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

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Hannah Murnen

Compact Membrane Systems

In a nutshell

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

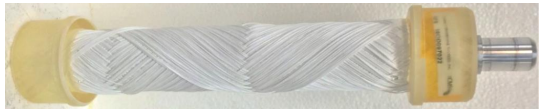
Perfluoropolymer membranes are an ideal system for solvent dehydration given their high chemical resistance and high flux and selectivity

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 — Spin out of DuPont

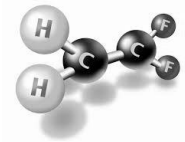
1994 — Initiate research program

2000 — Launch transformer application

2002 — In house manufacturing

2010 — Add fluoro chemistry capabilities (CAF)

2012 — Launch pervaporation for oil dehydration



2015 — Build commercial team and capabilities

2016 — Launch solvent applications

2017 — Expand into custom gas separations

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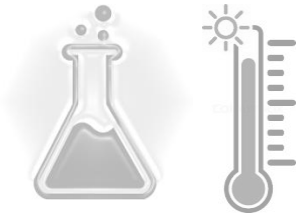
CMS is a technology player with platform and applications across multiple industries



High chemical and thermal resistance

Fluoropolymer chemistry expertise and know how

Industry application understanding

Petrochem
Pharma
Oil and Gas
Manufacturing
Wind Power
Marine
Power Gen
Aerospace
Chemicals

Membrane, prototype, manufacture, system design

IP in materials and applications

Effective in challenging environments where other materials fail

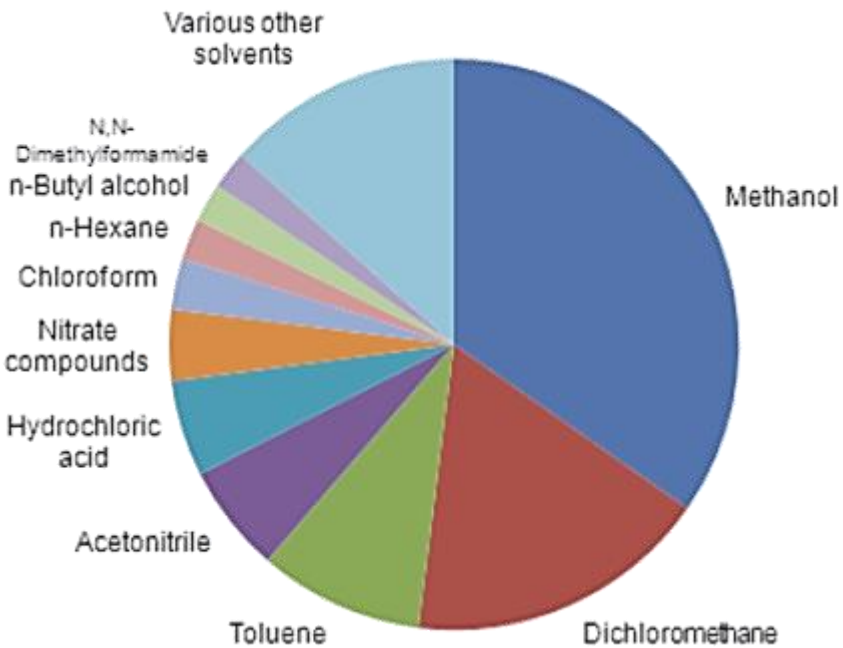
Applications in process chemistries and aggressive end products

Remove gases and water from organics

Why is solvent dehydration important in pharmaceutical production?

Solvent recovery and reuse is a big issue for API production

Total pharmaceutical use in 2006 of 128 MM Kg



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

- 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)

[1] Jimenez-Gonzalez, C., et al., Inter. J. Life Cycle Assessment 2004, 9(2), 114-121.
[2] Slater, C.S.; Savelski, M.J.; Hesketh, R.P. Abstracts of Papers, American Chemical Society 10th Green Chem. Eng. Conf., Washington DC, June 2006, American Chemical Society, 10.
[3] EPA TRI 2016, Pharmaceutical Industry

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Continuous processing is the way of the future

PHARMPRO.COM

Feature

Continuing Progress in Continuous Manufacturing

Process design, measurement, and control for enabling continuous processing adoption in pharmaceutical manufacturing.

By Doug Hausner, Jonathan Lustri, and Paul Brodbeck

The shift from batch to continuous production methods is transforming the future of pharmaceutical manufacturing. The potential economic gains from increasing capacity utilization and reducing the length of process development, product release times, and capital costs are driving the paradigm shift. Spurred by potential improvements to quality, patient safety, and the time required for breakthrough medicines to reach patients, even the U.S. Food and Drug Administration (FDA) has advocated a move to continuous manufacturing (CM).[1] However, with new methods come new challenges—particularly for process design, measurement, material traceability, and control.

Manufacturers, suppliers, and research institutions are collaborating to solve these challenges at projects across the globe, including the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), based at Rutgers, the State University of New Jersey. This article provides a summary of the status of continuous processing in the pharmaceutical industry and considerations—based in part on research at C-SOPS—for how manufacturers can overcome the challenges related to quality, compliance, material traceability, and process design and control.

Drivers for Continuous Manufacturing

The economic benefits of continuous methods over batch exist in nearly all areas of manufacturing and are the primary reason most industries have used continuous methods for decades. The FDA and other agencies have recently made it clear that they will not only accept CM, but that they support it as an enabler for true Quality by Design (QbD).

In the case of secondary solid

Pharmaceutical Manufacturing in the 21st Century-From Batch to Continuous Manufacturing-An FDA Perspective

presented by **Dr Sau (Larry) Lee**
followed by **Dirk Leister**

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CONTINUOUS
REVOLUTION

AT THE NOVARTIS-MIT CENTER FOR CONTINUOUS MANUFACTURING, SCIENTISTS ARE USING LEAN ENGINEERING PRINCIPLES AND SOPHISTICATED TECHNOLOGY TO MAKE A QUANTUM LEAP FORWARD IN THE WAY MEDICINES ARE MANUFACTURED

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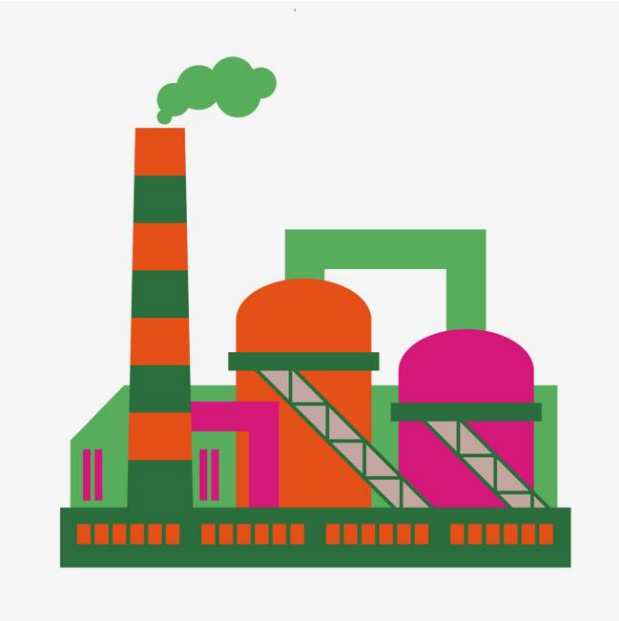
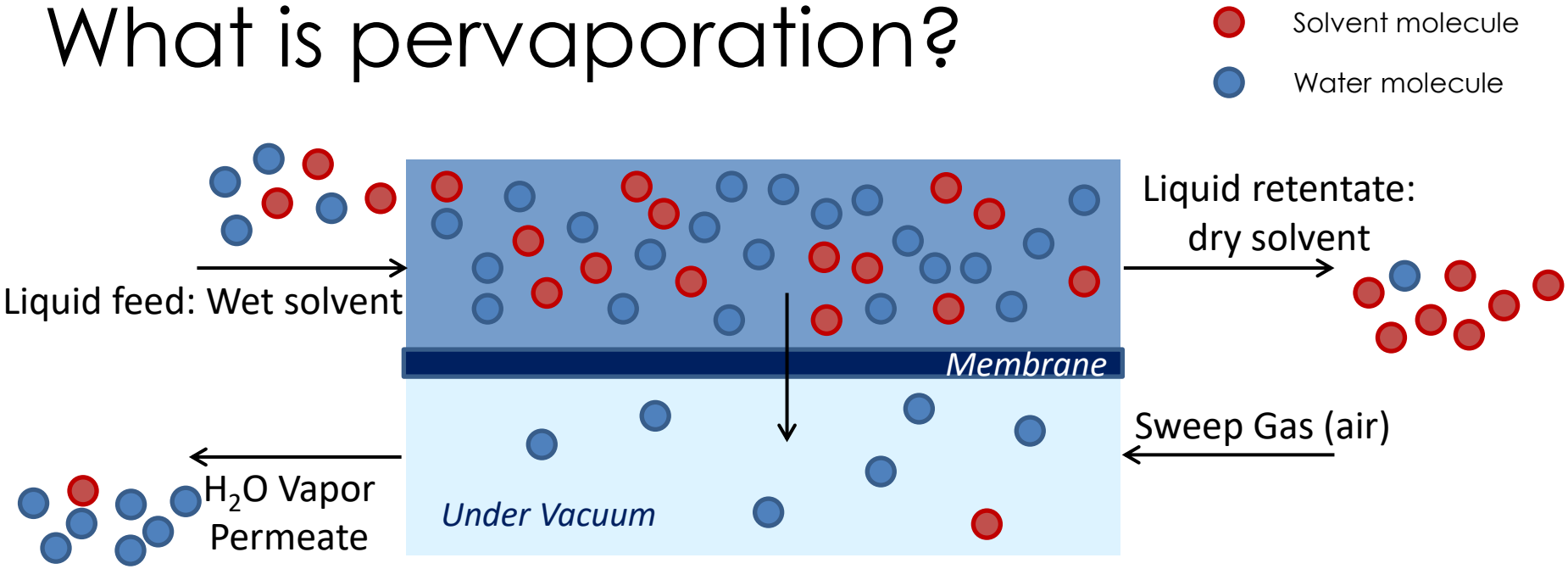
Where else could solvent dehydration be useful?

- Specialty chemical
- Semiconductor and electronic manufacturing
- Paint production



Overview of Pervaporation Technology

What is pervaporation?



$$\mathbf{H_2O\ Flux} = \underbrace{\left[\frac{\pi}{\delta}\right]}_{\text{Permeance}} \underbrace{(\gamma\, x\, P^o - p\, y)}_{\text{Driving force}}$$

x = water feed mole fraction
y = water permeate mole fraction
π = water permeability
γ = water activity coefficient
P^o = water vapor pressure
δ = membrane thickness
p = vacuum pressure

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What affects driving force?

$$\mathbf{H_2O\ Flux} = \underbrace{\left[\frac{\pi}{\delta}\right]}_{\text{Permeance}} \underbrace{(\gamma\ x\ P^o - p\ y)}_{\text{Driving force}}$$

π = water permeability
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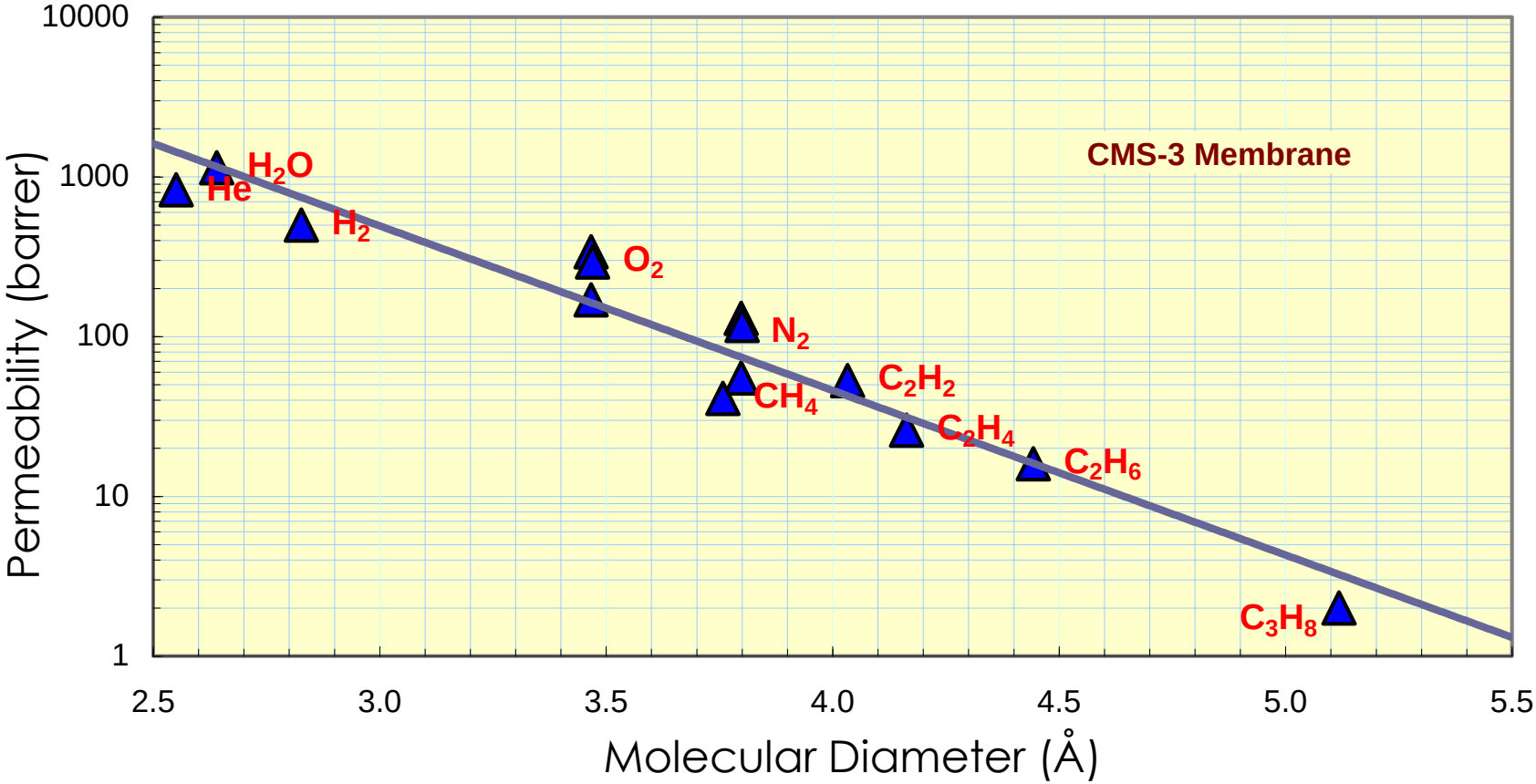
x = water feed mole fraction
P^o = feed water vapor pressure
y = water permeate mole fraction
p = vacuum pressure

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

What about selectivity?



Smaller molecules (e.g., H_20) go through membrane more quickly

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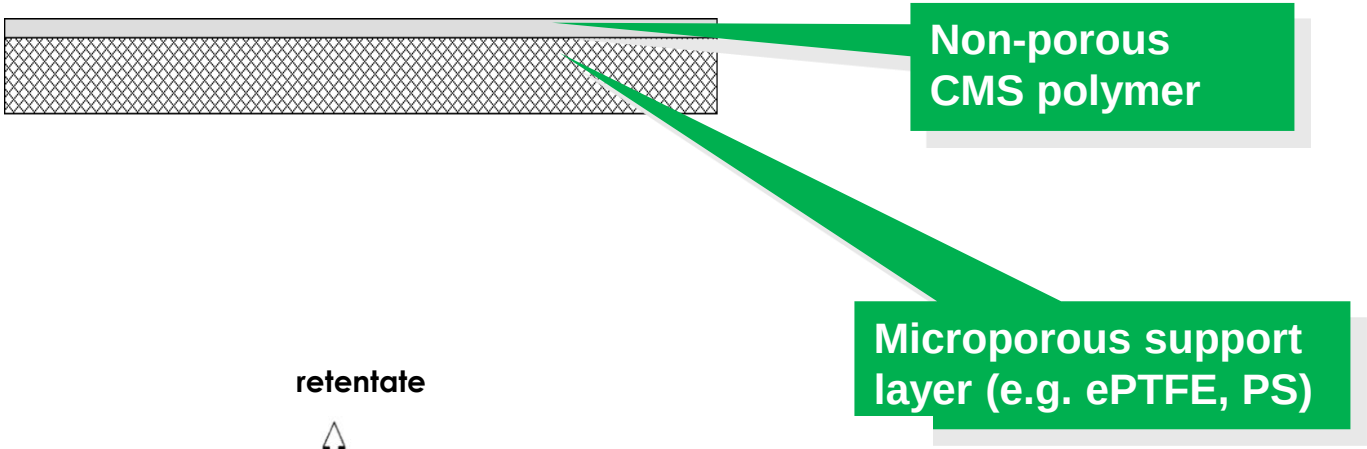
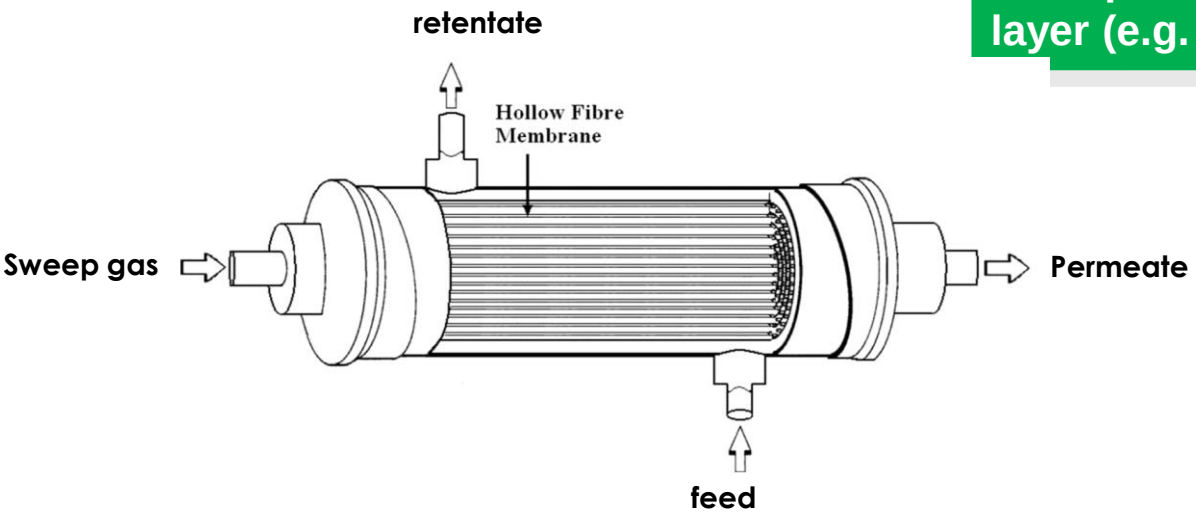
Membrane is a composite structure





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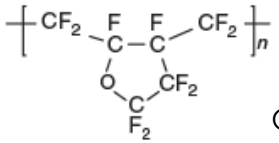
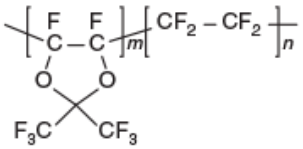
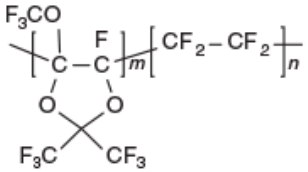
Custom Amorphous Fluouropolymer (CAF) platform



AGC

Cytop





Teflon AF

Chemours

Hyflon

SOLVAY

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

CMS value proposition: Develop custom amorphous fluouropolymers 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

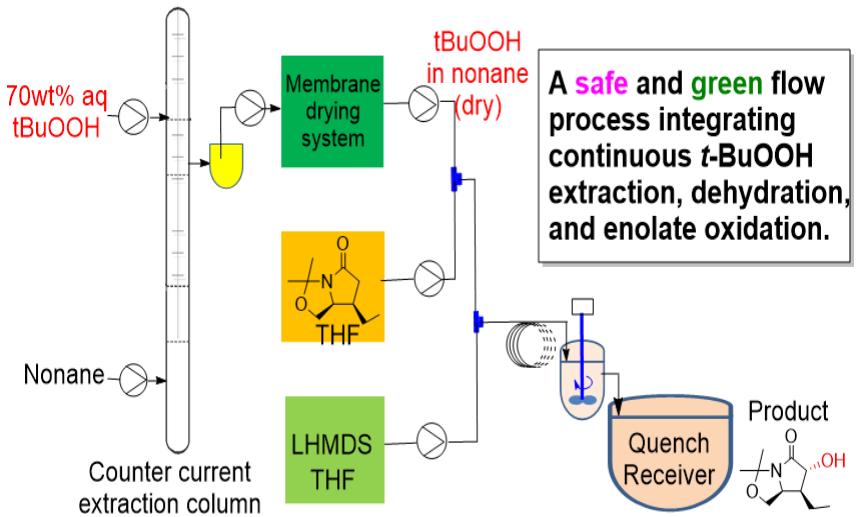
Considerations for a pervap system

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

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/acs.oprd.8b00083
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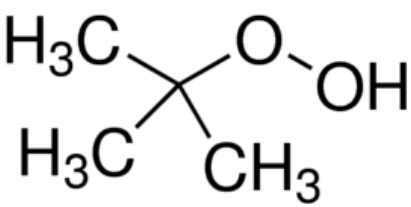
Objective – Safely use anhydrous TBHP for scaleup of a molecule



- 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

1 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

1 Compatible and effective with a variety of solvents

EPA target list of solvents	Effective with CMS technology?
Ethanol	√
Butanol	√
Tetrahydrofuran	√
Dimethylformamide	√
Methyl isobutyl ketone (MIK)	√
Acetonitrile	√ (low recovery)
Methyl tert-butyl ether (MTBE)	√
Acetone	√
Isopropanol (IPA)	√
Methanol	

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

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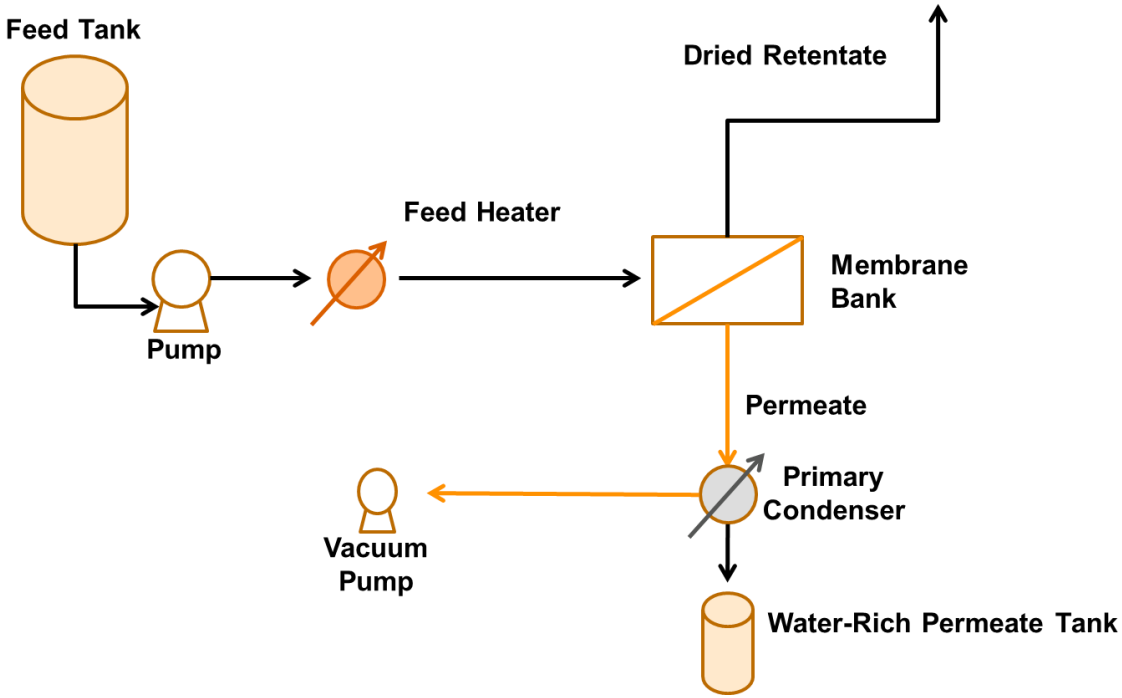
2 Quick assessment based on similar solvents

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?



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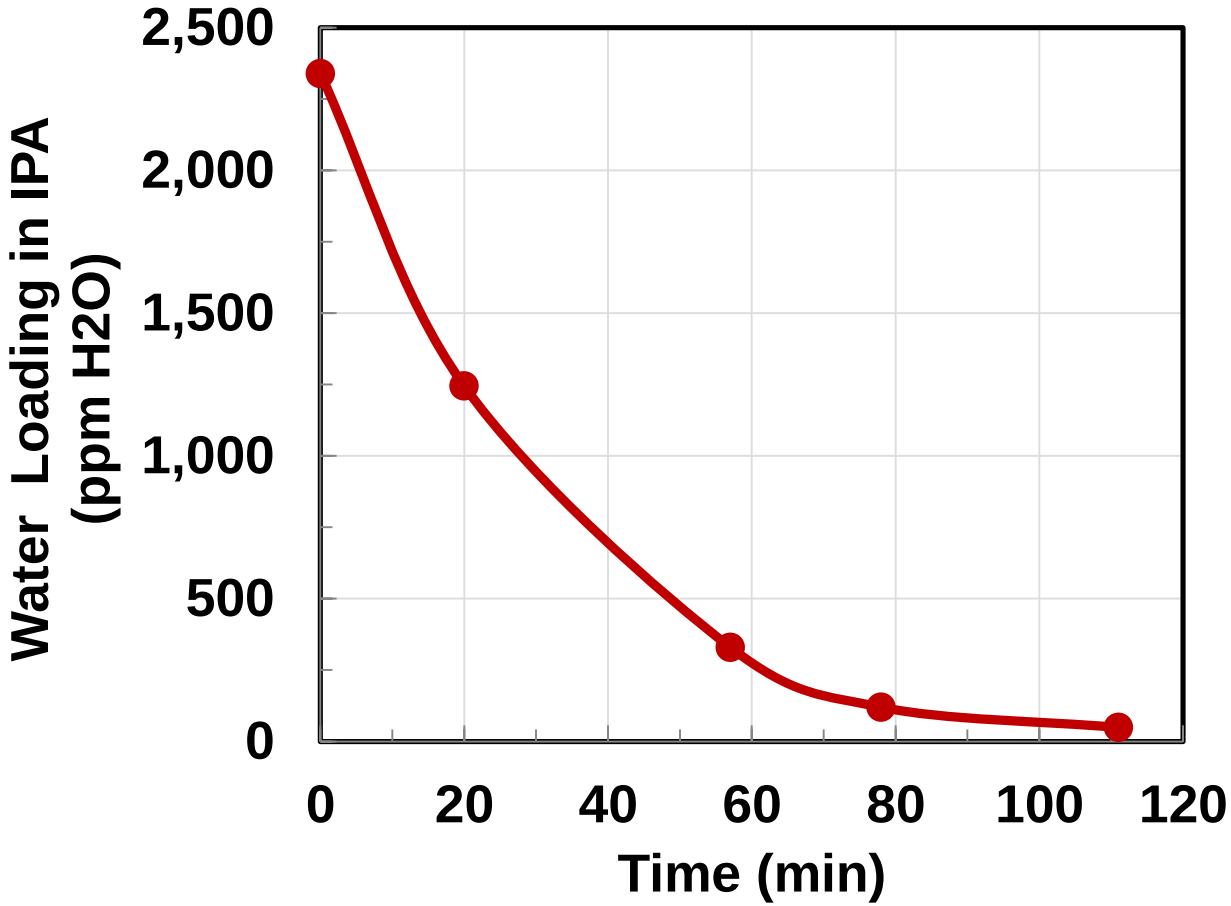
2 Quick assessment based on similar solvents

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



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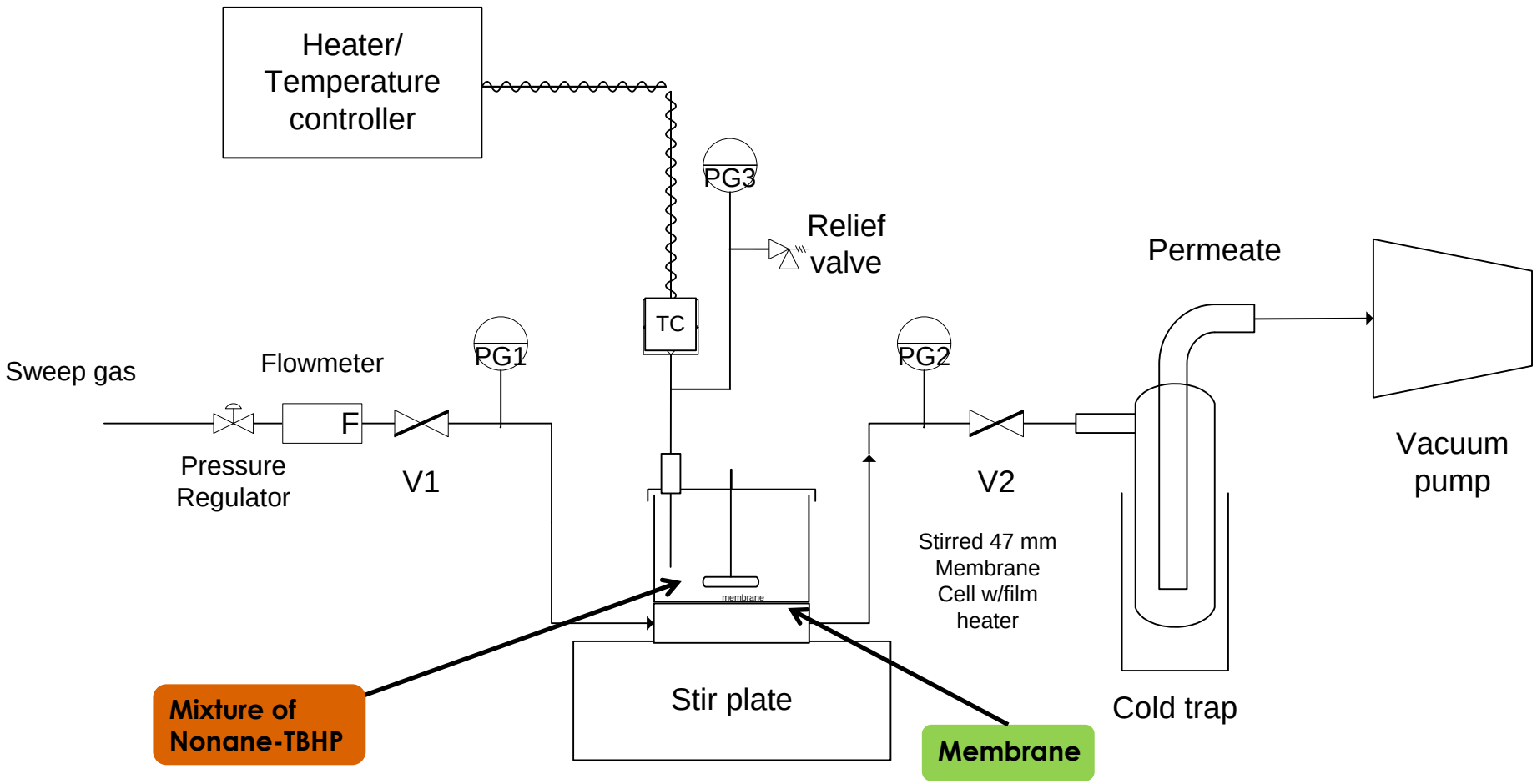
3 Feasibility test – measure activity coefficient



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3 Theoretical pervaporation model used to determine permeability and activity coefficient

$$ln\frac{x_i}{x_f} = \frac{\pi\gamma A P^o}{m\delta}\ \mathrm{t}$$

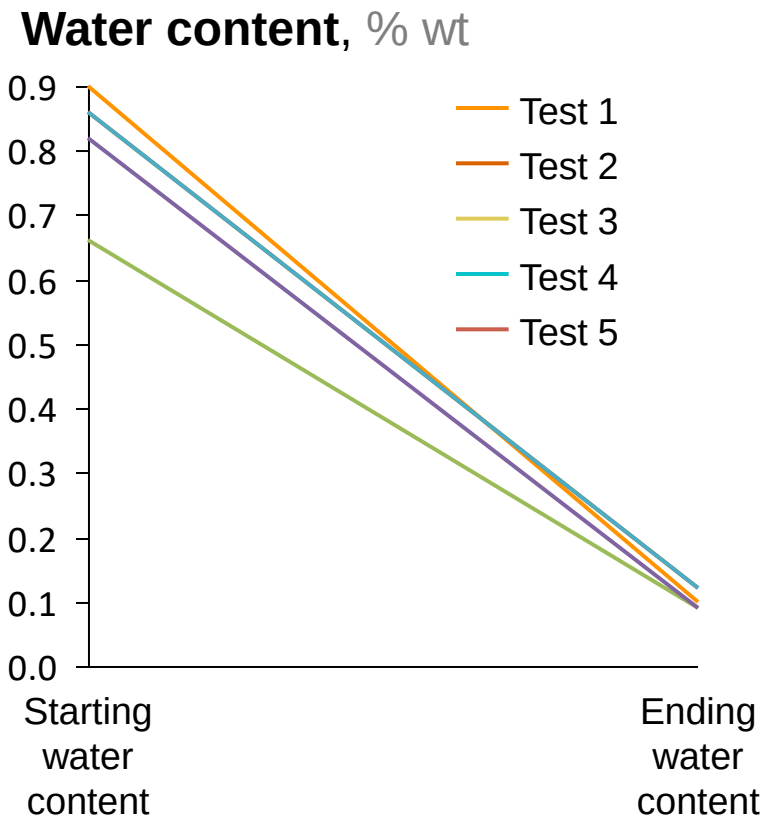
x_i =water initial mole fraction
x_f =water final mole fraction
π = water permeability
γ = water activity coefficient
A = membrane area
P^o= water vapor pressure
m = moles of TBHP solution
δ = membrane thickness
t = time

Assumptions

- Water partial pressure in permeate≈0
- m, π, γ, P^o≈constant

Once permeability and activity coefficient, membrane area can be determined for full system

3 For all tests, low water content was achieved & water permeability coefficient determined



	water permeability*activity coefficient		
Test #	(mol-μm/s-cm^2-cmHg)	(scc-μm/s-cm^2-cmHg)	(Barrer)
1	3.90E-07	0.0087	8728
2	4.03E-07	0.0090	9017
3	3.44E-07	0.0077	7705
4	4.09E-07	0.0091	9147
5	3.92E-07	0.0088	8780
Avg.	**3.88E-07**	**0.0087**	**8675**

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

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Design process

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4 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

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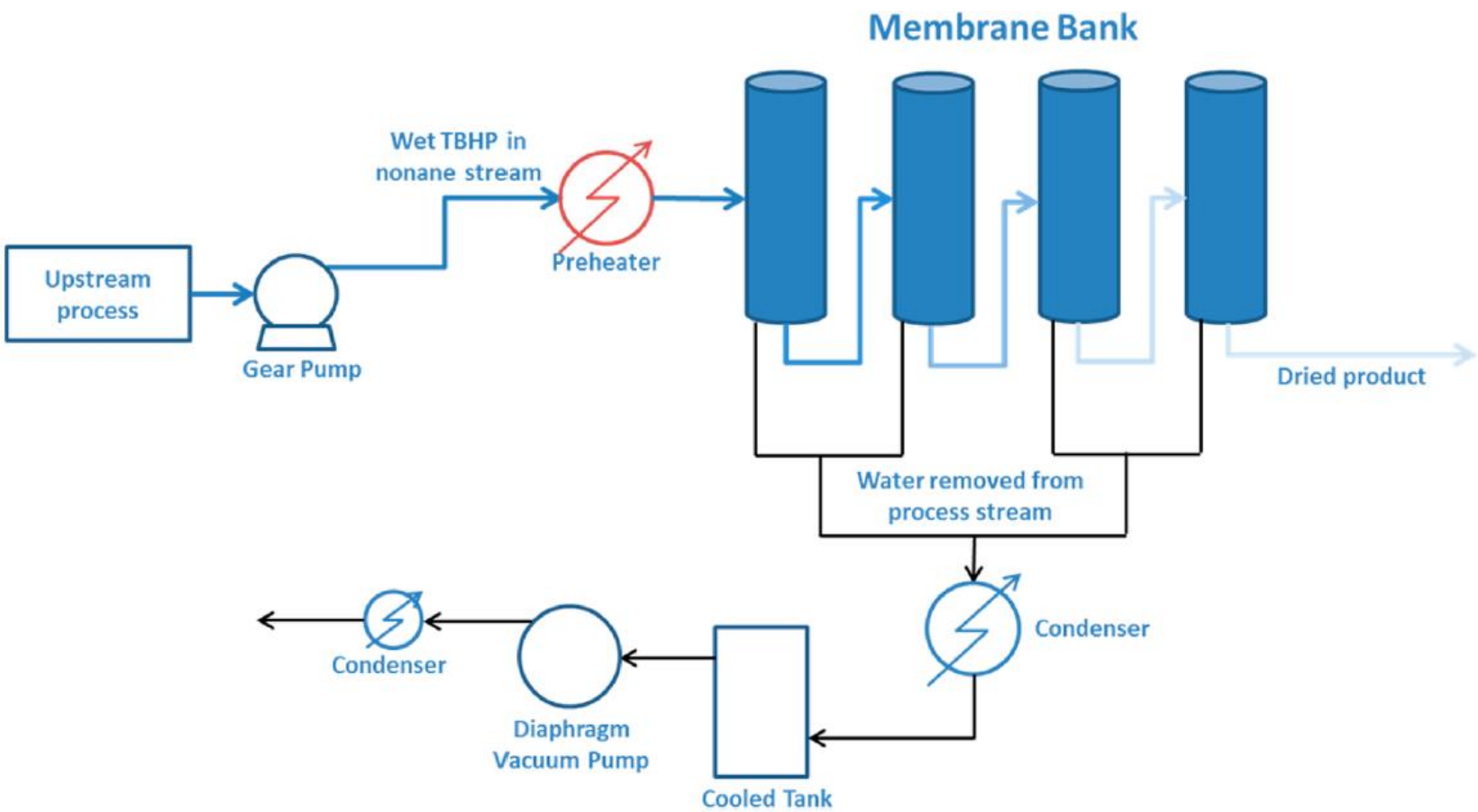
5 Develop system design and estimate



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6 System build

Compact Membrane Systems

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7 Membrane system installed and operational within 3 days

At contract manufacturing site in China

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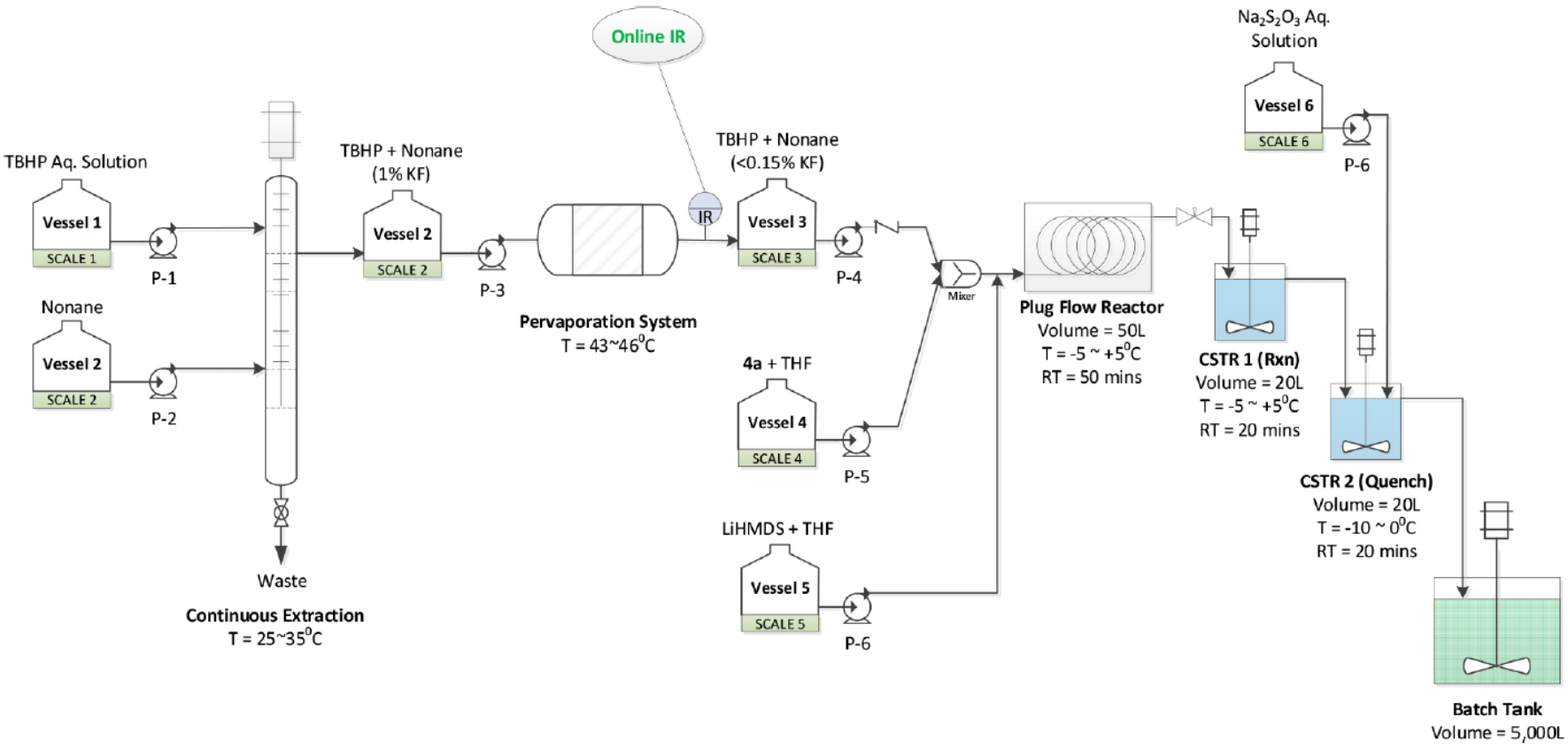
7 Able to run entire reaction using pervaporation system to provide anhydrous TBHP/Nonane



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

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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

Thank you for your attention

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