Using Membrane Pervaporation for the Dehydration and Degassing of Solvents for Reuse in Chemical Manufacturing

Scientific Update Conference
Prague, Czech Republic
June 25, 2018
Hannah Murnen
In a nutshell

Membrane pervaporation for dehydration of organic solvents is important across a number of industries, including pharmaceutical manufacturing (focus of this talk).

Perfluoropolymer membranes are an ideal system for solvent dehydration given their high chemical resistance and high flux and selectivity.

Design of these systems is intricate and requires a careful analysis of membrane, system and application requirements.

An example of a pharmaceutical system, designed in collaboration with Pfizer, will be used to demonstrate important design concepts and the eventual implementation of a successful system.
Introduction to Compact Membrane Systems
Compact Membrane Systems

- **1993**: Initiate research program
- **1994**: Spin out of DuPont
- **2000**: Launch transformer application
- **2010**: In house manufacturing
- **2012**: Launch pervaporation for oil dehydration
- **2015**: Add fluoro chemistry capabilities (CAF)
- **2016**: Build commercial team and capabilities
- **2017**: Launch solvent applications
- **2017**: Expand into custom gas separations

**Logos**:
- NIH
- USDA
- U.S. Department of Energy
- Pfizer

**Institutions**:
- NIH
- USDA
- U.S. Department of Energy
- Pfizer
CMS is a technology player with platform and applications across multiple industries.

High chemical and thermal resistance

Fluoropolymer chemistry expertise and know how

Membrane, prototype, manufacture, system design

Industry application understanding

IP in materials and applications

Effective in challenging environments where other materials fail

Applications in process chemistries and aggressive end products

Remove gases and water from organics

Petrochem
Pharma
Oil and Gas
Manufacturing
Wind Power
Marine
Power Gen
Aerospace
Chemicals
Why is solvent dehydration important in pharmaceutical production?
Solvent recovery and reuse is a big issue for API production

- API production often requires use of organic solvents
- Typical solvent use is 10-800 kg/kg of API
- Accounts for up to 60% of raw materials usage
- Solvent use is expensive (purchase, use, disposal)

Solvent purity can impact yield and efficacy of reaction, particularly in flow processes

---

3 EPA TRI 2016, Pharmaceutical Industry
Continuous processing is the way of the future
Where else could solvent dehydration be useful?

- Specialty chemical
- Semiconductor and electronic manufacturing
- Paint production
Overview of Pervaporation Technology
What is pervaporation?

\[ \text{H}_2\text{O Flux} = \left[ \frac{\pi}{\delta} \right] (\gamma \times P^0 - p \gamma) \]

- \( x \) = water feed mole fraction
- \( y \) = water permeate mole fraction
- \( \pi \) = water permeability
- \( \gamma \) = water activity coefficient
- \( P^0 \) = water vapor pressure
- \( \delta \) = membrane thickness
- \( p \) = vacuum pressure
What affects driving force?

\[ \text{H}_2\text{O Flux} = \left[ \frac{\pi}{\delta} \right] (\gamma x P^o - p y) \]

1. **Temperature**: high temperature gives high water vapor pressure
2. **Thermodynamics**: the higher the water activity, the better
3. **Composition**: the higher the water loading, the higher the driving force
4. **Permeate side pressure**: the lower the vacuum, the higher the driving force

\( \pi = \) water permeability  
\( \delta = \) membrane thickness  
\( \gamma = \) water activity coefficient  
\( x = \) water feed mole fraction  
\( P^o = \) feed water vapor pressure  
\( y = \) water permeate mole fraction  
\( p = \) vacuum pressure
What about selectivity?

Smaller molecules (e.g., H_2O) go through membrane more quickly
Membrane is a composite structure

- Microporous support layer (e.g. ePTFE, PS)
- Non-porous CMS polymer

Diagram showing:
- Sweep gas
- Feed
- Hollow Fibre Membrane
- Retentate
- Permeate
Custom Amorphous Fluoropolymer (CAF) platform

Amorphous fluoropolymers are known to have high free volume and be chemically resistant

**CMS value proposition:** Develop custom amorphous fluoropolymers for dehydration of difficult solvents used in manufacturing

- Control separation properties through the introduction of specific monomers to create unique copolymers
- Deep bench of materials - 16 active patents (7 issued)
- Utilize high free volume for high flux and tailor chemistry to allow high selectivity
Important characteristics of pervaporation

• Water goes through membrane, making the system **ideal for removing water from solvent** (NOT removing solvent from water)

• **Azeotropes are not an issue** for pervaporation

• **Separation is not perfect** – there will be some water in the solvent and some solvent in the water

• Can achieve **very high recovery** (>95%)

• **Everything is a tradeoff** – for example, you can get very dry, but you will give up recovery
System design
Considerations for a pervap system

- Compatibility
- Flow rates
- Pressure drop
- Solvent loss
- Vacuum level
- Series vs. parallel
- Membrane longevity
- Water level
- Impact of salt
- Batch vs. continuous
- Temperature gradients
- Recovery vs. purity
- Solvent mixture
- Solvent mixture
- Compatibility
- Flow rates
- Pressure drop
- Solvent loss
- Vacuum level
- Series vs. parallel
- Membrane longevity
- Water level
- Impact of salt
- Batch vs. continuous
- Temperature gradients
- Recovery vs. purity
- Solvent mixture
- Solvent mixture
Design process overview

1. Customer approaches with a separation need
2. Quick assessment based on similar solvents
3. Feasibility test – measure activity coefficient
4. Agree on important design parameters with customer
5. Develop system design and estimate
6. System build
7. Installation and startup
Case study: Dehydration of nonane/tert-butyl hydroperoxide (TBHP)

Continuous Production of Anhydrous tert-Butyl Hydroperoxide in Nonane Using Membrane Pervaporation and its Application in Flow Oxidation of a γ-Butyrolactam

Bryan Li, Steven M. Guinness, Steve Hoagland, Michael W. Fichtner, Hui Kim, Shelly Li, Robert John Maguire, James Christopher McWilliams, Jason Mustakis, Jeffrey Raggon, Dan Campos, Chris Voss, Evan Sohodski, Bryan Feyock, Hannah Murnen, Miguel Gonzalez, Matthew Johnson, Jiangping Lu, Xichun Feng, Xingfang Sun, Songyuan Zheng, and Baolin Wu

*Org. Process Res. Dev.*, Just Accepted Manuscript
DOI: 10.1021/acspord.8b00083
Publication Date (Web): May 23, 2018
Design process

1. Customer approaches with a separation need
2. Quick assessment based on similar solvents
3. Feasibility test – measure activity coefficient
4. Agree on important design parameters with customer
5. Develop system design and estimate
6. System build
7. Installation and startup
Objective – Safely use anhydrous TBHP for scaleup of a molecule

- Anhydrous tert-butyl hydroperoxide (TBHP) oxidizing agent in many chemical transformations (e.g., Sharpless epoxidation)
- Despite versatility in organic reactions, use of anhydrous TBHP greatly limited due to safety concerns
- Several explosion incidents associated with use of anhydrous TBHP (e.g., overheating during azeotropic distillation)
- Anhydrous TBHP not available on bulk scale – historically avoided for scale up use
- 70 wt% TBHP solution in water is readily available in bulk quantities

Need a method to continuously and safely dehydrate TBHP with minimal holdup volume
Customer approaches with a separation need

Questions to ask:
- What is target separation?
- Target purity and recovery?
- What alternative methods have been considered?
- Desired flow rate?
- Batch vs. continuous?
- Temperature constraints?
- Safety concerns?

Design considerations
- Compatibility
- Feasibility
- Economics
- Safety
### EPA target list of solvents

<table>
<thead>
<tr>
<th>EPA target list of solvents</th>
<th>Effective with CMS technology?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>✓</td>
</tr>
<tr>
<td>Butanol</td>
<td>✓</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>✓</td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>✓</td>
</tr>
<tr>
<td>Methyl isobutyl ketone (MIK)</td>
<td>✓</td>
</tr>
<tr>
<td>Acetonitrile (low recovery)</td>
<td>✓</td>
</tr>
<tr>
<td>Methyl tert-butyl ether (MTBE)</td>
<td>✓</td>
</tr>
<tr>
<td>Acetone</td>
<td>✓</td>
</tr>
<tr>
<td>Isopropanol (IPA)</td>
<td>✓</td>
</tr>
<tr>
<td>Methanol</td>
<td></td>
</tr>
</tbody>
</table>

Additional compatible solvents include: xylene, ethylbenzene, benzene, hexane, cyclohexane, chlorobenzene, ethyl acetate, etc.
Design process

1. Customer approaches with a separation need
2. Quick assessment based on similar solvents
3. Feasibility test – measure activity coefficient
4. Agree on important design parameters with customer
5. Develop system design and estimate
6. System build
7. Installation and startup
Quick assessment based on similar solvents

Steps to take

- Use similar solvent to size membrane bank - first order approximation of system cost
- Does that first order approximation meet the economic bar?
- Does it look practical for implementation?
Quick assessment based on similar solvents

- Can dry to 99+% solvent as needed
- Works effectively to break water-solvent azeotrope
Design process

1. Customer approaches with a separation need
2. Quick assessment based on similar solvents
3. Feasibility test – measure activity coefficient
4. Agree on important design parameters with customer
5. Develop system design and estimate
6. System build
7. Installation and startup
Feasibility test – measure activity coefficient

Mixture of Nonane-TBHP

Stir plate

Membrane

Vacuum pump

Cold trap

Permeate

Pressure Regulator

Flowmeter

Sweep gas

Heater/Temperature controller

Relief valve

PG1

PG2

PG3

Stirred 47 mm Membrane Cell w/film heater

TC

V1

Membrane

F

V2

Mixture of Nonane-TBHP
Theoretical pervaporation model used to determine permeability and activity coefficient

\[ \ln \left( \frac{x_i}{x_f} \right) = \frac{\pi \gamma A P^o}{m \delta} t \]

Assumptions
- Water partial pressure in permeate \( \approx 0 \)
- \( m, \pi, \gamma, P^o \approx \) constant

\( x_i \) = water initial mole fraction
\( x_f \) = water final mole fraction
\( \pi \) = water permeability
\( \gamma \) = water activity coefficient
\( A \) = membrane area
\( P^o \) = water vapor pressure
\( m \) = moles of TBHP solution
\( \delta \) = membrane thickness
\( t \) = time

Once permeability and activity coefficient, membrane area can be determined for full system
For all tests, low water content was achieved & water permeability coefficient determined.

Water content, % wt

<table>
<thead>
<tr>
<th>Test #</th>
<th>water permeability*activity coefficient</th>
<th>(Barrer)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mol-μm/s-cm²-cmHg)</td>
<td>(scc-μm/s-cm²-cmHg)</td>
</tr>
<tr>
<td>1</td>
<td>3.90E-07</td>
<td>0.0087</td>
</tr>
<tr>
<td>2</td>
<td>4.03E-07</td>
<td>0.0090</td>
</tr>
<tr>
<td>3</td>
<td>3.44E-07</td>
<td>0.0077</td>
</tr>
<tr>
<td>4</td>
<td>4.09E-07</td>
<td>0.0091</td>
</tr>
<tr>
<td>5</td>
<td>3.92E-07</td>
<td>0.0088</td>
</tr>
<tr>
<td>Avg.</td>
<td>3.88E-07</td>
<td>0.0087</td>
</tr>
</tbody>
</table>

Initial mass of TBHP solution=8 g
Sweep rate=100 cc/min
Design process

1. Customer approaches with a separation need
2. Quick assessment based on similar solvents
3. Feasibility test – measure activity coefficient
4. Agree on important design parameters with customer
5. Develop system design and estimate
6. System build
7. Installation and startup
Agree on important design parameters with customer

Questions to ask:

• Flow rates?
• Temperatures
• Safety rating (explosion proof)?
• Holdup volumes
• Controls?
• Integration points?
• Vacuum source?
• Available utilities
Design process

1. Customer approaches with a separation need
2. Quick assessment based on similar solvents
3. Feasibility test – measure activity coefficient
4. Agree on important design parameters with customer
5. Develop system design and estimate
6. System build
7. Installation and startup
Develop system design and estimate
Design process

1. Customer approaches with a separation need
2. Quick assessment based on similar solvents
3. Feasibility test – measure activity coefficient
4. Agree on important design parameters with customer
5. Develop system design and estimate
6. System build
7. Installation and startup
6 System build
Design process

1. Customer approaches with a separation need
2. Quick assessment based on similar solvents
3. Feasibility test – measure activity coefficient
4. Agree on important design parameters with customer
5. Develop system design and estimate
6. System build
7. Installation and startup
Membrane system installed and operational within 3 days

At contract manufacturing site in China
Able to run entire reaction using pervaporation system to provide anhydrous TBHP/Nonane

Continuous Production of Anhydrous tert-Butyl Hydroperoxide in Nonane Using Membrane Pervaporation and its Application in Flow Oxidation of a γ-Butyrolactam, Li, et al., Org. Process Res. Dev., Just Accepted Manuscript, DOI: 10.1021/acs.oprd.8b00083, Publication Date (Web): May 23, 2018
Summary

• Dehydration of solvents is important in the production of pharmaceutical compounds

• Pervaporation using perfluoropolymers is ideal for this unit operation

• A case study has been demonstrated for the dehydration of n-nonane and TBHP
The authors gratefully acknowledge the support of the US Department of Energy, Environmental Protection Agency and the National Institute of Health through Small Business Innovation Research (SBIR) Awards.