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RESEARCH LETTER

Pervaporation as a green drying process for tetrahydrofuran recovery in pharmaceutical synthesis

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The use of pervaporation technology as a green drying process for the recovery and reuse of the solvent, tetrahyrdofuran, in a pharmaceutical synthesis has been evaluated. A case study has been performed on a step in the synthesis of a new oncology drug. Pervaporation has been integrated with a constant volume distillation process to produce a hybrid system that allows for the recovery and reuse of tetrahydrofuran. An economic and environmental analysis shows that this is an effective technology for this application.

Keywords: pervaporation; solvent recovery; pharmaceutical synthesis; tetrahydrofuran

Introduction

The pharmaceutical industry has historically had one of the highest amounts of waste generated per unit of drug manufactured. The Sheldon study indicates that this industry has a relatively high E factor (25 to >100 kg/kg product) when compared with traditional chemical processing and petroleum refining (*1*). The product refers to the active pharmaceutical ingredient (API) in the final drug formulation. This waste is mainly composed of organic solvents, which typically ranges from 50% to 60% by mass (*2, 3*). These solvents are used for the various unit operations in pharmaceutical manufacture from facilitating reactions to various separation and purifications. Since the solvents are not consumed in the API reaction stoichiometry, they end up as waste, which must be either disposed or recycled. In addition, they are also a major concern from the toxicity that they represent when the overall manufacturing operation is evaluated (*4*). Therefore, research has been undertaken to investigate ways to practice the 12 principles of green chemistry (*5*) and use more benign solvents and reduce solvent usage in drug syntheses (*6*).

Solvent usage not only adds to the direct in-process waste for pharmaceutical operations but also accounts for a significant amount of the carbon footprint in drug manufacture (*3*). Energy use and emissions generated through the solvent life cycle can be large. The emissions generated to manufacture the average solvent are nearly twice the mass of the solvent produced, and waste disposal by incineration of the average solvent produces slightly over twice its mass in emissions (*7*). Therefore, if solvent can be recovered and reused within the manufacturing operation, it makes the operation greener. Increasing costs for virgin solvent purchase and waste disposal also drive innovative approaches to recover and reuse.

One of the areas of interest in designing greener processes is solvent recovery (*8*). Distillation is the predominate process for solvent separations in chemical processing, accounting for over 90% of the commercial operations (*9*). Distillation can be operated in various process modes (atmospheric, azeotropic, extractive, pressure, steam, vacuum, etc.) with single or multiple operations (*10*). Although many do not consider it a green technology because of its relatively high energy requirements and process inefficiencies, which result in greenhouse gas emissions (*9*). Currently, distillation is used for the majority of solvent separation processes in the pharmaceutical industry (*3*). Conventional distillation is a relatively straightforward method for separation of common solvent waste mixtures but is limited when dealing with those from the pharmaceutical industry where complex mixtures or azeotropes exit. In addition, the pharmaceutical industry utilizes batch operations requiring designs other than the traditional continuous distillation (*11*). Azeotropic and entrainer-based distillation processes increase the energy use, cost, and environmental burden of the separation operation. Therefore, to effectively practice solvent recovery in the pharmaceutical industry, new approaches need to be examined. This paper describes a greener operation integrating membrane

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pervaporation (PV) with a constant volume distillation (CVD) in a hybrid process for the recovery and reuse of tetrahydrofuran (THF) from a step in an oncology drug synthesis.

In many cases it is desired to dehydrate a batch process to reduce the water content that results from reactions, solvent usage patterns, washings, and so on. This is necessary for further processing of the intermediate or API in an anhydrous (water-free) mixture. This is typically performed by a distillation or extraction technique to reduce the water content to acceptable levels. Because of the fact that many of the organic solvents used in pharmaceutical manufacturing form azeotropes with water, the dehydration of these mixtures to low water concentrations (<1%) is quite difficult. Azeotropic and extractive/entrainer-based distillation techniques are conventionally used to break the azeotrope and produce an anhydrous solvent mixture. These methods generally require more energy and raw materials and generate more waste (*12*). These operations are prevalent throughout the industry, and therefore, methods for batch dehydration to enhance synthesis steps would produce a green alternative for the pharmaceutical industry.

Materials and methods

Since this paper describes a case study to assess the relative greenness of a solvent recovery operation in a drug synthesis, only the methods pertinent to the environmental analysis are presented. Description of drug process chemistry and pharmaceutical unit operations is beyond the scope of this paper.

Life cycle assessment software was used to evaluate the relative greenness of using a membrane PV operation versus a distillation route. SimaPro 7.1® (PRé Consultants, Amersfoort, The Netherlands) was used to determine life cycle inventories for the raw materials and energy utilized in the process. EcoSolvent® (Safety and Environmental Group, Zurich, Switzerland) was used to analyze the waste disposal part of the life cycle. SimaPro generates values for total emissions, which are a sum of the individual pollutants to air, soil, and water. These values are reported on a per kilogram of raw materials or waste, and on a per kilowatthour of process energy utilized. The emissions are scaled based on final API production values and summed for the overall life cycle analysis (LCA). Economic impacts are analyzed using data as provided by the pharmaceutical industry, equipment vendor, and literature sources and are described in the "Case study" and "Results and discussion" sections.

Case study

Background

The case study with Bristol-Myers Squibb involves a step in the synthesis of a new oncology (cancer) drug currently in clinical trials. In a step that produces an intermediate compound, a batch reactor contains (a) intermediate, (b) organic solvent, THF, and (c) water. The batch must be reduced to a water content of 0.5% before further processing. This step currently uses a batch CVD process, which is also known as a Dean–Stark process (*13*). This is necessary since the THF–water mixture has an azeotrope at 95.7% THF (at standard temperature and pressure). Similar to entrainer-based distillation, this requires an additional amount of solvent (in this case, THF) to be added to break the azeotrope and allow the batch water content to be reduced to the desired concentration. The function of the additional THF doubles both as the entrainer to push past the azeotrope and as reflux. The entrainer is pure THF, which must be added in significant amounts compared with the original batch charge of THF. This process is not considered green since the additional entrainer and other chemicals end up as waste. Process information for the pilot-scale production of the oncology drug API is given in Figure 1. These are based on producing a pilot batch of 68 kg of API (*13*). Aspen Plus® (AspenTech, Burlington, MA) process simulation software was used to determine thermodynamic data for the separation and energy requirements of the CVD process.

To make the operation greener, we investigated ways to reduce the additional THF entrainer and recover THF from the waste stream for reuse (*14*). This reduces the need to purchase virgin solvent and reduces the waste burden for the process, which further reduces the cost of the overall process in terms of solvent purchase and waste disposal. Through the use of life cycle assessment, we show how this innovation can reduce the environmental footprint of the process. This can be shown through the environmental savings achieved from not having to manufacture the THF solvent entrainer used and energy saved from not having to manufacture it. In addition, we show the environmental savings from not incinerating the waste. In the end this will make it a greener and cost-efficient process.

It is proposed to use PV membrane technology to dehydrate THF to the desired purity and recover it for the distillation operation. This avoids the purchase of substantial amounts of new THF and reduces the waste produced. PV is a membrane-separation process technology that is relatively low on a scale of technological and commercial maturity
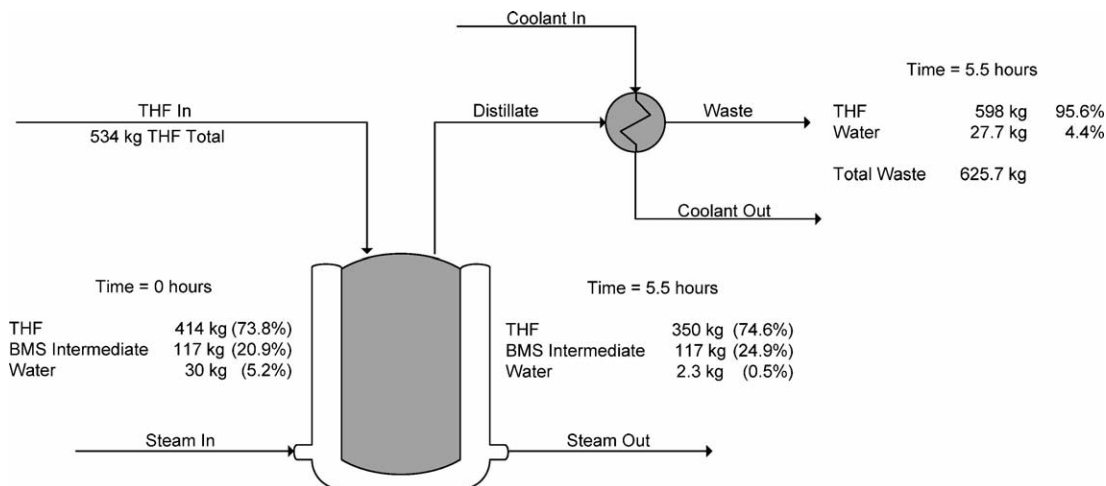
Figure 1. Process flow diagram for CVD process.

when compared with conventional separations such as distillation. It uses a highly selective membrane as a mass-separating agent to selectively separate components from a feed mixture. It is not limited by vapor–liquid equilibria and therefore can be used effectively in azeotropic mixtures.

In this application, PV will be used to selectively permeate water from a THF–water mixture, thus producing a purified solvent retentate and a permeate that is mostly water. PV units are typically not employed alone but are integrated into the process train of a separation scheme. The sequencing of separation operations depends on the relative advantages of each technology. When applied to a commercial-scale operation, as shown in Figure 2, the

distillation operation is greatly enhanced (*15, 16*). With PV, solvent can be more efficiently purified and dehydrated and then reused in the process. This membrane process not only helps reduce the waste generated for the particular operation but also reduces the fresh solvent needed. Through an LCA, we show that energy and waste are saved from not having to manufacture the solvent. Therefore, we use the terminology "green solvent drying" process.

Pervaporation has had commercial success in continuous processing of commodity chemicals, such as ethanol (*17*), and the recovery of organic solvents, such as isopropanol, from waste streams (*18, 19*). In these cases PV has been integrated with existing technologies to improve efficiency. PV has
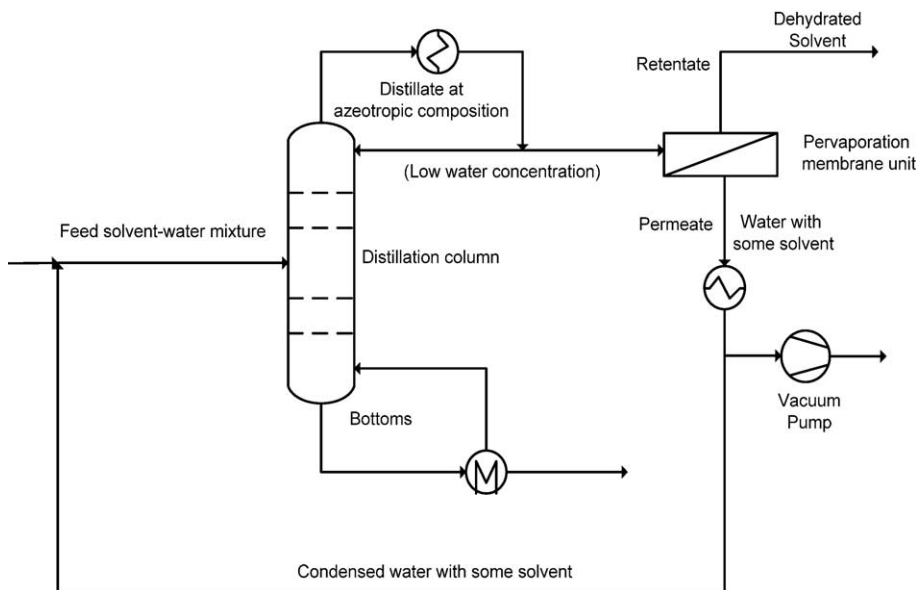

Figure 2. Integration of PV with traditional distillation in a continuous solvent dehydration operation for solvents with low water concentration azeotropes.

been shown to be effective in batch process integration with nonideal THF mixtures (*20*). Energy savings have been reported (*21*), but no studies have documented the life cycle emissions reductions. In addition, operating and capital cost savings have been reported (*21*) but not when combined with an LCA.

The challenge in this case study is how to effectively integrate this into a batch process that conforms to the requirements of the pharmaceutical industry. For example, issues such as solvent azeotropes, multiple solvents, solvent purity required, current good manufacturing practices (cGMP), Food and Drug Administration (FDA) regulations, processing time, and ease of use within a batch processing platform exist. This case study assumes that this is being done with a pharmaceutical synthesis in the development stages, where purity can be assessed and changes made. Solvent recycling in pharmaceutical manufacturing can be performed only as long as the operation conforms to regulatory requirements and the recycled solvent does not affect the quality of the intermediate or API (*3*).

Results and discussion

We are proposing to integrate a PV system with the current CVD process as our CVD–PV green drying improvement (Figure 3). We performed a design analysis of the proposed CVD–PV green drying process. The first step in this analysis is to investigate

the applicability of PV technology for integration into the pilot-scale API production process. Therefore, our analysis of PV applicability is based on this scale of the operation. We assume that scale-up to manufacturing would involve multiple batch production runs to achieve the desired annual API production. Polyvinyl alcohol (PVA) composite membranes (Sulzer Chemtech®, Neunkirchen-Heintz, Germany) are capable of separating a THF–water system (*22*). Previous studies by the authors have focused on modeling THF–water separations with Sulzer® 2210 PVA and ceramic membranes (*23*). Our investigations show that PV is capable of dehydrating the THF solvent to the level of purity (0.5% water) required. Other investigators have confirmed that PVA-based membranes are effective in the dehydration of THF–water mixtures (*24–29*).

The Sulzer PV membrane system can be sized to match the desired processing time by adding additional membrane modules. A unit can be purchased with all components that are of pharmaceutical grade. In this mode of operation, the PV membrane only "touches" the distillate from the CVD reactor and, therefore, there is no contact between the membrane and the intermediate compound. This is an advantage of employing this technology because of FDA regulations.

To analyze the green improvement, the development of a model of the proposed CVD–PV system was required. This is based on literature
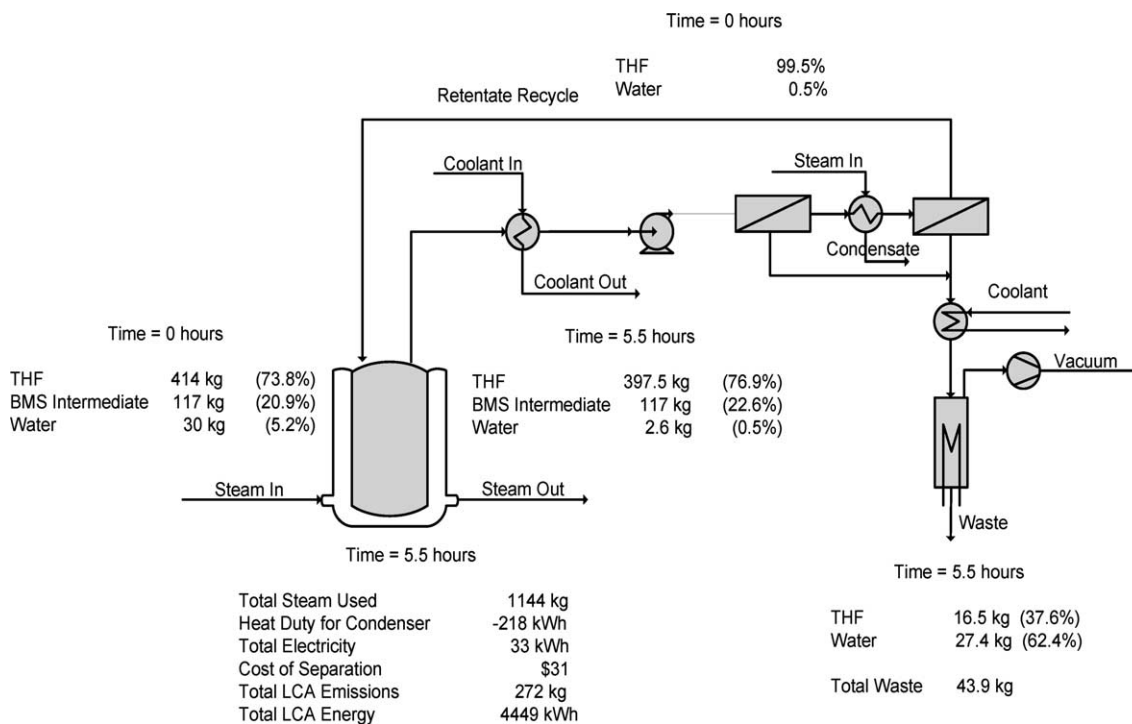
Figure 3. Proposed CVD–PV design based on current 68 kg pilot-scale operation.

related to THF–water thermodynamics vapor–liquid equilibria (VLE), design specifications provided by Sulzer, and process information provided by Bristol-Myers Squibb. The CVD process was analyzed first. This provides the baseline to compare the improvement and also serves as the basis for the additional PV system. The design model accounts for time of operation, utilities, and various membrane areas. A description of the development of the model is beyond the scope of this paper. Only the operational aspects of using the model to generate parameters for the environmental analysis are presented.

One of the principle functions of the model was to optimize the size of the PV unit (30). The results of the model show that there are some differences in environmental parameters depending on the size of the system (Table 1). The size of the system can increase only in module increments as provided by the vendor. The increase of waste produced is due to the larger amount of contact time the feed has with the membrane, causing more THF to permeate through the membrane. The total steam required is seen to be the lowest at 105 m^2. At the lower membrane area, the feed passes across the membrane more times to reach the required purity. This requires a large amount of steam sent to the CVD vessel to produce the vapor required. At higher membrane areas, the interstage heat exchangers become the larger consumers of steam. Another interesting part of the model is the decrease of the average separation factor with increasing membrane area. This directly reflects upon the decrease in driving force. The decrease in selectivity, however, does result in a reduction of operating time and the amount of passes across the membrane. This consequently decreases the amount of energy required, and the final mass within the vessel, but increases the amount of waste to be processed. Based on these factors, a membrane system size of 105 m^2 was used in our design. For our analysis, if more API is to be produced, it would be through multiple "campaigns" using the same batch size.

To estimate costs of operation, information from a variety of sources was obtained. Costs for purchase of fresh THF and dispose of the waste were provided by Bristol-Myers Squibb. Cost of utilities (steam, electricity, coolant, etc.) was obtained from standard design sources (31). PV system capital and operating costs were provided by Sulzer. A membrane replacement life of 3 years was assumed and three modules would need to be replaced in that time period. The membrane system and modules are based on the Sulzer design specifications and assume a membrane area of 35 m^2 for each module (105 m^2 total area). This information can be used to scale-up to manufacturing in determining the overall environmental and economic savings.

When the pilot-scale CVD process is compared with the proposed CVD–PV process, there are several major improvements observed (Figures 4 and 5). From a green perspective, the CVD–PV process reduces the additional THF entrainer significantly. Therefore, this modification to the process saves 535 kg THF (7.85 kg THF/kg API). There is a waste reduction in the CVD–PV process since the PV system recovers and recycles the purified THF distillate. Although a small amount of waste is still generated in the CVD–PV process, the waste is reduced from 625.7 kg waste (9.2 kg waste/kg API) to 43.9 kg waste (0.65 kg waste/kg API). The steam necessary to run the CVD process actually decreases when the PV unit is added, since the heating of fresh THF entrainer is lessened. There is an additional amount of electrical energy and steam necessary to operate the PV system, and this has been taken into account in our energy analysis. As will be shown, this is small when compared with the other savings obtained. The costs of virgin THF and waste disposal were calculated and compared for the CVD and CVD–PV processes. This is an important consideration in this case because of the relatively high cost of THF ($3.9/kg) and disposal costs ($0.42/kg) of the waste. These were the values used at the time of the study. Based on just this aspect of the CVD–PV design, this constitutes an improvement over the

Table 1. Mass and energy balances for CVD–PV systems with different membrane areas.

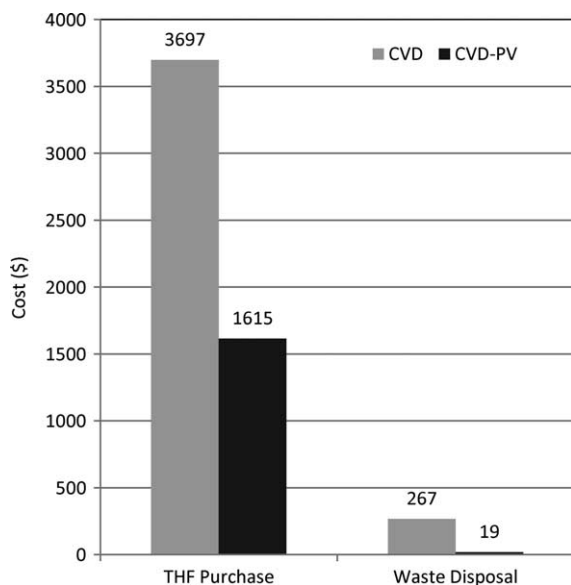|	Membrane area				
Process parameter	35 m^2	70 m^2	105 m^2	140 m^2	175 m^2
Time required (hr)	9.9	6.3	5.5	5.3	5.3
Final vessel mass (kg)	524	521	517	512	507
Waste generated (kg)	37	40	44	49	54
Condenser heat duty (kWh)	287	223	218	227	239
Electrical work (kWh)	59.5	37.7	33.0	31.9	31.8
Total steam required (kg)	1840	1220	1140	1200	1280

Figure 4. Pilot-scale improvements showing cost savings for THF purchase and waste disposal with the CVD–PV process compared with the current CVD process.

current process from an environmental and economic perspective. But this is only one part of the analysis.

An LCA was then performed over the entire operation. This was performed to estimate the environmental footprint of the process in terms of factors such as the energy and waste generated to manufacture fresh THF solvent, emissions produced to generate the energy required for the process, and emissions resulting from waste disposal (assuming
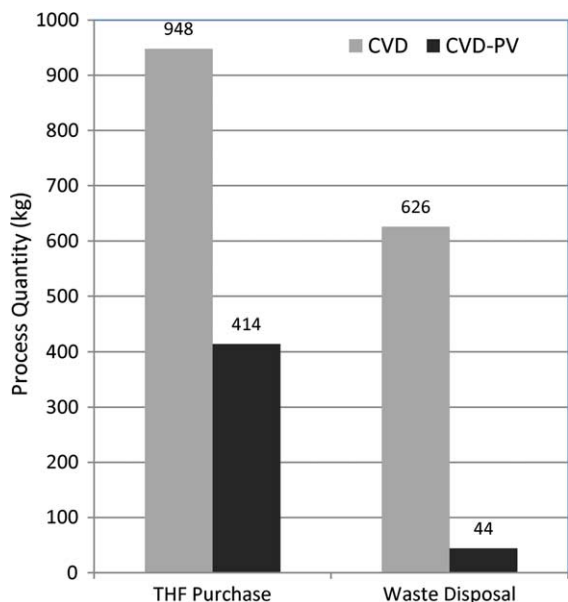

Figure 5. Pilot-scale improvements showing material savings in THF purchase and direct process waste with the CVD–PV process compared with the current CVD process.

incineration). This is considered a "modular" LCA approach. To perform this analysis, the manufacture of THF was studied. The LCA software, SimaPro 7.1®, was used with additional data sources added to determine the waste and energy needed to manufacture a functional unit (1.0 kg) of pure THF. The results of this analysis are shown in Table 2 for the major emissions categories and also for specific pollutants. This shows that THF production is a rather energy-intensive process, having a cumulative energy demand (CED) of 111 (MJ-Eq)/kg THF. The manufacturing process results in 5.65 kg emissions/kg of THF produced, and these are mainly greenhouse gas emissions from the large amount of energy needed to manufacture pure THF. Less than 2.5% of manufacturing life cycle emissions are released to air and soil. This information can be used to estimate life cycle emissions reductions based on not having to manufacture a certain amount of THF solvent. The results are linearly scalable to the amount of THF that will be used on an annual basis in producing the drug on the manufacturing scale.

SimaPro was also used to analyze the waste generated from using utilities such as steam and electricity that are required in the CVD and CVD–PV process. The process to make steam (at 3 bar) generates 0.226 kg emissions/kg steam of which 0.223 kg are CO_2. The life cycle emissions for 1 kWh of electricity generation are 0.762 kg of which 0.727 kg are CO_2. To analyze waste disposal (incineration) emissions, the EcoSolvent® software was utilized. The incineration of 1 kg of THF solvent waste results in 2.45 kg of life cycle emissions of which 2.44 kg are CO_2. All of the above methods calculate emissions produced for a particular functional unit (kg THF, kg waste, kWh energy, etc.). Therefore, our analysis can be scaled to any amount of THF used.

When the two processes are compared (Figure 6), the environmental footprints are clearly visible. The basis for this comparison is the THF used in the process. A total of 4390 kg of emissions are generated over the life cycle to produce 68 kg of API using the CVD process (64.6 kg life cycle emissions/kg API). The major pollutants generated over the entire life cycle for the CVD process (69%) result from the manufacture of THF. This is due to the large amount of THF required as entrainer and the relatively high amount of emissions that result from manufacturing THF. The emissions as result of the energy (steam) utilization for the CVD process account for 26% of the total life cycle emissions. Only a small amount of emissions (5.5%) are a result of the waste disposal. This is due to the energy recovered during incineration used to offset the waste and energy usage.

Table 2. Life cycle inventory (LCI) summary for producing 1 kg of THF.

Cumulative energy demand (MJ-Eq)	Air emissions (kg)	Water emissions (kg)	Soil emissions (kg)	Total life cycle emissions (kg)
	5.46 (CO_2)			
	0.00482 (CO)			
	0.0115 (SO_2)			
	0.0145 (CH_4)			
	0.00867 (NO_x)			
	0.00357 (Particulates)			
	0.00325 (NMVOC)	7.93×10^{-06} (VOCs)		
	0.0137 (Other)	0.126 (Other)		
111	5.52 (Total)	0.126 (Total)	0.00231 (Total)	5.65

When PV is integrated as shown in the CVD–PV pie chart, life cycle emissions are greatly reduced. The total emissions for a pilot-scale process are reduced to only 272 kg (4.0 kg life cycle emissions/kg API). Only a small amount of fresh THF is needed because the PV process is not 100% efficient (Figure 3). The utilities to operate the CVD–PV process are shown as emissions produced in electricity and steam generation, which, although they comprise a majority of the waste produced (91%), is small when compared with the magnitude of emissions in the CVD process.

There are still emissions from waste disposal since the PV system is not perfect but, again, small when compared with the CVD process.

A preliminary financial analysis of the CVD–PV process was performed. This included the capital cost of the PV system along with the operating costs associated with utilities, membrane replacement, THF purchase, and waste disposal. A depreciation period of 10 years and minimal rate of return of 17% were used in the financial analysis. It was determined that the purchase of a PV system to dehydrate THF
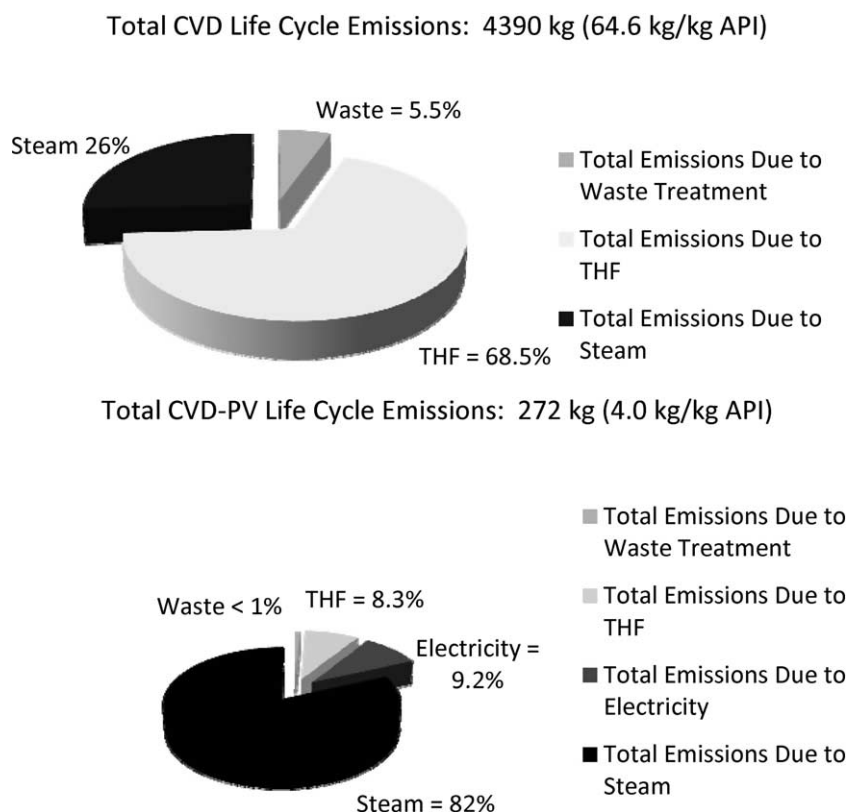

Figure 6. Use of LCA to compare life cycle emissions of CVD and CVD–PV processes for a pilot-scale production of 68 kg of API.
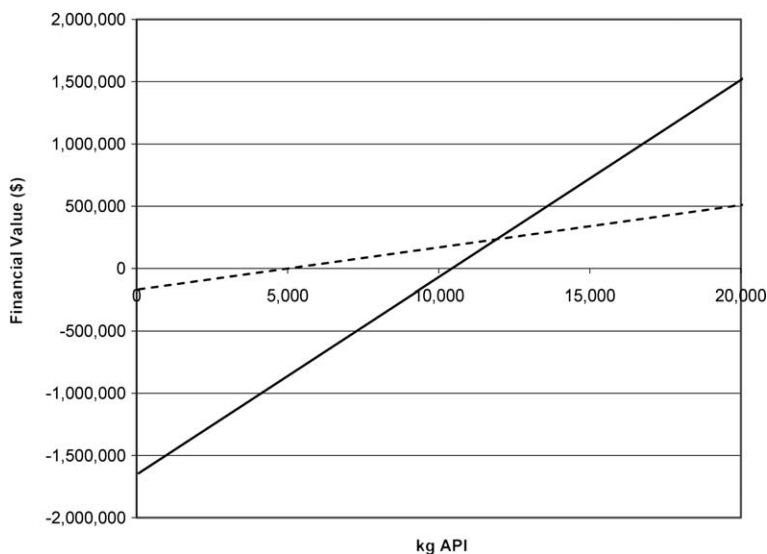
Figure 7. Economic analysis of the proposed THF green drying process as a function of API production. Net present value (NPV): ——; total annual savings (TAS): -----.

for one pilot-scale run of 68 kg API is not economical. To find the point in which this "green drying" process improvement is economical, a model was developed to predict when the net present value and total annual savings are equal. Figure 7 shows that the economic feasibility was found to be at a production level of 12,000 kg/year of API or 72,000 kg/year THF or other solvent processed. At this point the rate of return would be 24.2% and payback period is of 3 years. Therefore, this technology is most economical when used for a manufacturing-scale operation or for multiple drug campaigns as mentioned below.

To estimate environmental benefit of a manufacturing scale, a hypothetical scale-up calculation was performed. Table 3 shows the estimated pollution prevention impacts if this green improvement scaled up to 15,000 kg/year of API. The actual amount of API to be processed on a manufacturing scale is unknown at the present time since the drug is still under clinical trials. We used this estimate since it would correspond to a modest drug production rate (15 tonnes API/year), which is economically profitable for the use of the PV system on a manufacturing scale. For the production of 15,000 kg API/year, 91,300 kg of THF would be dehydrated in the process.

Tables 3 and 4 compare the parameters of the current CVD and proposed CVD–PV processes in terms of waste generated and energy used for the individual unit and process life cycle. The basis for these comparisons is the difference between the two processes in the additional THF entrainer used. As can be seen, using the CVD–PV process greatly

reduces the waste generated for the THF drying step from 132,000 kg to only 9,700 kg, yielding an overall reduction of 122,300 kg/year of hazardous waste reduced. The energy of the process decreases from 860,300 to 175,800 kWh, since the CVD–PV is more efficient in THF recycle avoiding the need to heat virgin THF for the batch. Annual operating costs are greatly reduced in this process. These were calculated based on utility costs (electricity, steam, cooling, etc.) and include "fresh" THF purchase and waste disposal costs. These are greatly reduced in the proposed CVD–PV process. At this scale of API production, the cost reduces from $516,000 to $6,850, netting a $509,150/year savings.

Using the SimaPro LCA tool, the waste generated to manufacture additional THF entrainer necessary for the current CVD process was determined. The total emissions produced to manufacture the required THF for the CVD process was 665,200 kg, and, since the CVD–PV process recovers and recycles the purified THF, there are only life cycle impacts associated with the small amount of THF make-up

Table 3. Pollution prevention comparison of CVD and CVD–PV processes to produce 15,000 kg/year API.

	Separation process		
	Process waste (kg)	Energy (kWh)	Operating cost ($)
CVD	132,000	860,300	516,000
CVD–PV	9,700	175,800	6,850
Reduction	122,300	684,500	509,150
% Reduction	92.7	79.6	98.7

Table 4. Pollution prevention life cycle comparison of CVD and CVD–PV processes to produce 15,000 kg/year API.

	LCA THF production	LCA process utilities	LCA waste incineration	Total life cycle	
	Total emissions (kg)	Total emissions (kg)	Total emissions (kg)	Total emissions (kg)	Total cumulative energy demand (kWh)
CVD	665,200	250,000	53,000	968,700	13,440,000
CVD–PV	4,983	54,500	399	59,900	981,000
Reduction	660,200	195,500	52,600	908,800	12,459,000
% Reduction	99.3	78.2	99.2	93.8	92.7

for the batch. Therefore, a waste reduction of 660,200 kg/year is estimated. CED decreases by 13,020,000 kWh/year, showing the significance of using a recovery process to avoid the energy necessary to manufacture virgin THF solvent. Process utilities were also analyzed by SimaPro to determine the emissions resulting from producing the energy required for both CVD and CVD–PV processes. The emissions decrease by 196,000 kg/year with the PV process. Waste disposal by incineration was evaluated by the EcoSolvent tool and emissions reduced from 53,300 to 399 kg/year.

An overall summary of the two processes shows the contribution of the various process improvements in the overall pollution prevention analysis. The total pollution reduction of 908,800 kg/year includes waste produced to manufacture THF, waste generated from process utilities, and waste from incineration. The overall CO_2 emissions are reduced by 887,500 kg/year. Total life cycle energy saved from using a CVD–PV process and from reducing virgin THF production is 12,460,000 kWh/year.

The proposed CVD–PV process has great applicability to other solvent mixtures; therefore, it has potential applicability to be used in other drug-manufacturing campaigns at the same manufacturing facility. This separation process can be used across multiproduct lines and, therefore, is termed a "platform technology." We have further analyzed the pollution prevention savings from using the PV system in multiple drug productions and larger volumes of solvents recovered in a manufacturing facility. It is assumed that since THF is such a common solvent in pharmaceutical manufacture, similar separations requiring PV exist with other drugs being manufactured at the same plant. By effectively optimizing the use of PV in the plant, its potential can be fully utilized. This approach fully uses the PV system for production of both the intended drug and other drugs/solvents.

Conclusions

The dehydration and reuse of the solvent, THF, in a synthesis step of an oncology drug have been evaluated. A hybrid system consisting of a batch CVD coupled with a membrane PV unit (CVD–PV) has been compared with the existing CVD process. The existing CVD is a process where THF is added as an entrainer solvent to push past the THF–water azeotrope and is later regarded as waste and incinerated. An economic and environmental assessment was performed comparing the greener solvent drying process to the conventional method. Significant economic savings and emissions reductions result from the reuse of the THF and reductions in the incineration of solvent waste. Through an examination of the solvent life cycle, reductions in emissions from THF manufacture, process utilities, and waste disposal are evaluated.

Acknowledgements

References

(1) Sheldon, R.A. *Chem. Ind.* **1997**, *1,* 12–15.
(2) Henderson, R.K.; Kindervater, J.; Manley, J.B. Presented at the 11th ACS Green Chemistry and Engineering Conference, Washington, DC, June 2007.
(3) Slater, C.S.; Savelski, M.J.; Carole, W.A.; Constable, D.J.C. In *Green Chemistry in the Pharmaceutical Industry*; Dunn, P., Wells, A., Williams, T., Eds.;

Wiley-VCH Verlag Publishers: Weinheim, Germany, 2010; pp 49–82.

(4) Slater, C.S.; Savelski, M.J. *Environ. Sci. Health* **2007**, *42*, 1595–1605.

(5) Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998; p 30.

(6) Constable, D.J.C.; Jiménez-González, C.; Henderson, R.K. *Org. Process Res. Dev.* **2007**, *11,* 133–137.

(7) Raymond, M.J.; Slater, C.S.; Savelski, M.J. *Green Chem.* **2010,** *12,* 1826–1834.

(8) Slater, C.S.; Savelski, M.J. *Innov. Pharm. Technol.* **2009,** *29,* 78–83.

(9) Ramzan, N.; Degenkolbe, S.; Witt, W. *Chem. Eng. J.* **2008,** *140,* 201–213.

(10) Doherty, M.F.; Fidkowski, Z.T.; Malone, M.F.; Taylor, R. In *Perry's Chemical Engineer's Handbook*, 8th ed.; Green, D.W., Perry, R.H., Eds.; McGraw-Hill: New York, 2007; pp 13-1–13-116.

(11) Barton, P.I. *Curr. Opin. Drug Discovery Dev.* **2000,** *3,* 707–713.

(12) Smallwood, I. *Solvent Recovery Handbook*, 2nd ed.; Taylor & Francis: Boca Raton, FL, 2002; pp 77–114.

(13) Slater, C.S.; Savelski, M.J.; Taylor, S.; Kiang, S.; LaPorte, T.; Spangler, L. Presented at the American Institute of Chemical Engineers annual meeting, Salt Lake City, UT, November 2007; Paper 223f.

(14) Taylor, S.; Kiang, S.; LaPorte, T.; Spangler, L.; Slater, C.S.; Savelski, M.J.; Hesketh, R.P. Presented at the 11th American Chemical Society Green Chemistry and Engineering Conference, Washington, DC, June 2007; Paper 37.

(15) Lipnizki, F.; Field, R.W.; Ten, P.-K. *J. Membr. Sci.* **1999,** *153,* 183–210.

(16) Van Hoof, V.; Van den Abeele, L.; Buekenhoudt, A.; Dotremont, C.; Leysen, R. *Sep. Purif. Methods* **2004,** *37,* 33–49.

(17) Baker, R.W. *Membrane Technology and Applications*, 2nd ed.; John Wiley & Sons: Chichester, England, 2004; pp 355–392.

(18) Kujawski, W. *J. Environ. Stud.* **2000,** *9,* 13–26.

(19) Urtiaga, A.; Gorri, E.; Ortiz, I. *Sep. Purif. Technol.* **2006,** *49*, 245–252.

(20) Koczka, K.; Manczinger, J.; Mizsey, P.; Fonyo, Z. *Chem. Eng. Proc.* **2007,** *46,* 239–246.

(21) Sommer, S.; Klinkhammer, B.; Melin, T. *Desalination* **2002,** *149,* 15–21.

(22) Sulzer Chemtech. *Pervaporation Membrane Information Brochure*; Neunkirchen-Heintz: Germany, 2004.

(23) McGinness, C.A.; Slater, C.S.; Savelski, M.J. *J. Environ. Sci. Health* **2008,** *43,* 1673–1684.

(24) Mencarini, J.; Coppola, R.; Slater, C.S. *Sep. Sci. Technol.* **1994,** *29,* 465–481.

(25) Neto, J.M.; Pinho, M.N. *Sep. Purif. Technol.* **2000,** *18,* 151–161.

(26) Gallego-Lizon, T.; Edwards, E.; Lobiundo, G.; dos Santos, L.F. *J. Membr. Sci.* **2002,** *197,* 309–319.

(27) Srinivasa Rao, P.; Sridhar, S.; Krishnaiah, A. *J. Appl. Polym. Sci.* **2006,** *102,* 1152–1161.

(28) Krishna Rao, K.; Subha, M.; Sairam, M.; Mallikarjuna, N.; Aminabhavi, T. *J. Appl. Polym. Sci.* **2007,** *103,* 1918–1926.

(29) Lu, J.; Nguyen, Q.; Zhou, L.; Xu, B.; Ping, Z. *J. Membr. Sci.* **2003,** *226,* 135–143.

(30) Moroz, T.; McGinness, C.; Schiavi, D.; Savelski, M.J.; Slater, C.S. Presented at the American Institute of Chemical Engineers annual meeting, Salt Lake City, UT, November 2007; Paper 330s.

(31) Peters, M.S.; Timmerhouse, K.D.; West, R.E. *Plant Design and Economics for Chemical Engineers*, 5th ed.; McGraw-Hill: New York, 2003.