design separation process...

Mass Fraction	
Primary Component	0.5
Secondary Component	0.5

Separation Process
DECANTER + DISTILLATION or I
The light phase of the decanter is sent to distillation where 2-MeTHF is recovered in the bottoms

Figure A 14. User interface for the recovery process selection guide. Shown is a 50-50 % wt. feed mixture of 2-MeTHF and water. Cells that require user input are highlighted in orange.

As seen in Figure A 14 the suggested separation process for this case is a decanter followed by distillation.

The fourth separation process that the recovery process selection guide provides is a decanter, followed by a distillation column, followed by either a pervaporation unit or an azeotropic distillation unit. One example mixture that would require this recovery process is a 50-50 % wt. mixture of 1-propanol and water. From the vapor-liquid equilibrium diagram in Figure A 15 it is clear that the thermodynamics for this mixture are more complex than previous mixtures mentioned due to the location of the azeotrope outside of the heterogeneous range. Figure A 16 shows the recovery process for this mixture. A decanter would first be used to split the two liquid phases that are formed, producing an organic phase with approximately 65 % wt. 1-propanol. After the decanter, a distillation column could be used to get to the azeotrope (~70 % wt. 1-propanol), and lastly a pervaporation unit or an azeotropic distillation system could be used to get past the azeotrope and reach the desired purity. A block flow diagram for this process can be seen in Figure A 17. The suggested recovery process by the recovery selection process guide agrees with this thermodynamic analysis, as seen in Figure A 18.

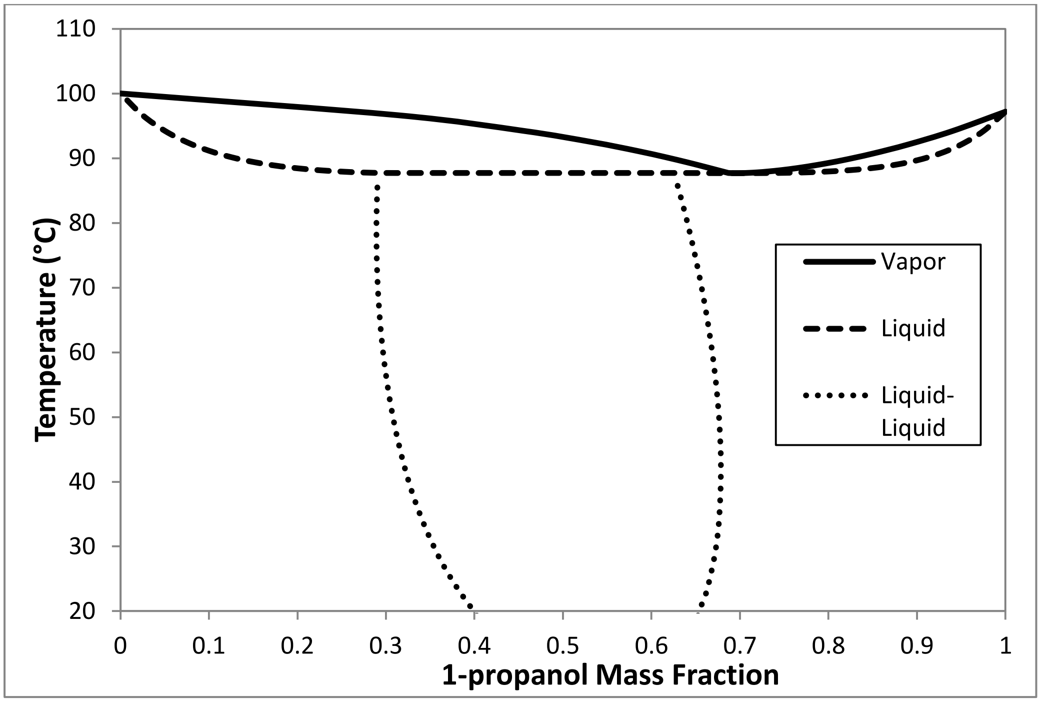


Figure A 15. Vapor-liquid equilibrium diagram for a binary mixture of 1-propanol and water created using Aspen Plus®.

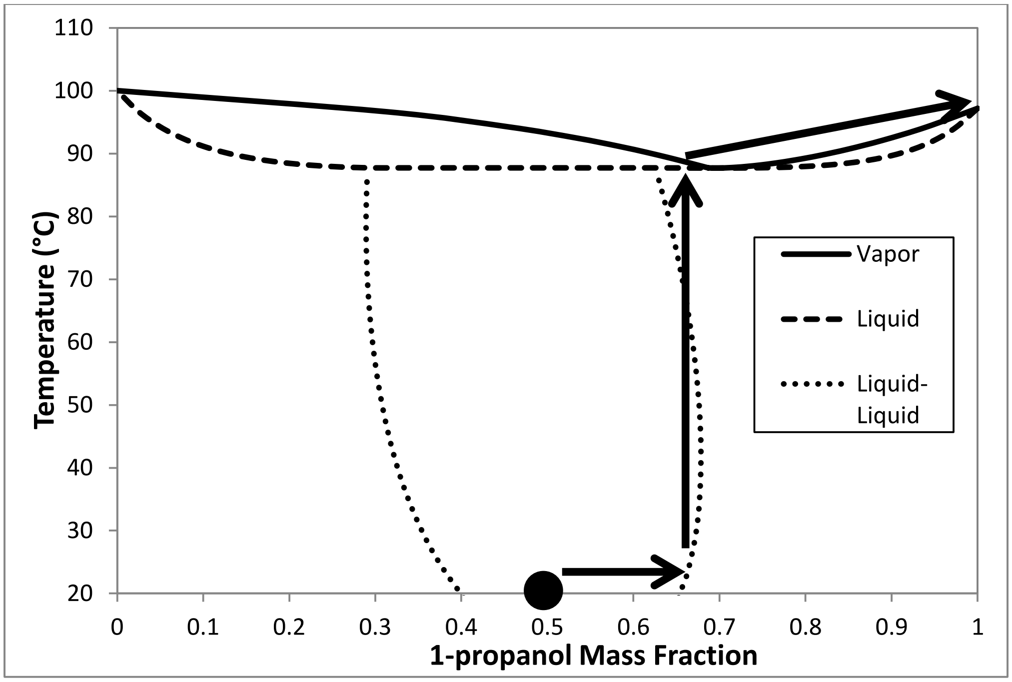


Figure A 16. Illustration of the process of decanting, distilling to get to the azeotrope, and pervaporation or azeotropic distillation to reach the desired purity.

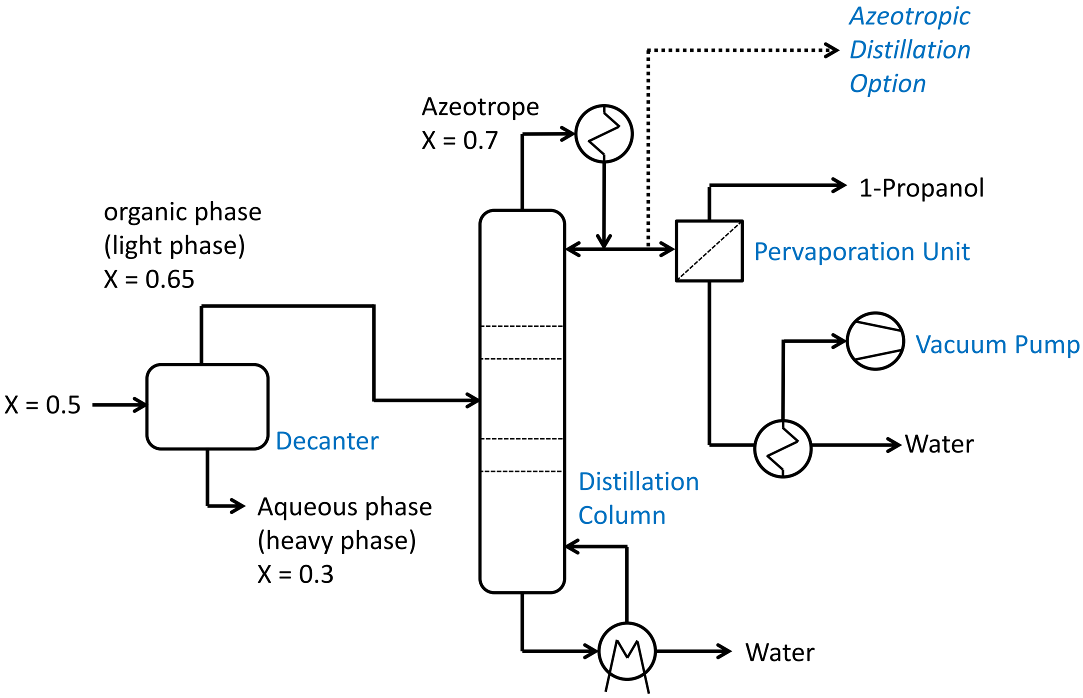
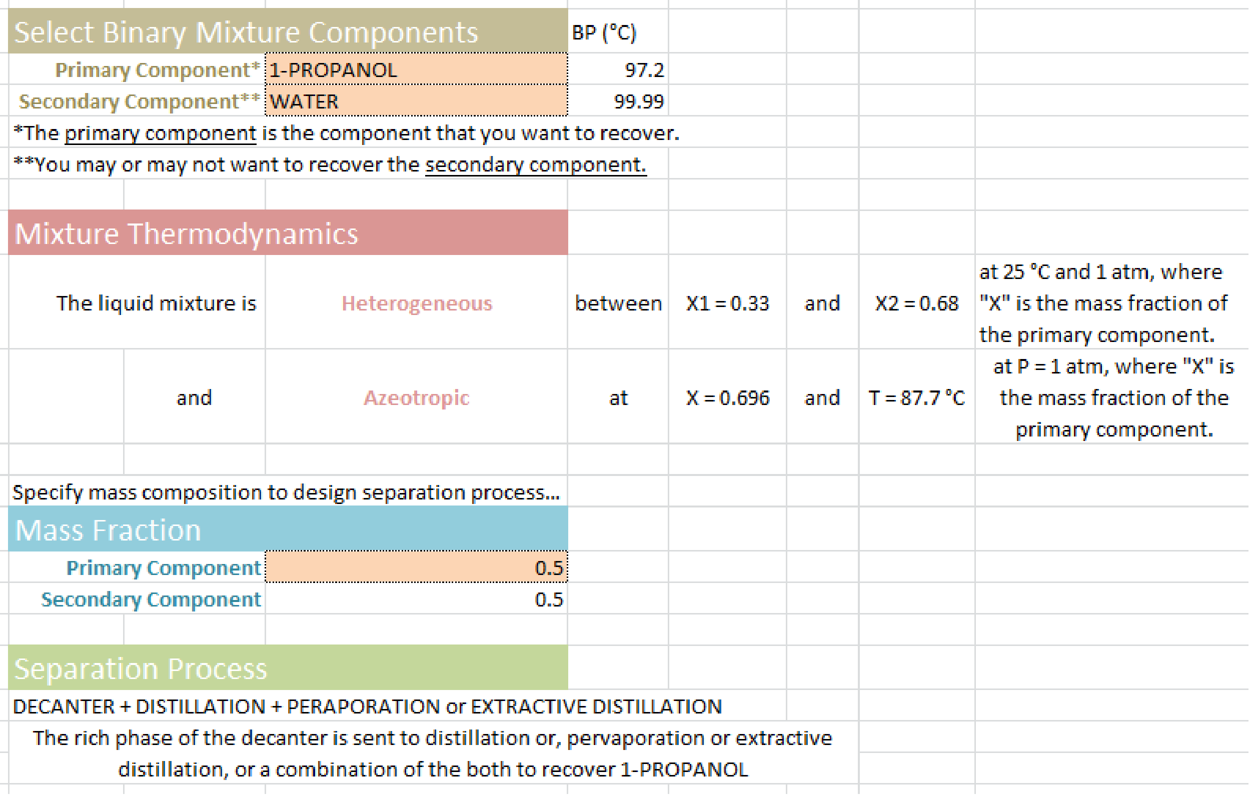


Figure A 17. Block flow diagram for the three step recovery process for a 50-50 % wt. mixture of 1-propanol and water. All mass fractions shown are mass fraction of 1-propanol in the mixture. Concentrations shown are for illustrative purposes.



Select Binary Mixture Components		BP (°C)
Primary Component*	1-PROPANOL	97.2
Secondary Component**	WATER	99.99

*The primary component is the component that you want to recover.

**You may or may not want to recover the secondary component.

Mixture Thermodynamics

The liquid mixture is	Heterogeneous	between	X1 = 0.33	and	X2 = 0.68	at 25 °C and 1 atm, where "X" is the mass fraction of the primary component.
and	Azeotropic	at	X = 0.696	and	T = 87.7 °C	at P = 1 atm, where "X" is the mass fraction of the primary component.

Specify mass composition to design separation process...

Mass Fraction	
Primary Component	0.5
Secondary Component	0.5

Separation Process

DECANTER + DISTILLATION + PERAPORATION or EXTRACTIVE DISTILLATION

The rich phase of the decanter is sent to distillation or, pervaporation or extractive distillation, or a combination of the both to recover 1-PROPANOL

Figure A 18. Screenshot of the recovery process selection guide for a 50-50 % wt. mixture of 1-propanol and water. The required user inputs are highlighted in orange.

The final separation process suggested by the recovery process selection guide is a distillation column, followed by a decanter, followed by another distillation column. This process could be employed on a mixture of 5 % wt. 2-MeTHF in water. As seen in Figure A 19, the mixture is initially not within the heterogeneous range; therefore, distillation is first required. After distillation to a composition near the azeotrope, a decanter can be used to separate the two liquid phases. The 2-MeTHF rich organic phase from the decanter can then be distilled to recover purified 2-MeTHF. The block flow diagram in Figure A 20 shows the recovery process for the mixture of 5 % wt. 2-MeTHF in water. The separation process determined by analyzing the system thermodynamic behavior matches the suggested separation by the Recovery Process Selection Guide in Figure A 21.

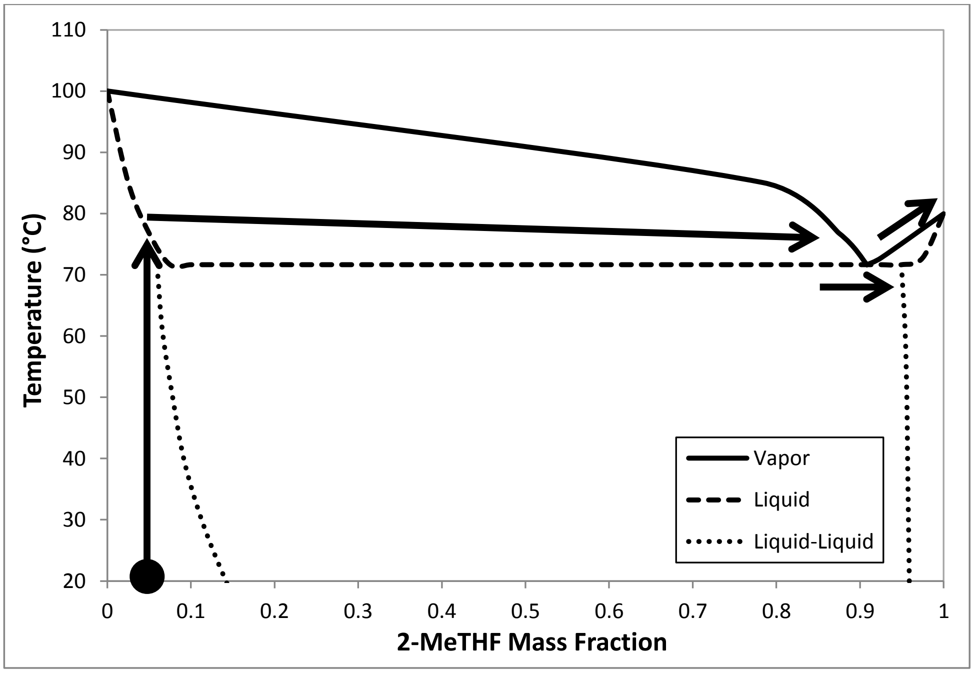


Figure A 19. Illustration of a purification process for a 5 % wt. mixture of 2-MeTHF in water. (1) Distillation from 5 % wt. 2-MeTHF to ~90 % wt. (2) Decanter to separate two liquid phases of the heterogeneous mixture. (3) Distillation to achieve purified 2-MeTHF.

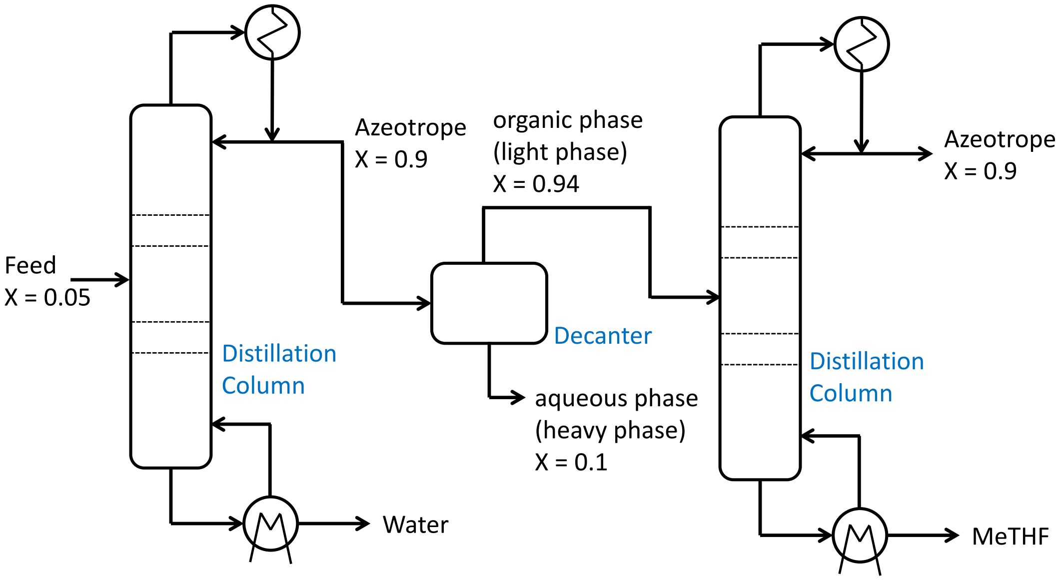
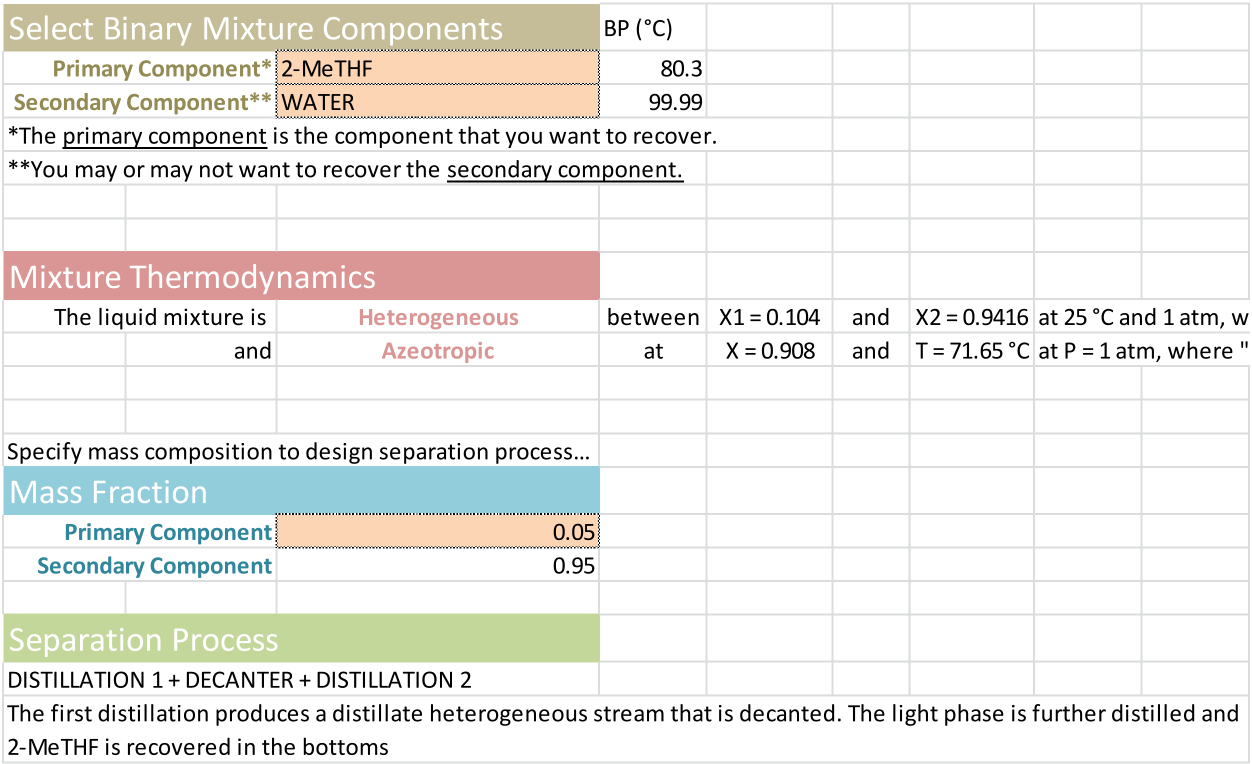


Figure A 20. Separation process for a 5 wt. % mixture of 2-MeTHF in water. Mass fractions shown are the mass fractions of 2-MeTHF in the mixture. Concentrations shown are for illustrative purposes.



Select Binary Mixture Components		BP (°C)				
Primary Component*	2-MeTHF	80.3				
Secondary Component**	WATER	99.99				
*The primary component is the component that you want to recover.						
**You may or may not want to recover the secondary component.						
Mixture Thermodynamics						
The liquid mixture is	Heterogeneous	between	X1 = 0.104	and	X2 = 0.9416	at 25 °C and 1 atm, w
and	Azeotropic	at	X = 0.908	and	T = 71.65 °C	at P = 1 atm, where "
Specify mass composition to design separation process...						
Mass Fraction						
Primary Component	0.05					
Secondary Component	0.95					
Separation Process						
DISTILLATION 1 + DECANTER + DISTILLATION 2						
The first distillation produces a distillate heterogeneous stream that is decanted. The light phase is further distilled and 2-MeTHF is recovered in the bottoms						

Figure A 21. User interface for the recovery process selection guide. Shown is a 5 % wt. feed mixture of 2-MeTHF in water. Cells that require user input are highlighted in orange.

Appendix C

UNIQUAC Thermodynamic Behavior Prediction vs. Experimental Data

In the following figures, the vapor liquid equilibrium prediction using UNIQUAC as the thermodynamic property method is compared with experimental data. The letter "x" refers to the mole fraction in the liquid, and "y" refers to the mole fraction in the gas. The experimental data references are shown at the bottom of the figures.

Acetone-Acetonitrile

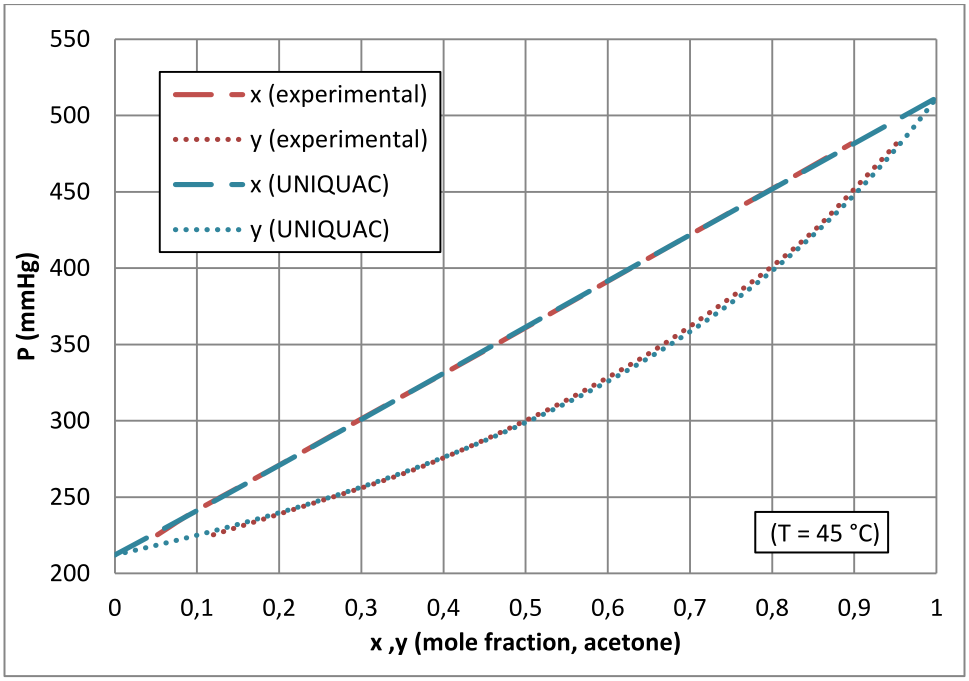


Figure A 22. *P-x-y* vapor-liquid equilibrium diagram for acetone and acetonitrile at a constant temperature of 45 °C. Experimental data reference: Brown I., Smith F.: Austr. J. Chem. 13, 30 (1960).

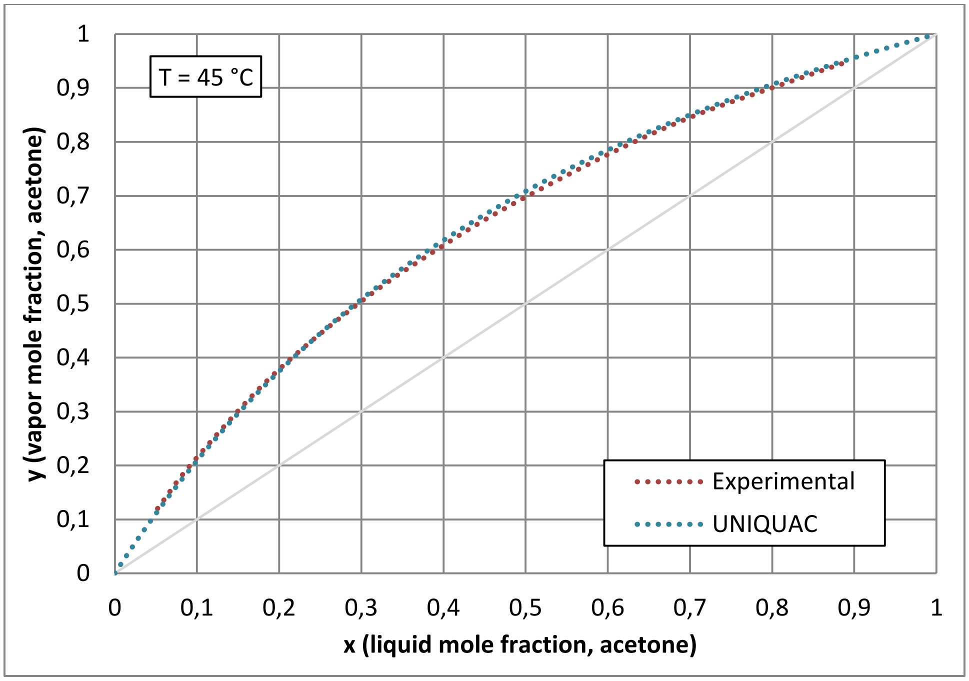


Figure A 23. *x-y* vapor-liquid equilibrium diagram for acetone and acetonitrile at a constant temperature of 45 °C. Experimental data reference: Brown I., Smith F.: Austr. J. Chem. 13, 30 (1960).

IPA-THF

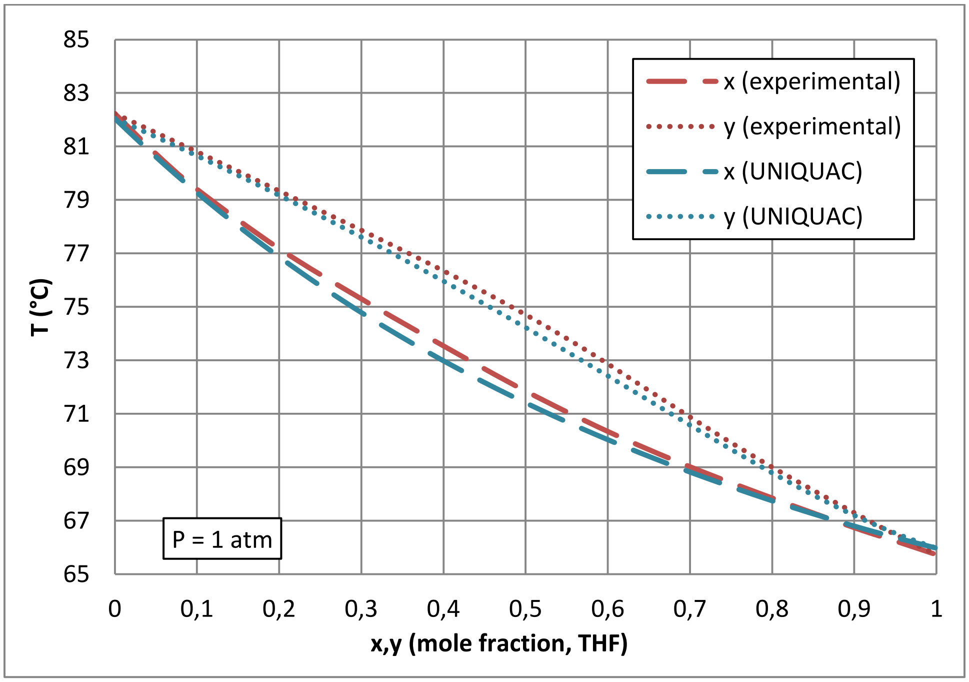


Figure A 24. *T-x-y* vapor-liquid equilibrium diagram for IPA and THF at a constant pressure of 1 atm. Experimental data reference: Sheblom T.V.: Liquid-Vapor Equilibrium in the System Tetrahydrofuran-Isopropyl Alcohol. Zh.Prikl.Khim. 42 (1969) 2389-2390.

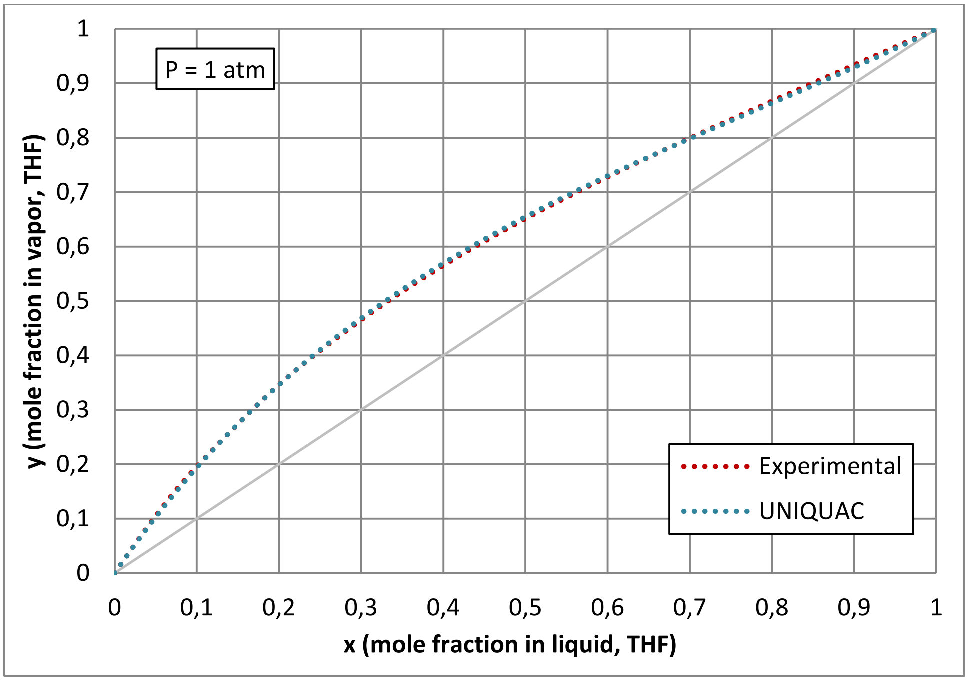


Figure A 25. *x-y* vapor-liquid equilibrium diagram for IPA and THF at a constant pressure of 1 atm. Experimental data reference: Sheblom T.V.: Liquid-Vapor Equilibrium in the System Tetrahydrofuran-Isopropyl Alcohol. Zh.Prikl.Khim. 42 (1969) 2389-2390.

Acetone-Toluene

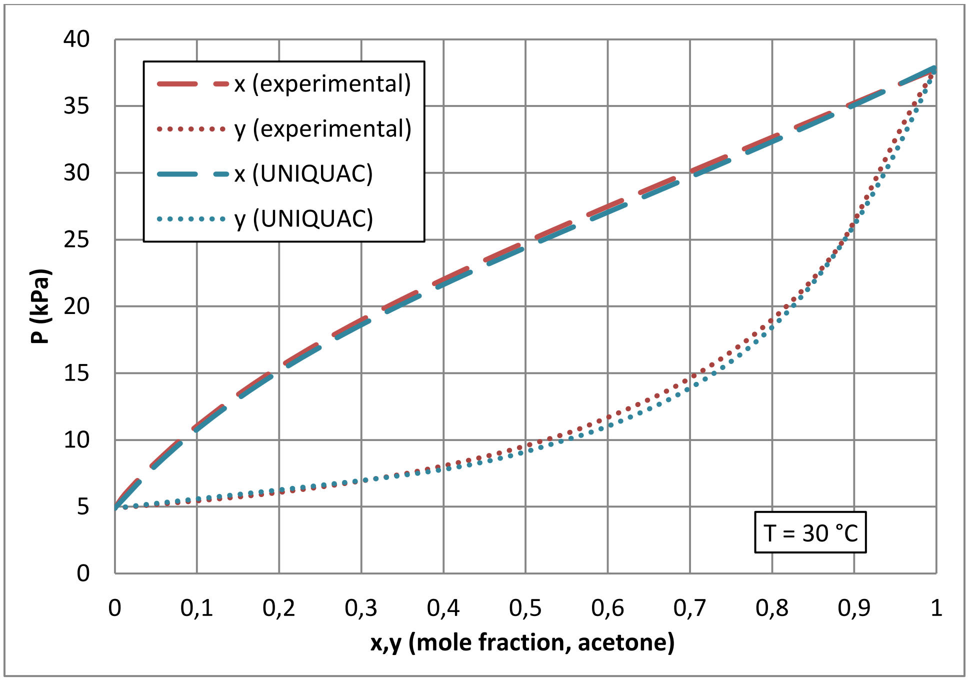


Figure A 26. *P-x-y* vapor-liquid equilibrium diagram for acetone and toluene at a constant temperature of 30 °C. Experimental data reference: Hopkins,J.A., V.R.Bhethanabotla and S.W.Campbell, J.Chem.Eng.Data, 39, 488 (1994).

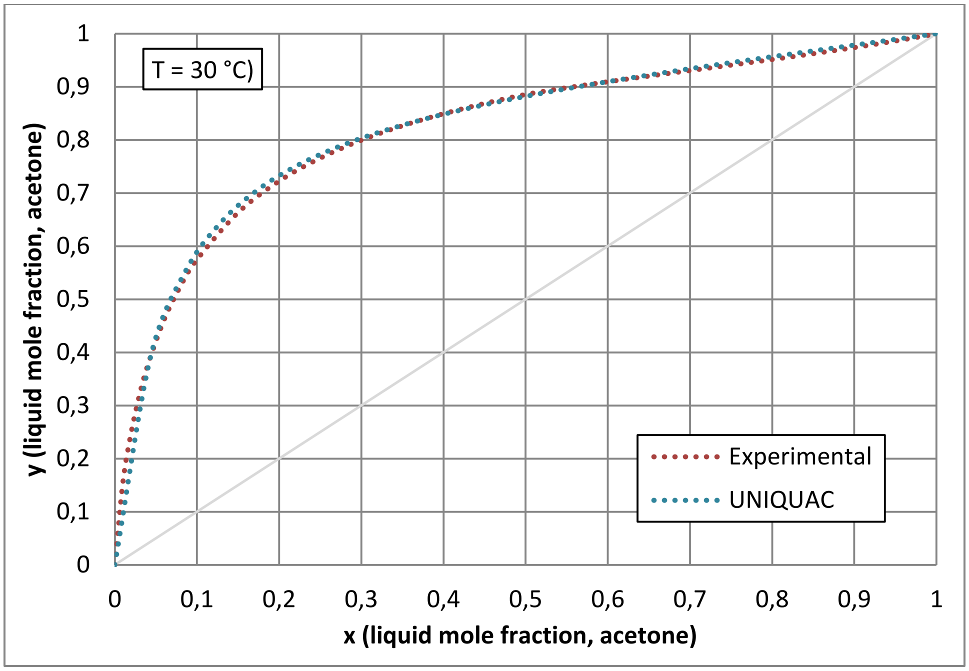


Figure A 27. *x*-*y* vapor-liquid equilibrium diagram for acetone and toluene at a constant temperature of 30 °C. Experimental data reference: Hopkins,J.A., V.R.Bhethanabotla and S.W.Campbell, J.Chem.Eng.Data, 39, 488 (1994).

IPA-Water

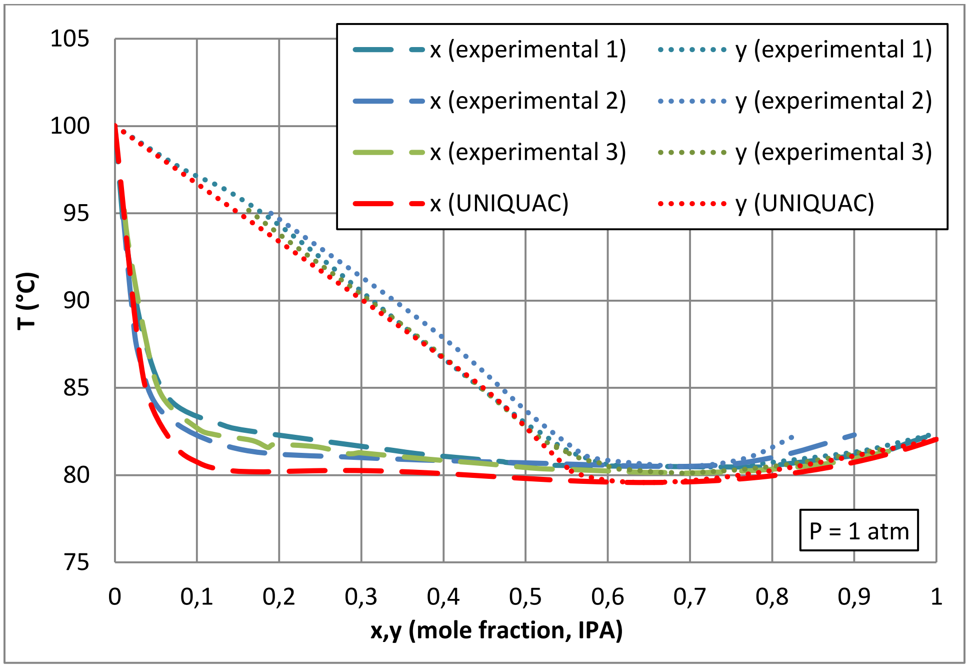


Figure A 28. *T*-*x*-*y* vapor-liquid equilibrium diagram for IPA and water at a constant pressure of 1 atm. Experimental data reference: 1. Kojima, Ochi and Kamazawa. Int. Chem. Eng., 9, 342 (1964), 2. Lebo R.B.: J. Am. Chem. Soc. 43, 1005 (1921), 3. Wilson A., Simons E. L.: Ind. Eng. Chem. 44, 2214 (1952).

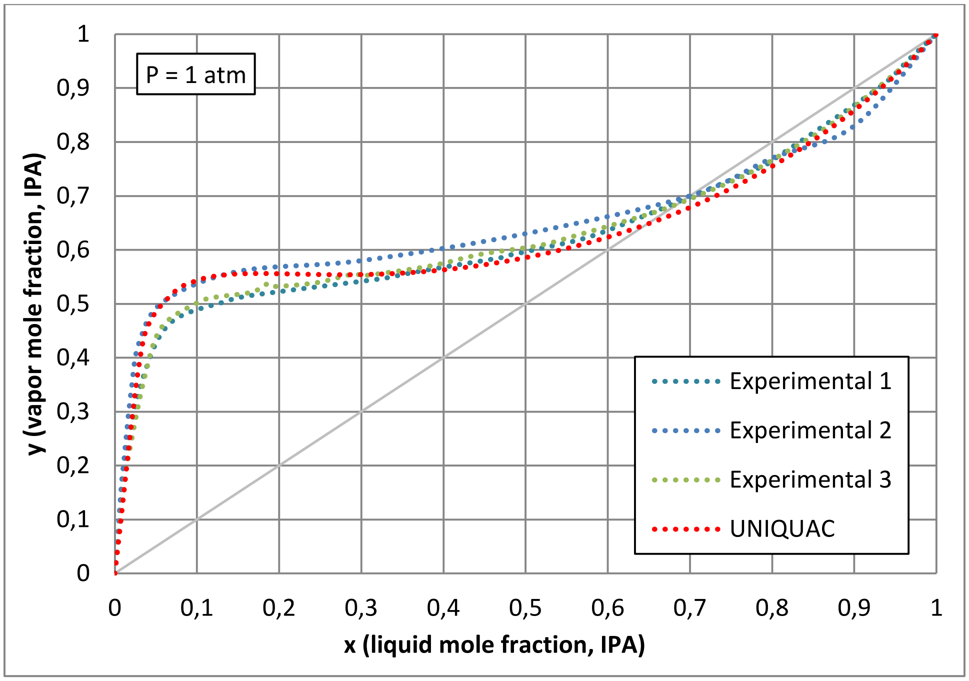


Figure A 29. *x-y* vapor-liquid equilibrium diagram for IPA and water at a constant pressure of 1 atm. Experimental data reference: 1. Kojima, Ochi and Kamazawa. Int. Chem. Eng., 9, 342 (1964), 2. Lebo R.B.: J. Am. Chem. Soc. 43, 1005 (1921), 3. Wilson A., Simons E. L.: Ind. Eng. Chem. 44, 2214 (1952).

Appendix D

Pervaporation Membrane Coefficients, Standard Temperature and Energy of Activation

Table A 2. Water and IPA pervaporation flux polynomial coefficients in commercial membranes

Component	**Membrane**	**Polynomial Coefficient**						**T_O (°C)**
		A	*B*	*C*	*D*	*E*	*F*	
Water	Sulzer PV 1001	0	0	2.555	-5.356	2.838	0	55
	Sulzer PV 2510	0	0	736.9	-2016	1807	-528.0	90
	Mitsui Zeolite NaA	$-1.00\cdot10^{5}$	$4.41\cdot10^{5}$	$-7.74\cdot10^{5}$	$6.68\cdot10^{5}$	$-2.98\cdot10^{5}$	$5.42\cdot10^{4}$	90
	Sulzer PV 2201	0	$-3.92\cdot10^{4}$	$1.38\cdot10^{5}$	$-1.82\cdot10^{5}$	$1.07\cdot10^{5}$	$-2.34\cdot10^{4}$	90
IPA	Sulzer PV 1001	0	0	$4.91\cdot10^{-2}$	$-9.06\cdot10^{-2}$	$4.22\cdot10^{-2}$	0	55
	Sulzer PV 2510	0	0	-29.17	79.26	-72.30	22.22	90
	Mitsui Zeolite NaA[a]	0	0	-3,134	9,063	-8,733	2,804	70
	Sulzer PV 2201	0	0	11.24	-29.29	25.39	-7.315	90

[a] Below an IPA mass composition of 0.954, the polynomial coefficients for this membrane are all zero, since no solvent is observed in the permeate below this mass composition.

Table A 3. Isopropanol flux polynomial function coefficients and energy of activation for commercial membranes (Shah, 2001; Qiao et al., 2005; Van Hoof et al., 2004).

Membrane	**$E_{i,water}$ (kJ/mol)**	**$E_{i,ipa}$ (kJ/mol)**
Sulzer PV 1001	44.46	35.67
Sulzer PV 2510	43.6	81.10
Mitsui Zeolite NaA	68.39	36.88
Sulzer PV 2201	62.7	94.90

Appendix E

Diagram representation of pervaporation calculations

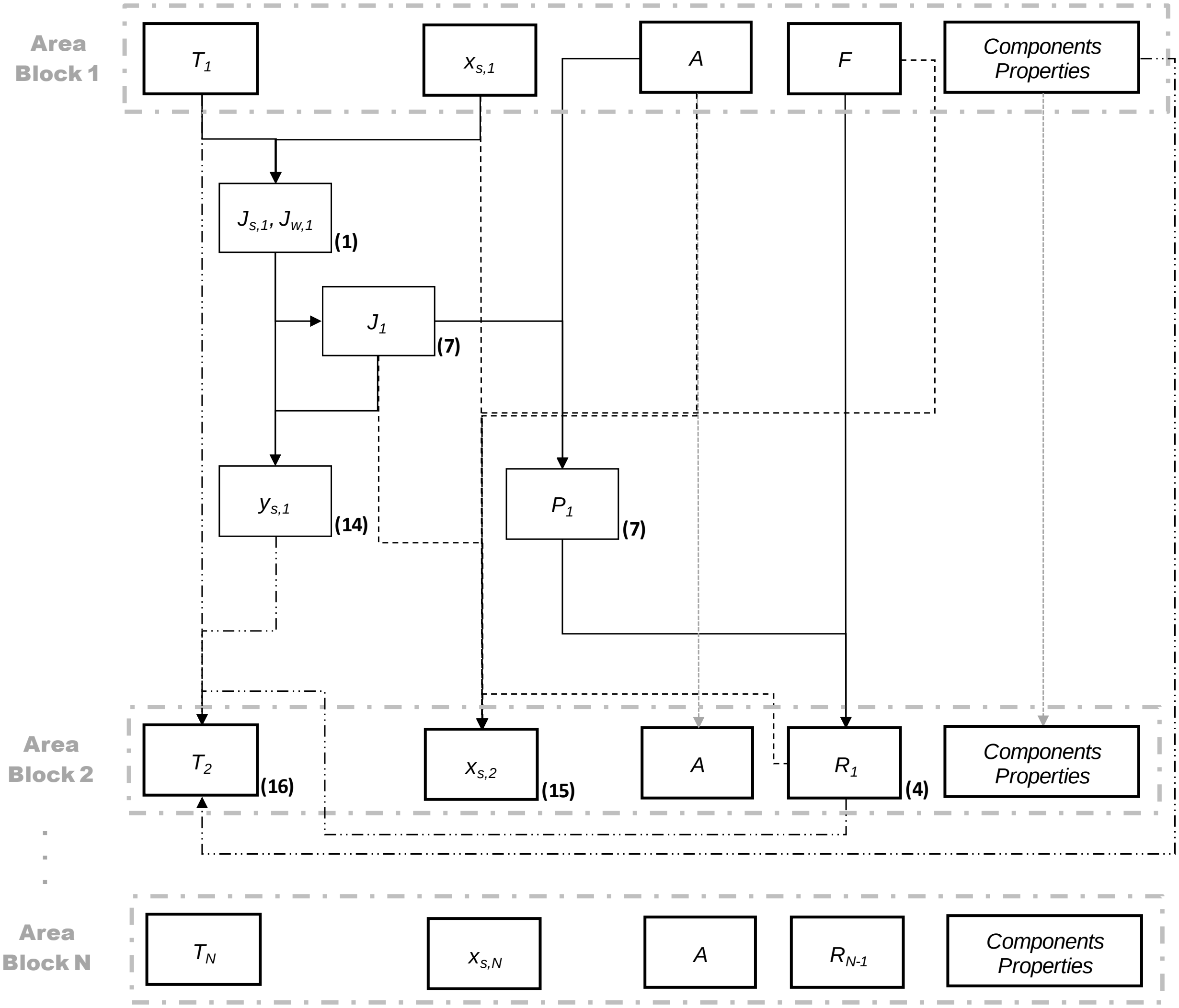


Figure A 30. Diagram representation of pervaporation membrane area, mass balance and energy balance calculation procedure

Appendix F

Detailed Organic Solvents LCI

Table A 4. Life cycle inventory summary for production and incineration of 1 kg of acetone and 1 kg of acetonitrile.

	Acetone		**Acetonitrile**	
	Manufacture	**Incineration**	**Manufacture**	**Incineration**
Total Raw Materials Used, kg	1.53E+00	0.00E+00	1.54E+00	0.00E+00
Total CED, MJ-Eq	6.48E+01	0.0E+00	5.86E+01	0.00E+00
Total Air Emissions, kg	1.83E+00	2.28E+00	1.97E+00	2.16E+00
CO_2, kg	1.80E+00	2.28E+00	1.95E+00	2.15E+00
CO, kg	1.89E-03	2.28E-05	2.14E-03	2.30E-05
Methane, kg	1.71E-02	0.00E+00	9.01E-03	0.00E+00
NO_X, kg	4.60E-03	2.60E-04	2.72E-03	9.45E-03
NMVOC, kg	3.52E-03	3.11E-06	1.65E-03	3.14E-06
Particulates, kg	5.92E-04	3.80E-05	9.61E-04	3.81E-05
SO_2, kg	6.88E-03	0.00E+00	3.86E-03	0.00E+00
Total Water Emissions, kg	2.56E-02	0.00E+00	1.44E-01	0.00E+00
VOCs, kg	3.98E-09	0.00E+00	2.58E-06	0.00E+00
Total Soil Emissions, kg	7.23E-07	0.00E+00	6.80E-04	0.00E+00
Total Emissions, kg	1.86E+00	2.28E+00	2.12E+00	2.16E+00

Table A 5. Cumulative energy demand summary for production of 1kg of acetone

Impact Category	**Acetone**	**Acetonitrile**
Nonrenewable, fossil (MJ-Eq)	6.24E+01	5.59E+01
Non-renewable, nuclear (MJ-Eq)	2.11E+00	2.26E+00
Renewable, biomass (MJ-Eq)	1.08E-01	1.61E-01
Renewable, wind, solar, geothermal (MJ-Eq)	2.51E-05	2.11E-02
Renewable, water (MJ-Eq)	1.29E-01	2.46E-01
Total (MJ-Eq)	**6.48E+01**	**5.86E+01**

Table A 6. Life cycle inventory for the manufacture and incineration of 1 kg IPA and 1kg of THF.

	IPA		**THF**	
	Manufacture	**Incineration**	**Manufacture**	**Incineration**
Total Raw Materials Used, kg	1.55E+00	0.00E+00	4.01E+00	0.00E+00
Total CED, MJ-Eq	6.01E+01	0.00E+00	1.28E+02	0.00E+00
Total Air Emissions, kg	1.66E+00	2.21E+00	5.52E+00	2.45E+00
CO_2, kg	1.63E+00	2.20E+00	5.46E+00	2.44E+00
CO, kg	2.25E-03	2.26E-05	4.82E-03	2.33E-05
Methane, kg	9.72E-03	0.00E+00	1.45E-02	0.00E+00
NO_X, kg	2.67E-03	2.59E-04	8.67E-03	2.62E-04
NMVOC, kg	1.75E-03	3.09E-06	3.25E-03	3.18E-06
Particulates, kg	8.40E-04	3.78E-05	3.57E-03	3.84E-05
SO_2, kg	5.36E-03	0.00E+00	1.15E-02	0.00E+00
Total Water Emissions, kg	5.42E-01	0.00E+00	1.26E-01	0.00E+00
VOCs, kg	1.08E-06	0.00E+00	7.93E-06	0.00E+00
Total Soil Emissions, kg	3.18E-04	0.00E+00	2.31E-03	0.00E+00
Total Emissions, kg	**2.20E+00**	**2.21E+00**	**5.65E+00**	**2.45E+00**

Table A 7. Cumulative energy demand summary for the manufacture of 1kg of IPA and 1 kg of THF

Impact category	**IPA**	**THF**
Nonrenewable, fossil (MJ-Eq)	5.73E+01	1.11E+02
Non-renewable, nuclear (MJ-Eq)	2.38E+00	1.31E+01
Renewable, biomass (MJ-Eq)	1.75E-01	6.02E-01
Renewable, wind, solar, geothermal (MJ-Eq)	2.24E-02	2.10E-01
Renewable, water (MJ-Eq)	2.31E-01	2.04E+00
Total (MJ-Eq)	**6.01E+01**	**1.28E+02**

Table A 8. Life cycle inventory summary for the manufacture and incineration of 1 kg toluene

	Manufacture	**Incineration**
Total Raw Materials Used, kg	1.36E+00	0.00E+00
Total CED, MJ-Eq	6.19E+01	0.00E+00
Total Air Emissions, kg	1.21E+00	3.36E+00
CO_2, kg	1.19E+00	3.35E+00
CO, kg	2.05E-03	2.28E-05
Methane, kg	1.23E-02	0.00E+00
NO_X, kg	2.06E-03	2.59E-04
NMVOC, kg	1.88E-03	3.11E-06
Particulates, kg	3.97E-04	3.79E-05
SO_2, kg	2.28E-03	0.00E+00
Total Water Emissions, kg	3.87E-03	0.00E+00
VOCs, kg	1.95E-09	0.00E+00
Total Soil Emissions, kg	3.46E-07	0.00E+00
Total Emissions, kg	**1.21E+00**	**3.36E+00**

Table A 9. Cumulative energy demand summary for the manufacture of 1kg of toluene

Impact category	**Total**
Nonrenewable, fossil (MJ-Eq)	6.05E+01
Non-renewable, nuclear (MJ-Eq)	1.29E+00
Renewable, biomass (MJ-Eq)	8.50E-02
Renewable, wind, solar, geothermal (MJ-Eq)	1.16E-05
Renewable, water (MJ-Eq)	5.34E-02
Total (MJ-Eq)	**6.19E+01**

Table A 10. *eco*THF$^{\text{TM}}$ and *eco*MeTHF$^{\text{TM}}$ Incineration LCI

Total Raw Materials Used, kg	1.39E-03
Total CED, MJ-Eq	-6.50E-01
Total Air Emissions, kg	8.15E-03
CO_2, kg	0.00E+00
CO, kg	2.32E-05
Methane, kg	0.00E+00
NO_X, kg	2.61E-04
NMVOC, kg	3.16E-06
Particulates, kg	3.83E-05
SO_2, kg	0.00E+00
Total Water Emissions, kg	0.00E+00
VOCs, kg	0.00E+00
Total Soil Emissions, kg	0.00E+00
Total Emissions, kg	**8.15E-03**

Appendix G

Utilities LCI

Kalamazoo Plant Utilities: Selamectin, Nelfinavir and Hydrocortisone Cases.

The method used in SimaPro® to calculate the electricity LCI was Eco-indicator 99 "H" (hierarchical). The power generating station that supplies electricity for the Kalamazoo plant uses a mixed fuel. SimaPro® has a method which was selected to calculate emissions based on mixed fuels. The electricity from fuel was calculated based on current US technologies. No technology description is provided because the dataset only describes the power plant generation portfolio of the country using current average technology per energy carrier. The process for the production of electricity does not include transformation or transportation as specified by the program. The total emissions, total raw materials used, and the energy used for the production of electricity can be seen in Table A 11.

Table A 11. Life cycle inventory for 1 kWh of electricity at Kalamazoo plant (US production mix)

Total Raw Materials Used, kg	3.98E-01
Total CED, MJ-Eq	3.60E+00
Total Air Emissions, kg	7.36E-01
CO_2, kg	7.27E-01
CO, kg	2.89E-04
Methane, kg	1.35E-03
NO_X, kg	1.43E-03
NMVOC, kg	1.06E-04
Particulates, kg	6.65E-04
SO_2, kg	3.94E-03
Total Water Emissions, kg	2.63E-02
VOCs, kg	3.59E-07
Total Soil Emissions, kg	9.05E-05
Total Emissions, kg	**7.62E-01**

The simulation was run on a basis of 1 kWh of electricity generated. The majority of emissions, a total of 96%, are to the air with emissions to water and soil making up the final 4%. Of the 0.736 kg of air emissions, 0.727 kg of air emissions are attributed to CO_2 with a variety of greenhouse gases and other components making up the remaining 0.009 kg. The total energy used for the process is 3.6 MJ-Eq and a summary of the sources of this energy can be seen in Table A 12. This electricity LCI was used for all Pfizer case studies presented.

A life cycle inventory was also completed for the production of 1 kg of steam from coal. The steam for the Kalamazoo plant is obtained from coal and is produced on-site. To produce 1 kg of steam at 170 psig, 0.0952 kg of coal is used. This is the basis that is used for the LCI. This LCI was also completed using SimaPro® by method of Eco-indicator 99 “H”. Coal is used in industrial boilers to make steam. The technologies used for the simulation are not specified but it is stated that current average US technology data are used. The data are for the cradle-to-gate resource requirements and emissions for the combustion of coal. As stated earlier, the simulation was run on a 0.0952 kg basis for coal and this can be seen in Table A 13.

Table A 12. Cumulative energy demand for 1 kWh electricity

Impact Category	**Total**
Nonrenewable, fossil (MJ-Eq)	2.50E+00
Non-renewable, nuclear (MJ-Eq)	9.10E-01
Renewable, biomass (MJ-Eq)	3.67E-02
Renewable, wind, solar, geothermal (MJ-Eq)	4.11E-03
Renewable, water (MJ-Eq)	7.65E-02
Total (MJ-Eq)	**3.60E+00**

Table A 13. Life cycle inventory for production of 1 kg of steam at 170 psig from coal

Total Raw Materials Used, kg	1.02E-01
Total CED, MJ-Eq	2.57E+00
Total Air Emissions, kg	2.32E-01
CO_2, kg	2.29E-01
CO, kg	8.95E-05
Methane, kg	4.54E-04
NO_X, kg	5.36E-04
NMVOC, kg	1.44E-05
Particulates, kg	3.02E-04
Total Water Emissions, kg	1.88E-04
Total Soil Emissions, kg	9.63E-05
Total Emissions, kg	**2.32E-01**

The total raw materials needed to make 0.0952 kg of coal is 0.102 kg. The total emissions to the air come to 0.232 kg. This is to combust only 0.0952 kg of coal. This process produces approximately two and a half times more emissions than the amount of coal used. CO_2 makes up 0.229 kg of the total air emissions. The large proportion of air emissions causes the emissions to water and soil to become negligible in terms of the total emissions. The total energy used to combust the coal is 2.57 MJ-Eq and a summary of the energy can be seen in Table A 14. This analysis includes the combustion of coal to make steam, which is included in the LCI. In addition, Table A 14 shows that no energy for the process is produced from a renewable source. All of the energy supplied is from non-renewable fossil fuels and nuclear energy.

Table A 14. Cumulative energy demand for the combustion of 0.0952 kg of coal

Impact Category	**Total**
Non-renewable, fossil (MJ-Eq)	2.56E+00
Non-renewable, nuclear (MJ-Eq)	5.23E-03
Renewable, biomass (MJ-Eq)	0.00E+00
Renewable, wind, solar, geothermal (MJ-Eq)	0.00E+00
Renewable, water (MJ-Eq)	0.00E+00
Total (MJ-Eq)	**2.57E+00**

Barceloneta Plant Utilities: Celecoxib Case

Table A 15. Life Cycle Inventory for 1 kg of Saturated Steam at 125 psig and 1 kWh of electricity at the Barceloneta Plant

	Saturated Steam at 125 psig	1 kWh of electricity
Total Raw Materials, kg	8.00E-02	3.47E-01
Total CED, MJ-Eq	3.40E+00	3.56E+00
Total Air Emissions, kg	2.57E-01	8.86E-01
CO_2, kg	2.49E-01	8.76E-01
CO, kg	1.37E-03	2.67E-03
Methane, kg	3.03E-04	1.54E-03
NO_X, kg	4.48E-03	1.66E-03
NMVOC, kg	1.55E-03	4.08E-04
Particulates, kg	1.03E-04	3.01E-04
SO_2, kg	3.75E-04	1.96E-03
Total Water Emissions, kg	3.99E-03	9.64E-02
VOCs	-	3.20E-08
Total Soil Emissions, kg	1.73E-04	1.20E-05
Total Emissions, kg	**2.61E-01**	**9.83E-01**

Average Chemical Plant Utilities: *eco*THF$^{\mathrm{TM}}$ and *eco*MeTHF$^{\mathrm{TM}}$ recoveries

Table A 16. Life Cycle Inventory for 1 kg of Saturated Steam at 125 psig and 1 kWh of electricity at the Barceloneta Plant

Total Raw Materials Used, kg	9.02E-02
Total CED, MJ-Eq	3.92E+00
Total Air Emissions, kg	2.24E-01
CO_2	2.23E-01
CO	5.84E-05
Methane	4.51E-04
NO_x	2.00E-04
NMVOC	6.04E-05
Particulates	4.61E-05
SO_2	3.82E-04
Total Water Emissions, kg	2.31E-03
VOCs	3.91E-07
Total Soil Emissions, kg	9.63E-05
Total Emissions, kg	2.26E-01

Appendix H

LCA Results of Case Studies

Table A 17. Base process selamectin process LCA

	Manufacture Acetonitrile	**Manufacture Acetone**	**Incineration Acetonitrile**	**Incineration Acetone**	**Total**
Amount Used, kg	60,840	23,660	60,840	23,660	-
Total Raw Materials Used, kg	9.35E+04	3.61E+04	*	*	1.30E+05
Total CED, MJ-Eq	3.57E+06	1.53E+06	0.00E+00	0.00E+00	5.10E+06
Total Air Emissions, kg	1.20E+05	4.33E+04	1.32E+05	5.40E+04	**3.49E+05**
CO_2, kg	1.18E+05	4.25E+04	1.31E+05	5.39E+04	3.45E+05
CO, kg	1.30E+02	4.47E+01	1.40E+00	5.40E-01	1.77E+02
Methane, kg	5.48E+02	4.05E+02	0.00E+00	0.00E+00	9.53E+02
NO_X, kg	1.66E+02	1.09E+02	5.75E+02	6.15E+00	8.56E+02
NMVOC, kg	1.00E+02	8.34E+01	1.91E-01	7.36E-02	1.84E+02
Particulates, kg	5.84E+01	1.40E+01	2.32E+00	8.98E-01	7.57E+01
SO_2, kg	2.35E+02	1.63E+02	0.00E+00	0.00E+00	3.98E+02
Total Water Emissions, kg	8.79E+03	6.05E+02	0.00E+00	0.00E+00	**9.39E+03**
VOCs, kg	1.57E-01	9.41E-05	0.00E+00	0.00E+00	1.57E-01
Total Soil Emissions, kg	4.14E+01	1.71E-02	0.00E+00	0.00E+00	**4.14E+01**
Total Emissions, kg	1.29E+05	4.39E+04	1.32E+05	5.40E+04	**3.59E+05**

*Air is used in incineration; however the amount cannot be quantified

Table A 18. Acetonitrile recovery process LCA

	Manufacture		**Incineration**		**Saturated Steam @ 170 psig**	**Electricity**	**Total**
	Acetonitrile	**Acetone**	**Acetonitrile**	**Acetone**			
Amount Used, kg or *kWh	9,671	23,660	9,671	23,660	105,350	*16,301	**-**
Total Raw Materials Used, kg	1.48E+04	3.60E+04	0.00E+00	0.00E+00	1.07E+04	6.49E+03	**6.80E+04**
Total CED, MJ-Eq	5.66E+05	1.53E+06	0.00E+00	0.00E+00	2.71E+05	5.87E+04	**2.44E+06**
Total Air Emissions, kg	1.89E+04	4.32E+04	2.08E+04	5.40E+04	2.44E+04	1.20E+04	**1.73E+05**
CO_2, kg	1.87E+04	4.24E+04	2.06E+04	5.39E+04	2.41E+04	1.19E+04	1.71E+05
CO, kg	2.06E+01	4.46E+01	2.21E-01	5.40E-01	9.43E+00	4.71E+00	8.01E+01
Methane, kg	8.66E+01	4.04E+02	0.00E+00	0.00E+00	4.78E+01	2.20E+01	5.60E+02
NO_X, kg	2.62E+01	1.09E+02	9.09E+01	6.15E+00	5.65E+01	2.33E+01	3.12E+02
NMVOC, kg	1.59E+01	8.32E+01	3.02E-02	7.36E-02	1.52E+00	1.73E+00	1.02E+02
Particulates, kg	9.24E+00	1.40E+01	3.67E-01	8.98E-01	3.18E+01	1.08E+01	6.71E+01
SO_2, kg	3.71E+01	1.62E+02	0.00E+00	0.00E+00	0.00E+00	6.42E+01	2.63E+02
Total Water Emissions, kg	1.39E+03	6.03E+02	0.00E+00	0.00E+00	1.98E+01	4.29E+02	**2.44E+03**
VOCs, kg	2.48E-02	9.38E-05	0.00E+00	0.00E+00	0.00E+00	5.85E-03	3.07E-02
Total Soil Emissions, kg	6.54E+00	1.71E-02	0.00E+00	0.00E+00	9.53E+00	1.48E+00	**1.76E+01**
Total Emissions, kg	2.03E+04	4.38E+04	2.08E+04	5.40E+04	2.45E+04	1.24E+04	**1.76E+05**

Table A 19. Base process vs. acetonitrile recovery LCA

	Base Process	**Recovery Process**	**Reduction***	**% Reduction**
Total Raw Materials Used, kg	1.30E+05	6.80E+04	6.20E+04	47.69%
Total CED, MJ-Eq	5.10E+06	2.44E+06	2.66E+06	52.15%
Total Air Emissions, kg	3.49E+05	1.73E+05	1.76E+05	50.43%
CO_2, kg	3.45E+05	1.71E+05	1.74E+05	50.43%
CO, kg	1.77E+02	8.01E+01	9.69E+01	54.75%
Methane, kg	9.53E+02	5.60E+02	3.93E+02	41.24%
NO_X, kg	8.56E+02	3.12E+02	5.44E+02	63.55%
NMVOC, kg	1.84E+02	1.02E+02	8.20E+01	44.57%
Particulates, kg	7.57E+01	6.71E+01	8.60E+00	11.36%
SO_2, kg	3.98E+02	2.63E+02	1.35E+02	33.92%
Total Water Emissions, kg	9.39E+03	2.44E+03	6.95E+03	74.01%
VOCs, kg	1.57E-01	3.07E-02	1.26E-01	80.45%
Total Soil Emissions, kg	4.14E+01	1.76E+01	2.38E+01	57.49%
Total Emissions, kg	**3.59E+05**	**1.76E+05**	**1.83E+05**	**50.97%**

*The reduction column contains the avoided emissions.

Table A 20. Acetone recovery LCA

	Manufacture Acetone	**Incineration Acetone**	**Sat'd Steam @ 170 psig**	**Electricity**	**Total**
Amount Used, kg or *kWh	3,101	3,101	33,249	*5,181	-
Total Raw Materials Used, kg	4.73E+03	0.00E+00	3.39E+03	2.06E+03	1.02E+04
Total CED, MJ-Eq	2.01E+05	0.00E+00	8.54E+04	1.87E+04	3.05E+05
Total Air Emissions, kg	5.67E+03	7.08E+03	7.71E+03	3.81E+03	**2.43E+04**
CO_2, kg	5.57E+03	7.06E+03	7.61E+03	3.77E+03	2.40E+04
CO, kg	5.86E+00	7.07E-02	2.98E+00	1.50E+00	1.04E+01
Methane, kg	5.30E+01	0.00E+00	1.51E+01	6.99E+00	7.51E+01
NO_X, kg	1.43E+01	8.06E-01	1.78E+01	7.41E+00	4.03E+01
NMVOC, kg	1.09E+01	9.64E-03	4.79E-01	5.49E-01	1.20E+01
Particulates, kg	1.84E+00	1.18E-01	1.00E+01	3.45E+00	1.54E+01
SO_2, kg	2.13E+01	0.00E+00	0.00E+00	2.04E+01	4.17E+01
Total Water Emissions, kg	7.92E+01	0.00E+00	6.25E+00	1.36E+02	**2.22E+02**
VOCs, kg	1.23E-05	0.00E+00	0.00E+00	1.86E-03	1.87E-03
Total Soil Emissions, kg	2.24E-03	0.00E+00	3.01E+00	4.69E-01	**3.48E+00**
Total Emissions, kg	5.75E+03	7.08E+03	7.72E+03	3.95E+03	**2.45E+04**

Table A 21. Acetonitrile and acetone recovery process LCA

	Manufacture		**Incineration**		**Saturated Steam @ 170 psig**	**Electricity**	**Total**
	Acetonitrile	**Acetone**	**Acetonitrile**	**Acetone**			
Amount Used, kg or *kWh	9,671	3,101	9,671	3,101	138,599	*21,482	-
Total Raw Materials Used, kg	1.48E+04	4.73E+03	0.00E+00	0.00E+00	1.41E+04	8.55E+03	**4.22E+04**
Total CED, MJ-Eq	5.66E+05	2.01E+05	0.00E+00	0.00E+00	3.56E+05	7.74E+04	**1.20E+06**
Total Air Emissions, kg	1.89E+04	5.67E+03	2.08E+04	7.08E+03	3.21E+04	1.58E+04	**1.00E+05**
CO$_2$, kg	1.87E+04	5.57E+03	2.06E+04	7.06E+03	3.17E+04	1.57E+04	9.93E+04
CO, kg	2.06E+01	5.86E+00	2.21E-01	7.07E-02	1.24E+01	6.21E+00	4.54E+01
Methane, kg	8.66E+01	5.30E+01	0.00E+00	0.00E+00	6.29E+01	2.90E+01	2.31E+02
NO$_X$, kg	2.62E+01	1.43E+01	9.09E+01	8.06E-01	7.43E+01	3.07E+01	2.37E+02
NMVOC, kg	1.59E+01	1.09E+01	3.02E-02	9.64E-03	2.00E+00	2.28E+00	3.11E+01
Particulates, kg	9.24E+00	1.84E+00	3.67E-01	1.18E-01	4.18E+01	1.43E+01	6.76E+01
SO$_2$, kg	3.71E+01	2.13E+01	0.00E+00	0.00E+00	0.00E+00	8.46E+01	1.43E+02
Total Water Emissions, kg	1.39E+03	7.92E+01	0.00E+00	0.00E+00	2.61E+01	5.65E+02	**2.06E+03**
VOCs, kg	2.48E-02	1.23E-05	0.00E+00	0.00E+00	0.00E+00	7.71E-03	3.25E-02
Total Soil Emissions, kg	6.54E+00	2.24E-03	0.00E+00	0.00E+00	1.25E+01	1.95E+00	**2.10E+01**
Total Emissions, kg	2.03E+04	5.75E+03	2.08E+04	7.08E+03	3.22E+04	1.64E+04	**1.03E+05**

Table A 22. Base process and recovery process LCA comparison

	Base Process	**Recovery Process**	**Reduction**	**% Reduction**
Total Raw Materials Used, kg	1.30E+05	4.22E+04	8.78E+04	67.54%
Total CED, MJ-Eq	5.10E+06	1.20E+06	3.90E+06	76.47%
Total Air Emissions, kg	**3.49E+05**	**1.00E+05**	**2.49E+05**	**71.35%**
CO$_2$, kg	3.45E+05	9.93E+04	2.46E+05	71.22%
CO, kg	1.77E+02	4.54E+01	1.32E+02	74.35%
Methane, kg	9.53E+02	2.31E+02	7.22E+02	75.76%
NO$_X$, kg	8.56E+02	2.37E+02	6.19E+02	72.31%
NMVOC, kg	1.84E+02	3.11E+01	1.53E+02	83.10%
Particulates, kg	7.57E+01	6.76E+01	8.10E+00	10.70%
SO$_2$, kg	3.98E+02	1.43E+02	2.55E+02	64.07%
Total Water Emissions, kg	**9.39E+03**	**2.06E+03**	**7.33E+03**	**78.06%**
VOCs, kg	1.57E-01	3.25E-02	1.24E-01	79.30%
Total Soil Emissions, kg	**4.14E+01**	**2.10E+01**	**2.04E+01**	**49.28%**
Total Emissions, kg	**3.59E+05**	**1.03E+05**	**2.56E+05**	**71.31%**

Table A 23. Nelfinavir case, base process LCA

	Manufacture IPA	Incineration IPA	Manufacture THF	Incineration THF	Total
Amount Used, kg	67,682	67,682	11,018	11,018	-
Total Raw Materials Used, kg	1.05E+05	*	4.42E+04	*	1.49E+05
Total CED, MJ-Eq	4.07E+06	0.00E+00	1.41E+06	0.00E+00	5.48E+06
Total Air Emissions, kg	1.12E+05	1.49E+05	6.08E+04	2.70E+04	**3.49E+05**
CO_2, kg	1.10E+05	1.49E+05	6.02E+04	2.69E+04	3.46E+05
CO, kg	1.53E+02	1.53E+00	5.32E+01	2.57E-01	2.07E+02
Methane, kg	6.58E+02	0.00E+00	1.60E+02	0.00E+00	8.18E+02
NO_X, kg	1.81E+02	1.75E+01	9.56E+01	2.88E+00	2.97E+02
NMVOC, kg	1.18E+02	2.09E-01	3.58E+01	3.50E-02	1.54E+02
Particulates, kg	5.69E+01	2.56E+00	3.93E+01	4.23E-01	9.92E+01
SO_2, kg	3.63E+02	0.00E+00	1.27E+02	0.00E+00	4.90E+02
Total Water Emissions, kg	3.67E+04	0.00E+00	1.39E+03	0.00E+00	**3.81E+04**
VOCs, kg	7.29E-02	0.00E+00	8.74E-02	0.00E+00	1.60E-01
Total Soil Emissions, kg	2.16E+01	0.00E+00	2.54E+01	0.00E+00	**4.70E+01**
Total Emissions, kg	1.49E+05	1.49E+05	6.22E+04	2.70E+04	**3.88E+05**

* Air is used in incineration; however the amount cannot be quantified

Table A 24. Nelfinavir case, IPA recovery process LCA

	Manufacture		Incineration		Sat'd Steam @ 170 psig	Electricity	Total
	IPA	THF	IPA	THF			
Amount, kg or *kWh	5,148	11,018	5,148	11,018	73,505	*10,953	-
Total Raw Materials Used, kg	7.97E+03	4.42E+04	0.00E+00	0.00E+00	7.50E+03	4.36E+03	6.40E+04
Total CED, MJ-Eq	3.10E+05	1.41E+06	0.00E+00	0.00E+00	1.89E+05	3.94E+04	1.95E+06
Total Air Emissions, kg	8.53E+03	6.08E+04	1.14E+04	2.70E+04	1.71E+04	8.06E+03	**1.33E+05**
CO_2, kg	8.39E+03	6.02E+04	1.13E+04	2.69E+04	1.68E+04	7.96E+03	1.32E+05
CO, kg	1.16E+01	5.32E+01	1.17E-01	2.57E-01	6.58E+00	3.17E+00	7.49E+01
Methane, kg	5.01E+01	1.60E+02	0.00E+00	0.00E+00	3.34E+01	1.48E+01	2.58E+02
NO_X, kg	1.38E+01	9.56E+01	1.33E+00	2.88E+00	3.94E+01	1.57E+01	1.69E+02
NMVOC, kg	9.00E+00	3.58E+01	1.59E-02	3.50E-02	1.06E+00	1.16E+00	4.70E+01
Particulates, kg	4.32E+00	3.93E+01	1.94E-01	4.23E-01	2.22E+01	7.28E+00	7.38E+01
SO_2, kg	2.76E+01	1.27E+02	0.00E+00	0.00E+00	0.00E+00	4.32E+01	1.98E+02
Total Water Emissions, kg	2.79E+03	1.39E+03	0.00E+00	0.00E+00	1.38E+01	2.88E+02	**4.48E+03**
VOCs, kg	5.54E-03	8.74E-02	0.00E+00	0.00E+00	0.00E+00	3.93E-03	9.68E-02
Total Soil Emissions, kg	1.64E+00	2.54E+01	0.00E+00	0.00E+00	7.08E+00	9.91E-01	**3.51E+01**
Total Emissions, kg	1.13E+04	6.22E+04	1.14E+04	2.70E+04	1.71E+04	8.35E+03	**1.37E+05**

Table A 25. Hydrocortisone case base process LCA

	Manufacture Toluene	**Manufacture Acetone**	**Incineration Toluene**	**Incineration Acetone**	**Total**
Amount Used, kg	233,913	23,687	233,913	23,687	
Total Raw Materials Used, kg	3.17E+05	3.62E+04	*	*	3.54E+05
Total CED, MJ-Eq	1.45E+07	1.54E+06	0.00E+00	0.00E+00	1.60E+07
Total Air Emissions, kg	2.83E+05	4.34E+04	7.85E+05	5.41E+04	**1.17E+06**
CO_2, kg	2.78E+05	4.25E+04	7.83E+05	5.39E+04	1.16E+06
CO, kg	4.79E+02	4.47E+01	5.33E+00	5.40E-01	5.30E+02
Methane, kg	2.88E+03	4.05E+02	0.00E+00	0.00E+00	3.28E+03
NO_X, kg	4.83E+02	1.09E+02	6.07E+01	6.15E+00	6.58E+02
NMVOC, kg	4.39E+02	8.35E+01	7.27E-01	7.37E-02	5.23E+02
Particulates, kg	9.30E+01	1.40E+01	8.86E+00	8.99E-01	1.17E+02
SO_2, kg	5.33E+02	1.63E+02	0.00E+00	0.00E+00	6.96E+02
Total Water Emissions, kg	9.04E+02	6.05E+02	0.00E+00	0.00E+00	**1.51E+03**
VOCs, kg	4.56E-04	9.42E-05	0.00E+00	0.00E+00	5.50E-04
Total Soil Emissions, kg	8.09E-02	1.71E-02	0.00E+00	0.00E+00	**9.81E-02**
Total Emissions, kg	2.84E+05	4.40E+04	7.85E+05	5.41E+04	**1.17E+06**

* Air is used in incineration; however the amount cannot be quantified

Table A 26. Total LCA for toluene and acetone recovery in Hydrocortisone case

	Sat'd Steam @ 170 psig	**Electricity**	**Total**
Amount Used, kg or *kWh			
Total Raw Materials Used, kg	5.78E+03	2.47E+03	8.25E+03
Total CED, MJ-Eq	1.46E+05	2.23E+04	1.68E+05
Total Air Emissions, kg	1.32E+04	4.57E+03	**1.77E+04**
CO_2, kg	1.30E+04	4.51E+03	1.75E+04
CO, kg	5.07E+00	1.79E+00	6.87E+00
Methane, kg	2.57E+01	8.38E+00	3.41E+01
NO_X, kg	3.04E+01	8.87E+00	3.93E+01
NMVOC, kg	8.16E-01	6.58E-01	1.47E+00
Particulates, kg	1.71E+01	4.13E+00	2.12E+01
SO_2, kg	0.00E+00	2.44E+01	2.44E+01
Total Water Emissions, kg	1.07E+01	1.63E+02	**1.74E+02**
VOCs, kg	0.00E+00	2.23E-03	2.23E-03
Total Soil Emissions, kg	5.46E+00	5.62E-01	**6.02E+00**
Total Emissions, kg	1.32E+04	4.73E+03	**1.79E+04**

Table A 27. Hydrocortisone case base process toluene and acetone recovery LCA

	Base Process	**Recovery Process**	**Reduction**	**% Reduction**
Total Raw Materials Used, kg	3.54E+05	8.25E+03	3.45E+05	97.67%
Total CED, MJ-Eq	1.60E+07	1.68E+05	1.58E+07	98.95%
Total Air Emissions, kg	**1.17E+06**	**1.77E+04**	**1.15E+06**	**98.48%**
CO_2, kg	1.16E+06	1.75E+04	1.14E+06	98.49%
CO, kg	5.30E+02	6.87E+00	5.23E+02	98.70%
Methane, kg	3.28E+03	3.41E+01	3.25E+03	98.96%
NO_X, kg	6.58E+02	3.93E+01	6.19E+02	94.04%
NMVOC, kg	5.23E+02	1.47E+00	5.22E+02	99.72%
Particulates, kg	1.17E+02	2.12E+01	9.55E+01	81.80%
SO_2, kg	6.96E+02	2.44E+01	6.71E+02	96.49%
Total Water Emissions, kg	**1.51E+03**	**1.74E+02**	**1.34E+03**	**88.48%**
VOCs, kg	5.50E-04	2.23E-03	-1.68E-03	-304.76%
Total Soil Emissions, kg	**9.81E-02**	**6.02E+00**	**-5.92E+00**	**-6034.66%**
Total Emissions, kg	**1.17E+06**	**1.79E+04**	**1.15E+06**	**98.47%**

Table A 28. Base process LCA for IPA-Water

	Manufacture IPA	**Manufacture Water**	**Incineration IPA**	**Incineration Water**	**Total**
Amount Used, kg	2,560,845	2,905,539	2,560,845	2,905,539	
Total Raw Materials Used, kg	3.97E+06	2.58E+03	*	*	3.97E+06
Total CED, MJ-Eq	1.54E+08	3.50E+04	0.00E+00	0.00E+00	1.54E+08
Total Air Emissions, kg	4.24E+06	1.99E+03	5.66E+06	9.88E+06	**1.98E+07**
CO_2, kg	4.18E+06	1.97E+03	5.63E+06	9.86E+06	1.97E+07
CO, kg	5.77E+03	3.83E+00	5.80E+01	6.59E+01	5.90E+03
Methane, kg	2.49E+04	3.36E+00	0.00E+00	0.00E+00	2.49E+04
NO_X, kg	6.84E+03	3.13E+00	6.63E+02	7.53E+02	8.26E+03
NMVOC, kg	4.48E+03	3.04E-01	7.91E+00	8.98E+00	4.49E+03
Particulates, kg	2.15E+03	1.93E+00	9.67E+01	1.10E+02	2.36E+03
SO_2, kg	1.37E+04	5.15E+00	0.00E+00	0.00E+00	1.37E+04
Total Water Emissions, kg	1.39E+06	1.40E+03	0.00E+00	0.00E+00	**1.39E+06**
VOCs, kg	2.76E+00	1.52E-03	0.00E+00	0.00E+00	2.76E+00
Total Soil Emissions, kg	8.15E+02	3.48E-01	0.00E+00	0.00E+00	**8.16E+02**
Total Emissions, kg	5.63E+06	3.39E+03	5.66E+06	9.88E+06	**2.12E+07**

* Air is used in incineration; however the amount cannot be quantified

Table A 29. LCA for IPA recovery process

	Manufacture		Incineration		Sat'd Steam	Electricity	Total
	IPA	Water	IPA	Water	@ 125 psig		
Amount Used, kg or *kWh	12,438	2,905,539	12,438	2,905,539	5,112,607	*811,348	
Total Raw Materials Used, kg	1.93E+04	2.58E+03	*	*	4.09E+05	2.82E+05	7.12E+05
Total CED, MJ-Eq	7.48E+05	3.50E+04	0.00E+00	0.00E+00	1.74E+07	2.89E+06	2.11E+07
Total Air Emissions, kg	2.06E+04	1.99E+03	2.75E+04	9.88E+06	1.31E+06	7.19E+05	**1.20E+07**
CO_2, kg	2.03E+04	1.97E+03	2.74E+04	9.86E+06	1.27E+06	7.11E+05	1.19E+07
CO, kg	2.80E+01	3.83E+00	2.82E-01	6.59E+01	7.00E+03	2.17E+03	9.27E+03
Methane, kg	1.21E+02	3.36E+00	0.00E+00	0.00E+00	1.55E+03	1.25E+03	2.92E+03
NO_X, kg	3.32E+01	3.13E+00	3.22E+00	7.53E+02	2.29E+04	1.35E+03	2.50E+04
NMVOC, kg	2.17E+01	3.04E-01	3.84E-02	8.98E+00	7.92E+03	3.31E+02	8.29E+03
Particulates, kg	1.04E+01	1.93E+00	4.70E-01	1.10E+02	5.27E+02	2.44E+02	8.93E+02
SO_2, kg	6.67E+01	5.15E+00	0.00E+00	0.00E+00	1.92E+03	1.59E+03	3.58E+03
Total Water Emissions, kg	6.74E+03	1.40E+03	0.00E+00	0.00E+00	2.04E+04	7.82E+04	**1.07E+05**
VOCs, kg	1.34E-02	1.52E-03	0.00E+00	0.00E+00	0.00E+00	2.60E-02	4.09E-02
Total Soil Emissions, kg	3.96E+00	3.48E-01	0.00E+00	0.00E+00	8.84E+02	9.74E+00	**8.99E+02**
Total Emissions, kg	2.74E+04	3.39E+03	2.75E+04	9.88E+06	1.33E+06	7.98E+05	**1.21E+07**

Table A 30. IPA-water base process and recovery process comparison

	Base Process	Recovery Process	Reduction	% Reduction
Total Raw Materials Used, kg	3.97E+06	7.12E+05	3.26E+06	82.06%
Total CED, MJ-Eq	1.54E+08	2.11E+07	1.33E+08	86.36%
Total Air Emissions, kg	**1.98E+07**	**1.20E+07**	**7.84E+06**	**39.59%**
CO_2, kg	1.97E+07	1.19E+07	7.81E+06	39.65%
CO, kg	5.90E+03	9.27E+03	-3.37E+03	-57.09%
Methane, kg	2.49E+04	2.92E+03	2.20E+04	88.26%
NO_X, kg	8.26E+03	2.50E+04	-1.68E+04	-203.19%
NMVOC, kg	4.49E+03	8.29E+03	-3.80E+03	-84.56%
Particulates, kg	2.36E+03	8.93E+02	1.47E+03	62.14%
SO_2, kg	1.37E+04	3.58E+03	1.01E+04	73.87%
Total Water Emissions, kg	**1.39E+06**	**1.07E+05**	**1.28E+06**	**92.32%**
VOCs, kg	2.76E+00	4.09E-02	2.72E+00	98.52%
Total Soil Emissions, kg	**8.16E+02**	**8.99E+02**	**-8.25E+01**	**-10.11%**
Total Emissions, kg	**2.12E+07**	**1.21E+07**	**9.13E+06**	**43.07%**

Table A 31. *eco*THF™ "extractive distillation" recovery case LC emissions.

	***eco*THF™ Manufacture**	***eco*THF™ Incineration**	**Steam**	**Electricity***	**Glycerol**	**Total**
Amount used, kg (*kWh)	17,625	17,625	13,125,000	1,950,000	3,793.5	-
Total Raw Materials Used, kg	9.39E+06	2.45E+01	1.18E+06	7.76E+05	2.12E+04	**1.14E+07**
Total CED, MJ-Eq	1.08E+05	-1.15E+04	5.14E+07	7.02E+06	2.69E+05	**5.88E+07**
Total Air Emissions, kg	2.56E+04	1.44E+02	2.94E+06	1.44E+06	6.80E+03	**4.41E+06**
CO$_2$, kg	2.45E+04	0.00E+00	2.92E+06	1.42E+06	6.66E+03	4.37E+06
CO, kg	1.29E+02	4.09E-01	7.67E+02	5.64E+02	4.34E+01	1.50E+03
Methane, kg	4.79E+01	0.00E+00	5.91E+03	2.63E+03	1.69E+01	8.61E+03
NO$_X$, kg	5.75E+02	4.60E+00	2.63E+03	2.79E+03	1.82E+01	6.01E+03
NMVOC, kg	5.18E+01	5.57E-02	7.93E+02	2.07E+02	3.05E+00	1.06E+03
Particulates, kg	1.72E+01	6.75E-01	6.05E+02	1.30E+03	8.94E+00	1.93E+03
SO$_2$, kg	3.12E+02	0.00E+00	5.01E+03	7.68E+03	1.48E+01	1.30E+04
Total Water Emissions, kg	6.01E+02	0.00E+00	3.03E+04	5.13E+04	2.03E+03	**8.43E+04**
VOCs, kg	1.03E-01	0.00E+00	5.13E+00	7.00E-01	1.04E-02	5.94E+00
Total Soil Emissions, kg	3.67E+01	0.00E+00	1.26E+03	1.76E+02	6.73E+00	**1.48E+03**
Total Emissions, kg	2.63E+04	1.44E+02	2.97E+06	1.49E+06	8.83E+03	**4.49E+06**

Table A 32. *eco*THF™ “distillation + pervaporation” recovery case LC emissions

	***eco*THF™ Manufacture**	***eco*THF™ Incineration**	**Steam**	**Electricity***	**Total**
Amount Used, kg (*kWh)	28,125	28,125	2,475,000	352,500	-
Total Raw Materials Used, kg	1.50E+07	3.91E+01	2.23E+05	1.40E+05	**1.54E+07**
Total CED, MJ-Eq	1.73E+05	-1.83E+04	9.70E+06	1.27E+06	**1.11E+07**
Total Air Emissions, kg	4.08E+04	2.29E+02	5.54E+05	2.59E+05	**8.55E+05**
CO$_2$, kg	3.91E+04	0.00E+00	5.51E+05	2.56E+05	8.47E+05
CO, kg	2.06E+02	6.53E-01	1.45E+02	1.02E+02	4.53E+02
Methane, kg	7.65E+01	0.00E+00	1.12E+03	4.76E+02	1.67E+03
NO$_X$, kg	9.17E+02	7.34E+00	4.96E+02	5.04E+02	1.92E+03
NMVOC, kg	8.27E+01	8.89E-02	1.50E+02	3.74E+01	2.70E+02
Particulates, kg	2.74E+01	1.08E+00	1.14E+02	2.34E+02	3.77E+02
SO$_2$, kg	4.98E+02	0.00E+00	9.45E+02	1.39E+03	2.83E+03
Total Water Emissions, kg	9.59E+02	0.00E+00	5.72E+03	9.27E+03	**1.60E+04**
VOCs, kg	1.64E-01	0.00E+00	9.67E-01	1.27E-01	1.26E+00
Total Soil Emissions, kg	5.85E+01	0.00E+00	2.38E+02	3.19E+01	**3.29E+02**
Total Emissions, kg	4.19E+04	2.29E+02	5.60E+05	2.69E+05	**8.71E+05**

Table A 33. *eco*MeTHF^{TM} recovery LC emissions

	eco**MeTHF**^{TM} **Manufacture**	***eco*****MeTHF**^{TM} **Incineration**	**Steam**	**Electricity***	**Total**
Amount used, kg (*kWh)	37,500	37,500	1,837,500	217,500	-
Total Raw Materials Used, kg	4.54E+06	5.21E+01	1.66E+05	8.66E+04	**4.79E+06**
Total CED, MJ-Eq	-7.50E+05	-2.44E+04	7.20E+06	7.83E+05	**7.21E+06**
Total Air Emissions, kg	6.08E+03	3.06E+02	4.12E+05	1.60E+05	**5.78E+05**
CO_2, kg	5.63E+03	0.00E+00	4.09E+05	1.58E+05	5.73E+05
CO, kg	2.49E+02	8.70E-01	1.07E+02	6.29E+01	4.20E+02
Methane, kg	-3.52E+01	0.00E+00	8.28E+02	2.94E+02	1.09E+03
NO_X, kg	5.18E+02	9.79E+00	3.68E+02	3.11E+02	1.21E+03
NMVOC, kg	9.23E+01	1.19E-01	1.11E+02	2.31E+01	2.26E+02
Particulates, kg	4.73E+01	1.44E+00	8.46E+01	1.45E+02	2.78E+02
SO_2, kg	-1.71E+02	0.00E+00	7.02E+02	8.57E+02	1.39E+03
Total Water Emissions, kg	1.02E+03	0.00E+00	4.25E+03	5.72E+03	**1.10E+04**
VOCs, kg	2.09E-01	0.00E+00	7.18E-01	7.81E-02	1.00E+00
Total Soil Emissions, kg	7.28E+01	0.00E+00	1.77E+02	1.97E+01	**2.69E+02**
Total Emissions, kg	7.16E+03	3.06E+02	4.16E+05	1.66E+05	**5.89E+05**

Table A 34. *eco*MeTHF^{TM} recovery LC emissions comparison.

	Chemical THF Base Case	***eco*****MeTHF**^{TM} **Recovery Case**	**Emissions Reduction**
Total Raw Materials Used, kg	1.50E+07	4.79E+06	**1.02E+07**
Total CED, MJ-Eq	4.93E+08	7.21E+06	**4.86E+08**
Total Air Emissions, kg	2.99E+07	5.78E+05	**2.93E+07**
CO_2, kg	2.96E+07	5.73E+05	2.90E+07
CO, kg	1.82E+04	4.20E+02	1.78E+04
Methane, kg	5.44E+04	1.09E+03	5.33E+04
NO_X, kg	3.35E+04	1.21E+03	3.23E+04
NMVOC, kg	1.22E+04	2.26E+02	1.20E+04
Particulates, kg	1.35E+04	2.78E+02	1.32E+04
SO_2, kg	4.31E+04	1.39E+03	4.17E+04
Total Water Emissions, kg	4.73E+05	1.10E+04	**4.62E+05**
VOCs, kg	2.97E+01	1.00E+00	2.87E+01
Total Soil Emissions, kg	8.66E+03	2.69E+02	**8.39E+03**
Total Emissions, kg	**3.04E+07**	**5.89E+05**	**2.98E+07**

Appendix I

Detailed Economic Results of Case Studies

Table A 35. Economic analysis of acetonitrile recovery in the selamectin process based on annual operating costs

	Base Process	Recovery Process	Savings
Acetone Purchased ($/year)	24,370	24,370	0
Acetonitrile Purchased ($/year)	247,619	39,361	208,258
Incineration ($/year)	10,901	4,300	6,601
Distillation Utilities ($/year)	--	3,737	-3,737
Total ($/year)	**282,890**	**71,768**	**211,122**

Table A 36. Economic analysis of acetone recovery in the selamectin process based on annual operating costs

	Base Process	Recovery Process	Savings
Acetone Purchased ($/year)	24,370	3,194	21,176
Incineration ($/year)	3,052	400	2,652
Distillation Utilities ($/year)	--	1,183	-1,183
Total ($/year)	**27,422**	**4,777**	**22,645**

Table A 37. Economic analysis of acetonitrile and acetone recovery in the selamectin process based on annual operating costs

	Base Process	Recovery Process	Savings
Acetone Purchased ($/year)	24,370	3,194	21,176
Acetonitrile Purchased ($/year)	247,619	39,361	208,258
Incineration ($/year)	10,901	1,648	9,253
Distillation Utilities ($/year)	--	4,920	-4,920
Total ($/year)	**282,890**	**49,123**	**233,767**

Table A 38. Economic analysis of toluene recovery in Hydrocortisone case based on annual operating costs

	Base Process	Recovery Process	Savings
Acetone Purchased ($/year)	24,398	-	24,398
Toluene Purchased ($/year)	215,200	-	215,200
Incineration ($/year)	33,230	-	33,230
Distillation Utilities ($/year)	--	1,754	-1,754
Total ($/year)	**272,828**	**1,754**	**271,074**

Table A 39. Economic analysis of IPA recovered based on annual operating costs

	Base Process	Recovery Process	Savings
Isopropanol Purchased ($/year)	2,361,099	11,468	2,349,631
Incineration ($/year)	2,733,192	1,458,989	1,274,203
Distillation Utilities ($/year)	--	307,545	-307,545
Total ($/year)	**5,094,291**	**1,778,002**	**3,316,289**

Appendix J

Skid Investment Cost Calculation

Three distillation column vendor quotations, including the corresponding column dimensions and characteristics, are presented in Table A 40. Given the column dimensions and characteristics, it was assumed that the quotations could be used to estimate a packed column of 20 ft. in height and 1.5 ft. in diameter, including auxiliary equipment. These quotations were provided in February 2010. Assuming an inflation of 2.5 %[a], the average cost of these quotations in 2013 would be:

$$\left[\frac{US\$\ (400{,}000+875{,}000+825{,}000)}{3}\right]\cdot\left(1+\frac{2.5}{100}\right)^{(2013-2010)} = US\$\ 753{,}823$$

If we assume that the shipment and installation cost is 100% of the capital cost, then the final cost would be US$ 1,507,647.

Table A 40. Distillation column vendor quotations

Company	Quote[a] (US$)	Estimation Range	Diam. (ft.)	Height (ft.)	Reboiler (ft^2)	Condenser (ft^2)	Preheater (ft^2)	Other
ARTISAN[b]	400,000	+/-30%	1	25	50	50	20	packed
APV[c]	875,000	-	2	19	NS[d]	NS[d]	NA[e]	trays
KMPS[f]	825,000	+/-20%	1	27	25	35	NA[c]	packed

[a] All quotations are F.O.B. and include bottoms and distillate/reflux pumps, and other auxiliary equipment such as instruments, valves, piping, relief valves, etc.

[b] Includes a feed pump, a 20 ft^2 preheater and a distillate accumulator.

[c] Size: 10x12x35 ft., in WxLxH. Includes a reflux pump, besides the distillate.

[d] Not Specified

[e] Not Available

[f] Includes a 35 gallon reflux drum and a 10 ft^2 preheater. The approximate height is 35 ft.

In January 2003, the cost of Sulzer type pervaporation units containing PERVAP® 2510 type membranes, with a membrane area of 70 m^2 and 140 m^2 was 390,000 and 480,000 euros, respectively. The equipment size cost exponent is therefore:

$$n = \frac{\ln\left(\frac{480}{390}\right)}{\ln\left(\frac{140}{70}\right)} = 0.3$$

---

[a] http://www.tradingeconomics.com/united-states/inflation-cpi, June 2013.

In January 2003, the cost of the euro was 1.05 dollars[b]. Therefore, a 140 m^2 pervaporation unit costed, in 2003, US$ 504,000. Accounting for an inflation of 2.5 %, the cost in 2013 would be:

$$US\$\ 504{,}000 \cdot \left(1 + \frac{2.5}{100}\right)^{(2013-2003)} = US\$\ 645{,}163$$

A pervaporation unit with 210 m^2 of membrane area would have a cost of:

$$US\$\ 645{,}163 \cdot \left(\frac{210}{140}\right)^{0.3} = US\$\ 728{,}483$$

Assuming a shipment and installation cost of 100 % the capital cost, the final pervaporation unit cost would be US$ 1,456,965.

Therefore, a skid containing a distillation and pervaporation unit as described above would cost:

$$US\$\ 1{,}507{,}647 + US\$\ 1{,}456{,}965 = US\$\ 2{,}964{,}612$$

---

[b] http://www.oanda.com/currency/historical-rates/

Appendix K

Underwood Minimum Reflux Ratio Calculation

The following Underwood minimum-reflux equations were used:

$$\sum_i \frac{\alpha_i \cdot x_{i,D}}{\alpha_i - \theta} = R_m - 1$$

and

$$\sum_i \frac{\alpha_i \cdot x_{i,F}}{\alpha_i - \theta} = 1 - q$$

were:

- α_i is the relative volatility of component *i* to the reference component, and is calculated as:
  - ○ $\alpha_i{}^N = \alpha_N \cdot \alpha_{N-1} \cdot \cdots \cdot \alpha_2 \cdot \alpha_1$, were *N* is the number of stages, and
  - ○ $\alpha = \frac{K_i}{K_r} = \frac{y_i \cdot x_r}{y_r \cdot x_i}$, were *r* is the reference component.
- $x_{i,D}$ is the distillate molar fraction of component *i*,
- θ is calculated using the second Underwood equation,
- R_m is the minimum reflux ratio,
- $x_{i,F}$ is the molar fraction in the feed of component *i*,
- and q is defined as:

- $q = \frac{H_{F,vap.sat.} - H_F}{H_{f,vap.sat.} - H_{f,liq.sat.}}$, were $H_{F,vap.sat.}$ is the feed enthalpy at the saturated vapor state, $H_{f,liq.sat.}$ is the feed enthalpy at the saturated liquid state, and H_F is the real feed enthalpy.

Table A 41 shows the calculation of the R_m for the selamectin and hydrocortisone cases, with the equations shown above. The distillate molar fractions and the feed enthalpies were obtained from Aspen Plus®. For the hydrocortisone case, x_D is defined as the specification acetone purity, but in the hydrocortisone case, x_D is the result of obtaining the required acetonitrile purity in the bottoms. The value of θ was guessed to satisfy the second Underwood equation until the difference between both sides of the equation was smaller than a magnitude of 10^{-7}. The difference is shown as the *Dif.* value.

Table A 41. Minimum reflux ratio (Rm) calculation for the selamectin and hydrocortisone cases

	Selamectin Case		**Hydrocortisone Case**	
	Acetone	*Acetonitrile (reference component)*	*Acetone*	*Toluene (reference component)*
$x_{i,D}$	0.7	0.3	0.98	0.02
α_i	2.29	1	5.76	1
$x_{i,F}$	0.28	0.72	0.09	0.91
H_F	-8635.096	BTU/lbmol	-9149.672	BTU/lbmol
$H_{F,vap.sat.}$	6324.976	BTU/lbmol	10074.27	BTU/lbmol
$H_{f,liq.sat.}$	-6750.69	BTU/lbmol	-5252.085	BTU/lbmol
q	1.144115489		1.254306193	
$1-q$	-0.14411549		-0.254306193	
θ	1.6389135		3.0445282	
$\sum_i \frac{\alpha_i \cdot x_{i,F}}{\alpha_i - \theta}$	-0.1441154		-0.254306198	
Dif.	-9.1862E-08		4.7634E-09	
R_m	0.987447155		1.067646436	

Appendix L

List of Acronyms and Abbreviations

ACS: American Chemical Society

atm: Atmosphere (unit of pressure)

CED: Cumulative Energy Demand

CO: Carbon Monoxide

CO_2: Carbon Dioxide

CO_2eq: Carbon Dioxide Equivalent

*eco*MeTHF^{TM}: Biobased 2-methyl tetrahydrofuran produced by PennAKem

*eco*THF^{TM}: Biobased tetrahydrofuran produced by PennAKem

EPA: United States Environmental Protection Agency

ft.: Feet (unit of length)

g: Grams (unit of mass)

HETP: Height Equivalent to Theoretical Plate

HK: Heavy Key

HVWS: High Volume Waste Stream

IPA: Isopropanol or (also known as isopropyl alcohol)

IRR: Internal Rate of Return

kg: Kilogram (unit of mass)

kWh: Kilowatt-hour (unit of energy)

LCA: Life Cycle Assessment

LCE: Life Cycle Emissions

LCEA: Life Cycle Emissions Avoided

LCI: Life Cycle Inventory

LK: Light Key

LVWS: Low Volume Waste Stream

m^2: Square Meter/s (unit of area)

m^3: Cubic Meter/s (unit of volume)

MeTHF: 2-methyl tetrahydrofuran

MJ: Megajoules (unit of energy)

MM: Million

NAICS: North American Industry Classification System

NMVOCs: Non-methane volatile organic compounds

NO_x: Nitrogen Oxides

NPV: Net Present Value

OCS: Operating Cost Savings

P: Pressure

P2: Pollution Prevention

RRSA: Reflux Ratio Sensitivity Analysis

SO_2: Sulfur Dioxide

THF: Tetrahydrofuran

TRI: Toxic Release Inventory (from the EPA)

US$: United States Dollars

VOCs: Volatile Organic Compounds

wt.: weight

yr: year/s (unit of time)