• Introduction

• A non-thermal solvent exchange.

• Removal of Excess reagents via OSN.

• Reaction product purification.

• Removal of oligomers from a reaction mixture.
Applications of Organic solvent Nanofiltrations

• Solvent operations
  • Concentration of solutes in solvents
  • Solvent exchanges (high - boiling solvent to low boiling solvent)
  • Purifications - separation of high and medium MW species in solvent.

• Catalyst recyle and reuse
• Dynamic kinetic resolution
• Chiral separations (host-guest interactions)
• Biotransformations
Example 1: Non-thermal solvent exchange.
Example 1: Non-thermal solvent exchange

• Solvent switch $\text{H}_2\text{O} \rightarrow \text{acetone}$

Problem
• Synthesis of 1 carried out in $\text{H}_2\text{O}$

• Following synthetic step performed in acetone, for which it has been determined that $\text{H}_2\text{O}$ content must be less than 1%.

• Under standard distillation conditions 1 undergoes rapid degradation.

• Loss of 1 is typically 20% but can be as high as 40%.
Example 1: Non-thermal solvent exchange

• Solvent switch $\text{H}_2\text{O} \rightarrow \text{acetone}$
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• Solvent switch $\text{H}_2\text{O} \rightarrow \text{acetone}$

Water exchanged for acetone at room temperature
Solute: 1.2TEA salt MW salt = 376 (free acid 174)
pressure 20 bar, Starmem 120 (MWCO = 200 Da)
Yield 1 in acetone 75%

<table>
<thead>
<tr>
<th>origin</th>
<th>1 (g)</th>
<th>$\text{H}_2\text{O}$ wt/wt %</th>
</tr>
</thead>
<tbody>
<tr>
<td>sm</td>
<td>11.5</td>
<td>/</td>
</tr>
<tr>
<td>permeate 1</td>
<td>0.2</td>
<td>6.95</td>
</tr>
<tr>
<td>permeate 2</td>
<td>1.0</td>
<td>4.84</td>
</tr>
<tr>
<td>permeate 3</td>
<td>0.9</td>
<td>3.82</td>
</tr>
<tr>
<td>permeate 4</td>
<td>0.5</td>
<td>1.91</td>
</tr>
<tr>
<td>permeate 5</td>
<td>0.6</td>
<td>0.92</td>
</tr>
<tr>
<td>permeate 6</td>
<td>0.6</td>
<td>1.05</td>
</tr>
<tr>
<td>retentate</td>
<td>8.6</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Example 1: Non-thermal solvent exchange

- Solvent switch $H_2O \rightarrow$ acetone
Example 1: Non-thermal solvent exchange

- Solvent switch $\text{H}_2\text{O} \rightarrow \text{acetone}$

<table>
<thead>
<tr>
<th>+ ve</th>
<th>- ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Exchange high boiling point to low boiling point solvent easy</td>
<td>- Long term membrane stability after 6 days in contact with the triethylamine salt of 1 membrane degradation observed</td>
</tr>
<tr>
<td>- Yield of 1 is competitive with present distillation process</td>
<td>- More stable crosslinked membrane (MWCO = 230) didn't work rejection of 1 was almost 0</td>
</tr>
<tr>
<td>- Chemical purity is better with nanofiltration as no degradation of 1 was observed</td>
<td>- Use of free acid as solute and an RO membrane failed rejection of 1 was 69%</td>
</tr>
</tbody>
</table>
Example 2: Removal of excess reagents
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• Transesterification reaction from a methyl ester to a benzyl ester in a molecule whose functionality amongst others includes a secondary alcohol.

Problem
• Reaction require a large excess of Benzyl alcohol

• Excess Benzyl alcohol must be removed prior to the following synthetic step

• Removal of the excess benzyl alcohol via distillation is not an option.
Example 2: Removal of excess reagents

• Options to remove benzyl alcohol.

\[
\begin{align*}
\text{OH} & \quad \text{R} \quad \text{R'} \\
\text{CO}_2\text{Me} & \quad \xrightarrow{\text{benzyl alcohol}} \\
\text{OH} & \quad \text{R} \quad \text{R'} \\
& \quad \text{O}_\text{O} \quad \text{Ph} \\
\text{MW} = 278 & \quad 372 & \quad 354
\end{align*}
\]

• **Chromatography**: works well but requires a large quantity of silica.

• **Nanofiltration**
Example 2: Removal of excess reagents

- Direct OSN of the reaction mixture.

\[
\begin{align*}
R & \quad \text{benzyl alcohol} \\
& \xrightarrow{\text{R, } \text{R'}} \quad \text{impurity A} \\
& \quad \text{impurity B}
\end{align*}
\]

\[
\begin{align*}
R & \quad \text{OH} \\
& \xrightarrow{\text{R, } \text{R'}} \quad \text{OH} \\
& \quad \text{CO}_2\text{Me} \\
& \quad \text{Ph}
\end{align*}
\]

M.W = 278 372 354

Insufficient separation of benzyl alcohol and product

<table>
<thead>
<tr>
<th>membrane</th>
<th>Pressure (bar)</th>
<th>Flux (L m(^{-2}) h(^{-1}))</th>
<th>Rejection (product)</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starmem – 120 (MWCO 200)</td>
<td>20</td>
<td>14</td>
<td>50%</td>
<td>Insufficient separation of benzyl alcohol and product</td>
</tr>
</tbody>
</table>
Example 2: Removal of excess reagents

- OSN of reaction mixture after acylation.

\[
\begin{align*}
\text{M.W} & = (R_1=\text{CH}_3) \ 320 \\
& = (R_1=\text{CH}_3\text{CH}_2) \ 334 \\
\text{impurity A} & = 372 \\
\text{impurity B} & = 354 \\
(R_1=\text{CH}_3) & = 150 \\
(R_1=\text{CH}_3\text{CH}_2) & = 164
\end{align*}
\]

<table>
<thead>
<tr>
<th>( R_1 )</th>
<th>membrane</th>
<th>Pressure (bar)</th>
<th>Flux (L m(^{-2}) h(^{-1}))</th>
<th>Rejection (acylated product)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH3</td>
<td>Starmem – 120 (MWCO 200)</td>
<td>20</td>
<td>24</td>
<td>85%</td>
<td>Benzyl ester separated from acylated product, impurities remain</td>
</tr>
<tr>
<td>CH3CH2</td>
<td>Starmem – 122 (MWCO 220)</td>
<td>20</td>
<td>48</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

Yield acyl ester in the retentate (\( R = \text{CH}_3\text{CH}_2^- \)) = 88%

Impurities A and B can be removed with a second filtration over a membrane with MWCO = 400
Example 2: Removal of excess reagents

- OSN after selective oxidation.

\[
\begin{align*}
\text{OH} & \quad \text{R'} \\
\text{R} & \quad \text{R} \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\text{M.W} = \begin{array}{ccc}
278 & 372 & 354 \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Pressure (bar)</th>
<th>Flux (L m(^{-2}) h(^{-1}))</th>
<th>Rejection (product)</th>
<th>Rejection (impurity A)</th>
<th>Rejection (impurity B)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starmem – 122</td>
<td>20</td>
<td>7</td>
<td>67%</td>
<td>92%</td>
<td>100%</td>
<td>Product obtained in the permeate not 100% pure</td>
</tr>
<tr>
<td>(MWCO 220)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 2: Removal of excess reagents

- Summing up.

**Removal of excess benzyl alcohol**

- Failed directly on reaction mixture.

- Possible on product after further transformation
  2 filtration steps required.

- Possible after oxidation process.
  Product obtained in the permeate
  Not 100% pure
Example 3 : Reaction product purification
Example 3: Reaction product purification

- A reaction that failed gave a mixture of product MW = 200 and a dimer MW = 368.
- Reaction mixture can be purified by chromatography but not used here.

| Removal of dimer from product | Starmem 122 (MWCO 220 Da) | GC area % |  |
|-------------------------------|---------------------------|----------|
| membrane                     | Toluene | methanol | product | RRT1.13 | Dimer |
| solvent                       |         |          | starting material |  |
| Pressure (bar)                | 20      | 10       | toluene permeate  | 56.1  | 1   | 36.9 |
| Flux (L m⁻² h⁻¹)              | 1.7     | 3.6      | methanol permeate | 95.6  | 1.8 | 1.8 |
| Dimer rejection               | 96%     | 87%      | retentate         | 91.9  | 1   | 4.6 |
|                              |         |          |                   | 42.8  | 4.9 | 47.8 |
Example 4: Removal of oligomers from a reaction mixture
Example 4 : Removal of oligomers from a reaction mixture

Problem :
• Organometallic reaction that is an equilibrium reaction.

• Reaction produces product (MW 670) and a number oligomers with MW > 1000

• Quantity of oligomers can be as high as 20%

• Oligomers are difficult to analyse and are not visible using HPLC

• These oligomers block the active sites of silica and thus prevent automated chromatographic techniques.
## Example 4: Removal of oligomers from a reaction mixture

### Removal of oligomers

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Desal GH (MWCO 1000 Da)</th>
<th>Analysis results wt/wt%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
<td>Acetic acid</td>
<td></td>
</tr>
<tr>
<td>Pressure (bar)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Flux (L m(^{-2}) h(^{-1}))</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Rejection product</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Yield isolated product</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Purification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>63</td>
<td>21.7</td>
</tr>
<tr>
<td>Crystallization</td>
<td>78</td>
<td>13.9</td>
</tr>
<tr>
<td>Nanofiltration</td>
<td>83</td>
<td>10.1</td>
</tr>
</tbody>
</table>
### Example 4: Removal of oligomers from a reaction mixture

**Membrane-extraction-technology results**

<table>
<thead>
<tr>
<th>Membrane</th>
<th>Desal GH (MWCO 1000 Da)</th>
<th>MET-L3431H (MWCO 700 Da)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solvent</strong></td>
<td>Acetic acid</td>
<td>THF</td>
</tr>
<tr>
<td><strong>Pressure (bar)</strong></td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td><strong>Flux (L m(^{-2}) h(^{-1}))</strong></td>
<td>7.7</td>
<td>87</td>
</tr>
<tr>
<td><strong>Rejection product</strong></td>
<td>97%</td>
<td>89.5</td>
</tr>
<tr>
<td><strong>Diafiltration volume</strong></td>
<td>/</td>
<td>35</td>
</tr>
<tr>
<td><strong>Yield isolated product</strong></td>
<td>30%</td>
<td>98.5</td>
</tr>
</tbody>
</table>
Example 4: Removal of oligomers from a reaction mixture

- MET process development

Membrane 1: MET-L2431H (MWCO = 700)
  Pressure 10 bar, 30°C
  Flux 28 l m\(^{-2}\) h\(^{-1}\)
  Product rejection = 58.5%

Membrane 2: MET-L1813H (MWCO = 230)
  Pressure 60 bar, 30°C
  Flux 5 l m\(^{-2}\) h\(^{-1}\)
  Product rejection = 99.6%

Yield product 98.5%

Oligomeric impurity at end process 2%
Summary

• Nanofiltration over Solvent Resistant Membranes offers several opportunities for use in scale – up.
• Technique is complementary to other separation techniques already available
• Scale-up is relatively easy
• Solvent/energy use is potentially low.
Acknowledgements

- Dirk Lauwers
- Tom Dedroog
- Membrane extraction technology