

Analysis of Separation Methods for Isopropanol Recovery in the Celecoxib Process

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Various approaches to solvent recovery have been studied for the manufacturing process of celecoxib, the active ingredient in Celebrex[®]. A design case study has been performed by Rowan University with Pfizer through a green engineering partnership program. The manufacturing operation at Barceloneta, Puerto Rico was evaluated and several green engineering alternatives for the purification and recovery of isopropanol from waste streams proposed. This separation is complex due to the multiple waste streams generated, with varying compositions of isopropanol, ethanol, methanol, water and dissolved solids. Overall goals were waste minimization and isopropanol recovery and purification. The group performed a conceptual study of distillation, extraction, reactive distillation, adsorption, and membrane-based processes. Through use of computer simulation and literature/design methodologies, traditional methods were shown to be unable to obtain high isopropanol purities with the equipment available. Both molecular sieve adsorption and membrane pervaporation appear to have the most promise to effectively recover and purify isopropanol. Several green design approaches were evaluated using distillation combined with either molecular sieve adsorption or membrane pervaporation. The case study describes equipment and processing issues, and estimates environmental impacts and costs.

INTRODUCTION

Rowan University and Pfizer have partnered through our Engineering Clinics program to examine green engineering approaches to solvent minimization in the celecoxib process^{1,2,3}. This project is one of several academic industrial partnerships with pharmaceutical and specialty chemical companies that have been conducted at Rowan University⁴. These projects are funded by industry through the Rowan Engineering Clinic program and by the U.S. Environmental Protection Agency Pollution Prevention grant program. The projects involve a process case study or problem that has a green chemistry/green engineering component. Depending on the nature of the projects, they can be “paper” projects that are design based or experimentally-based. This particular project is funded through the Pfizer Green Chemistry Program.

The project objectives were the investigation of solvent recovery alternatives to minimize waste from the celecoxib process. Celecoxib is the active ingredient in the top-selling arthritis pain medicine, Celebrex[®]. The objectives of the student project team were to compare the current process route with green engineering options.

- Waste stream reduction and isopropanol (IPA) recovery
- Define operational sequences
- Equipment and process steps required

- Estimate costs and environmental impacts
- Make proposals and recommendations

Students reviewed documentation on the “history” of the celecoxib process and the various process chemistries. Some of the previously suggested approaches for solvent recovery were also analyzed. A review of the capabilities of the existing equipment at Barceloneta to recover IPA from the waste was done. It was desired to work with the current capital assets, but several alternative processes involving new equipment were evaluated.

RESULTS AND DISCUSSION

The first step in the process was to analyze the waste flows per batch of celecoxib. Figure 1 shows the waste streams of interest in the minimization and recovery. This is a very efficient process with an E-factor of 9.0, but since the annual production is large, solvent waste reduction and recovery represent a significant opportunity. The study compared waste minimization options for combined waste composed of the three streams and a segregated approach. The segregated approach take streams with similar properties (centrifuge wash and dryer distillates) and combines for separation/recovery and the mother liquor (filtrate) stream is either pre-concentrated for sale or incinerated. This approach reduces the separation burden on the existing equipment inventory in Barceloneta and eliminates sending the high TDS mother liquor stream through the proposed separation process train. Based on batch flows, yearly production estimates and equipment availability, an equipment utilization schedule was developed for each process alternative described.

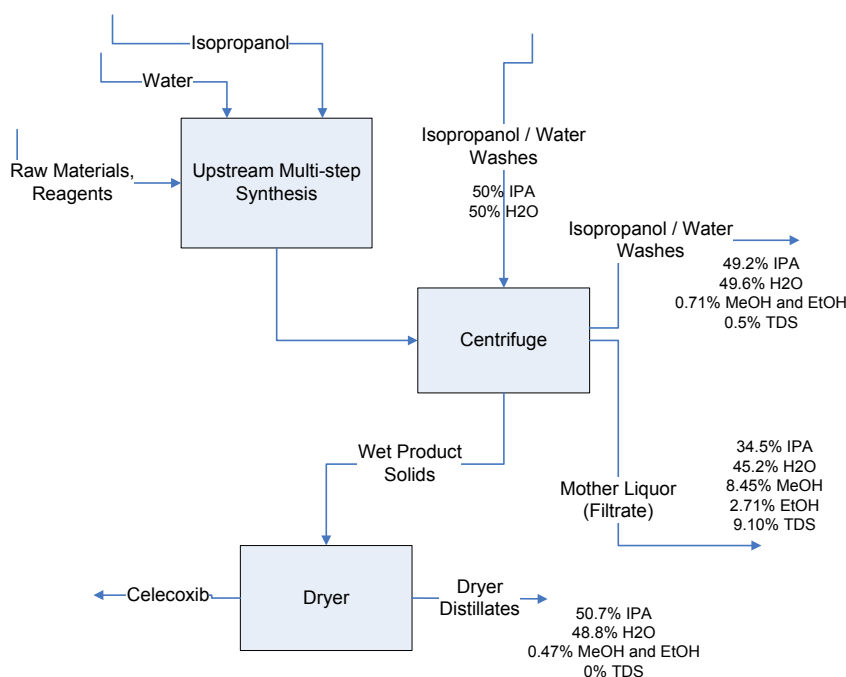


Figure 1. General celecoxib process flow diagram⁵

The process design review involved an analysis of both traditional and non-traditional separation methods such as distillation, liquid, liquid extraction, extractive distillation, reactive distillation, molecular sieve adsorption, and membrane pervaporation. ASPEN Plus was

utilized to develop design models for the equilibrium-based separations. Conventional distillation is limited in obtaining pure IPA from the waste due to the fact that water forms an azeotrope with IPA at 87.4 wt%. The azeotrope is not pressure sensitive, which limits the use of pressure-swing distillation. Distillation to the azeotrope was proposed as the first step in sequential separations train followed with a more advanced separation operation. This effectively leverages the advantages of each technology. There is no “magic bullet” for a one step recovery operation.

Extractive distillation was evaluated for the combined waste stream. These processes involve a tertiary phase to purify the IPA composition past the azeotropic composition. Various mass separating agents (MSA) were investigated through literature review and using ASPEN Plus. Using diisopropyl ether as the MSA produced a 99% pure IPA product, but required a high operating pressure (30 atm) distillation column. A process using ethylene glycol produced a 94% purity IPA product, but needed high column utilization (4 columns). Dimethyl sulfoxide as a MSA produces 99% purity IPA product, but also has a high column utilization (4 columns). All of these proposed alternatives exceed equipment capabilities at Barceloneta and therefore were not considered for a full-scale design analysis^{6,5}.

Molecular sieve adsorption was also evaluated. Even though this is not in the equipment inventory at Barceloneta, this option was considered since the process is used widely in commercial ethanol drying. These systems are not modeled in standard ASPEN Plus, therefore vendor and literature investigations were undertaken. Typically, these systems are used for low water removal in solvent drying applications and therefore it was proposed that this process follow distillation in a design sequence. To optimize the process the azeotropic overhead from the distillation column was sent to the molecular sieve in vapor form. A dual column sieve system was used to allow for IPA production and regeneration cycles. Based on the information obtained from various design literature and vendor sources, a capital cost of \$500,000 (base module) with a total installed cost of \$1.5 MM was estimated. IPA product with a purity of 99.5% can be obtained.

Pervaporation was considered as one of the advanced separation methods. Various configurations were examined using the equipment available at the plant. These included:

- Pervaporation units run in series or parallel
- Distillation followed by pervaporation
- Distillation followed by pervaporation followed by another distillation column

The basis for the design is a pervaporation system using 2 pressure vessels with 3 membrane modules of 35 m² each (total system area = 210 m²).

The aforementioned combinations were then modeled using the combined waste streams and just separating the segregated waste of dryer distillates and centrifuge wash. Empirical models were developed for trans-membrane mass transfer using Excel and an Aspen user block with literature data^{7,8} and a simplified cross-flow model. Additional design information was obtained from Sulzer. Selling the mother liquor or incineration options were evaluated in the segregated waste recovery approach. These models have limitations in their ability to predict multicomponent transport systems such as this case with the small amounts of the methanol and ethanol.

Based on scheduling of the pervaporation system, only the segregated dryer-distillates and centrifuge wash streams are treated. The distillation-pervaporation option is predicted to yield an IPA purity of 98.4% based using as a representative design basis of 1000 kg/hr feed. Higher feed rates significantly decrease IPA product purity. To purify this further with the same membrane area and feed rate, a distillation-pervaporation-distillation scheme is proposed. The use of the “polishing” distillation column increases IPA purity to 99.1%. The pervaporation system does require additional utilities such as steam (for inter-stage heaters) and electricity for vacuum system and coolant system, but these are small when compared to the overall energy saved^{5,6}.

A thorough design analysis was conducted on the “base case” and the various green design alternatives, distillation-pervaporation, distillation-pervaporation-distillation, and distillation-molecular sieve adsorption. For each of these a further analysis was done on the sale of the mother liquor or incineration. A summary will be shown for the distillation-pervaporation with mother liquor sold case.

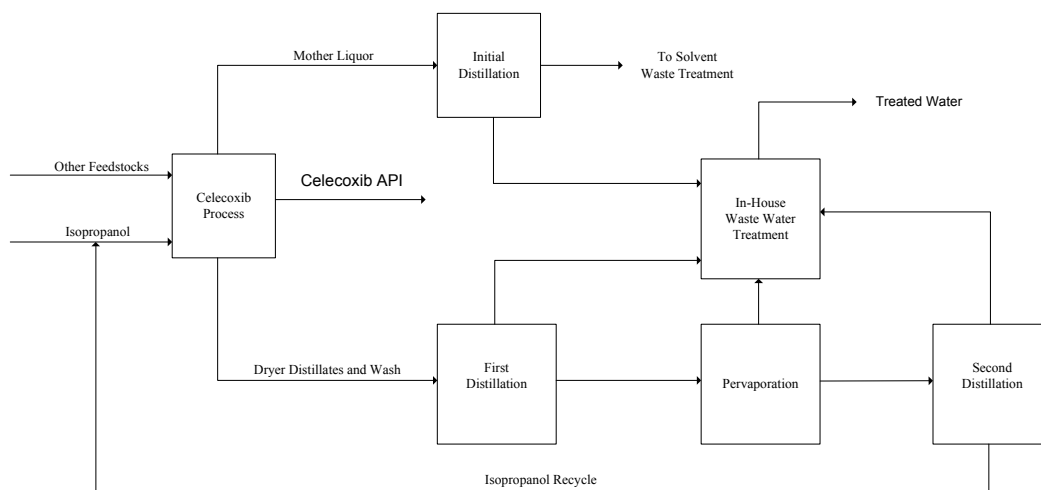


Figure 2. Proposed distillation-pervaporation-distillation process flow diagram

The process scheme shown in Figure 2, recovers 2325 kg/batch of IPA at a purity of 99.1%. This represents 57% of the IPA recovered from the total waste streams. The utilities for the proposed recovery scheme are 10,000 kg/batch of steam, 59 kWh/batch of electricity, and 91,200 gal/batch of cooling water. A comparison of annual operating costs to the base case was performed. A comparison of annual operating costs of the proposed option to the base case shows a 72% savings. The base case annual cost of \$5.28 MM is reduced to \$1.46 MM with the “green design”.⁵ The significant difference comes from the reduction in the cost to purchase fresh IPA and reduction in the waste disposal costs. There are still costs associated with the purchase of IPA, but 43% less than the base case. The cost of utilities required for the distillation-pervaporation-distillation “green design” is small when compared to the overall savings.

The economic conclusions of the green design alternatives indicate that pervaporation and molecular sieve options provide comparable operating savings (64-73%) to the base case. The molecular sieve option requires a \$1.5 MM capital investment. Since the pervaporation system already is available at the plant site, this provides a non-capital intensive alternative to

molecular sieve adsorption. The “best approach” in using the pervaporation option is to use the “touch-up” second distillation to get 99.1% isopropanol purity which only requires an additional 0.51% increase in operating costs, but yields a 72% savings overall. The option with selling the concentrated mother liquor decreases operating costs by 24%^{5,6}.

The environmental analysis of the green process designs involved several steps and only a summary of those are presented here. In order to perform a life cycle analysis (LCA), the system boundaries, purposes and functional units were chosen. This was followed by a life cycle inventory where inputs of mass and energy, and outputs of emissions and products were quantified. Finally, environmental impacts were characterized for the various “green” process alternatives.

Since isopropanol was the solvent to be recovered, the primary focus was on its life cycle. Figure 3 shows the LCA system boundaries for the proposed distillation-pervaporation-distillation and sell mother liquor option. This LCA includes the emissions produced from the manufacture of virgin IPA as well as those from the process modifications (pervaporation and distillation processes). Since mother liquor is concentrated for sale, we assumed for analysis that this could be considered generic solvent and therefore the manufacture of that would be avoided. An analysis of the proposed process to the base case indicates that emissions are reduced from 22,837 to 1,857 kg/batch. Resultant CO₂ emissions are estimated to be reduced from 20,260 to 1,066 kg/batch⁵.

The overall environmental conclusions are that all pervaporation and molecular sieve adsorption options provide substantial life cycle emissions savings compared to the base case. These range from 64 to 93 % in overall emissions (and 65 to 96% CO₂ emissions) depending on the process alternative (Figure 4). Selling the mother liquor significantly reduces life cycle emissions, improving alternatives by 75%. When the recommended green process design of pervaporation-distillation-pervaporation & selling mother liquor is analyzed on a yearly basis, the following life cycle waste reductions are determined. A yearly savings of 16.63 MM kg of emissions a year, for a 92% reduction from the base case is estimated. The CO₂ reductions parallel this as well, with yearly reductions estimated at 11.55 MM kg/yr for a 95% reduction.⁵

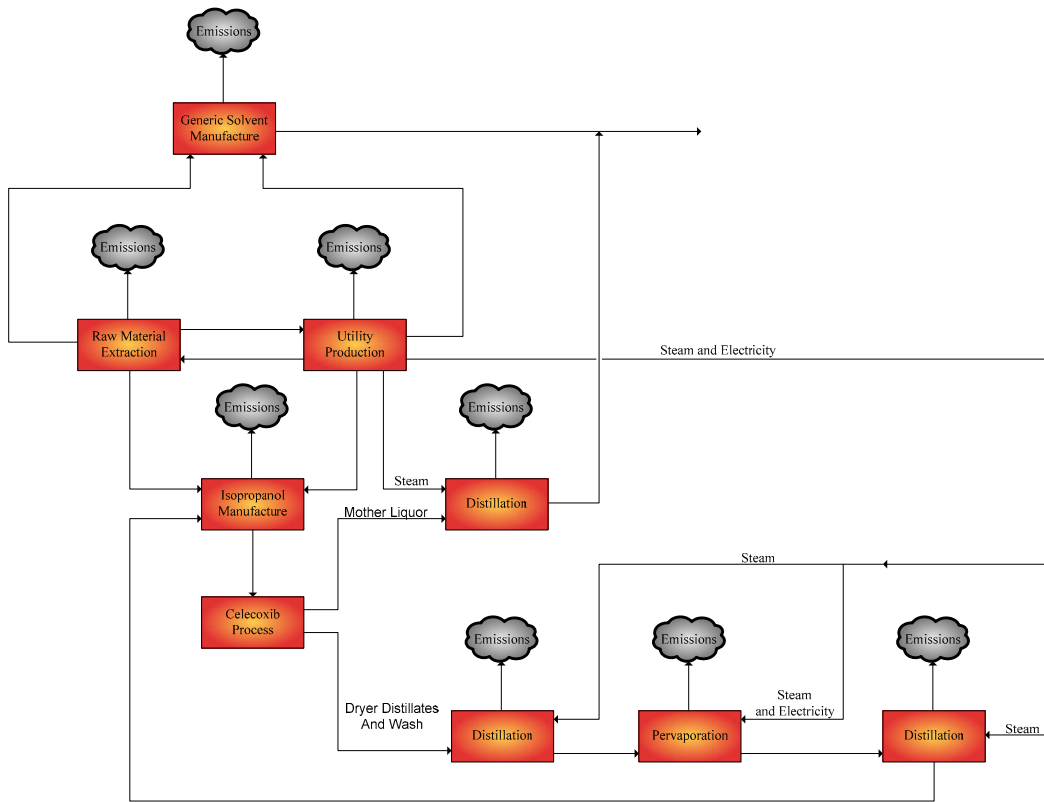


Figure 3. LCA system boundaries for the distillation-pervaporation-distillation & sell mother liquor process option.

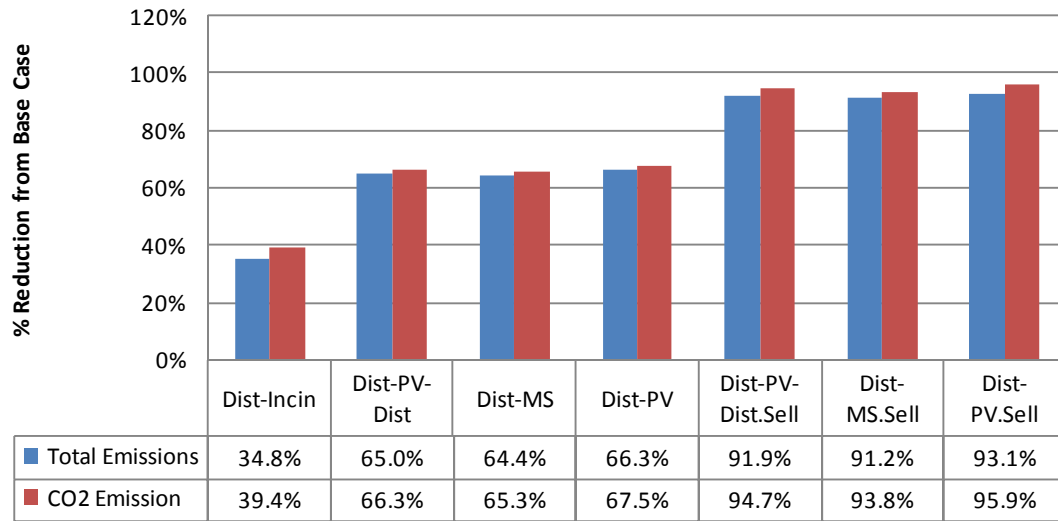


Figure 4. Analysis of life cycle waste reductions from the various process alternatives.

CONCLUSIONS

The distillation-pervaporation-distillation process with sale of mother liquor is the recommended green engineering alternative. This option takes advantage of the current capital equipment at Barceloneta and could be implemented with minor equipment modifications such as the purchase of newer membranes. Further pilot testing is recommended to verify the models presented.

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