Applications of Organic Solvent Nanofiltration in the Process Development of Active Pharmaceutical Ingredients

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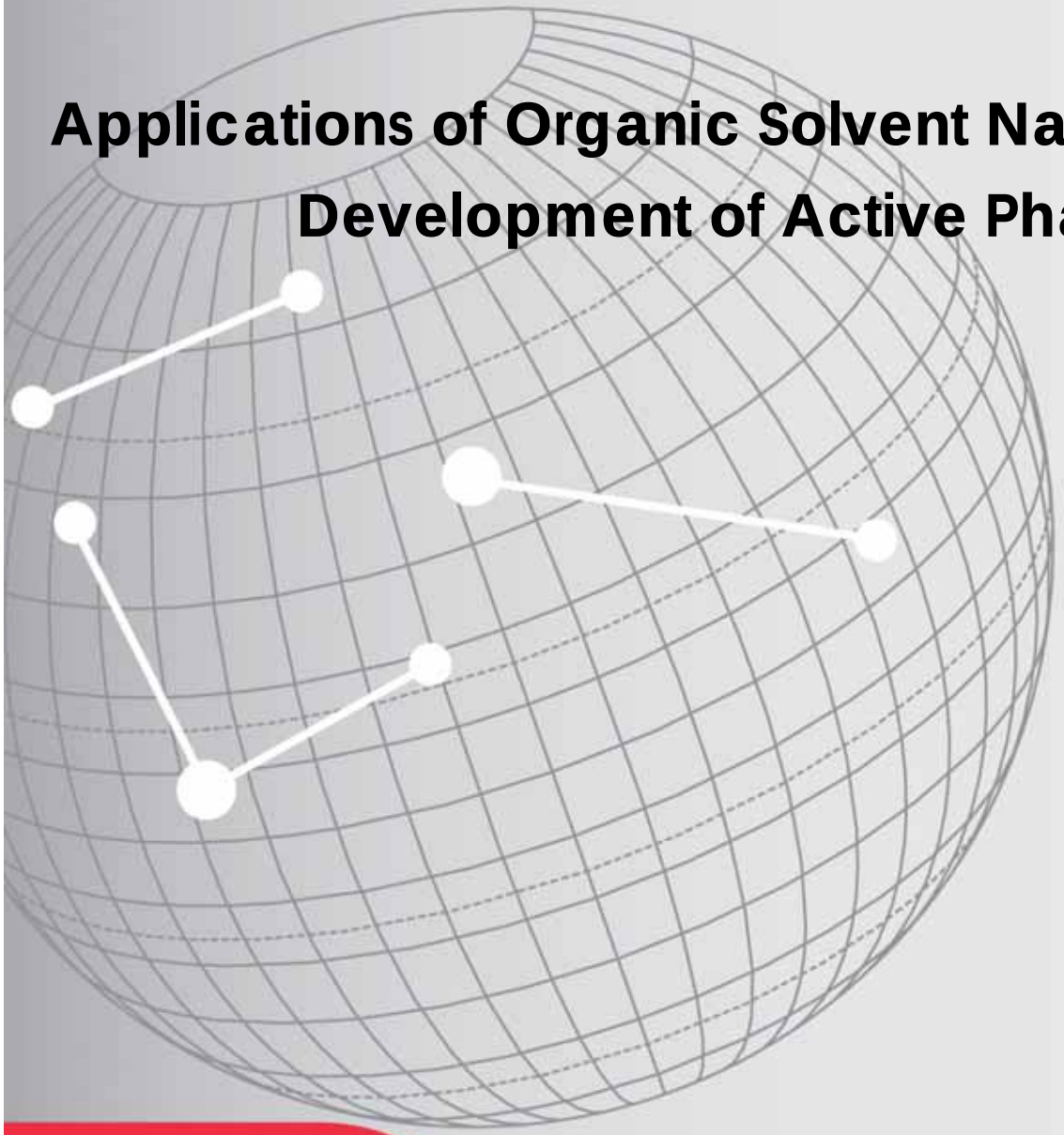

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- **Introduction**
- **A non-thermal solvent exchange.**
- **Removal of Excess reagents via OSN.**
- **Reaction product purification.**
- **Removal of oligomers from a reaction mixture.**

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.

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•Solvent switch $H_2O \rightarrow$ acetone

Problem

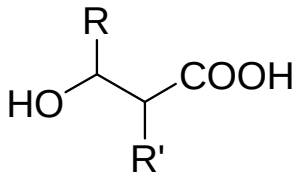
• Synthesis of 1 carried out in H_2O

• Following synthetic step performed in acetone,

for which it has been determined that H_2O 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%.



1

M.W. = 174

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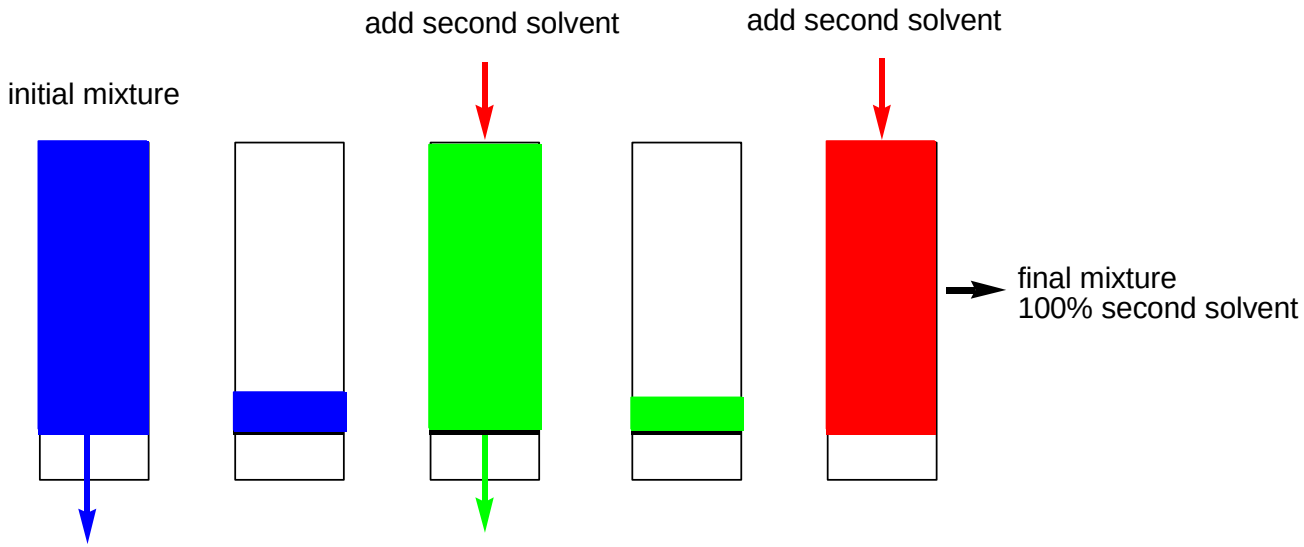
Example 1 : Non-thermal solvent exchange

- Solvent switch $H_2O \rightarrow$ acetone



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Example 1 : Non-thermal solvent exchange

•Solvent switch $H_2O \rightarrow$ 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%

origin	1 (g)	H_2O wt/wt %
sm	11.5	/
permeate 1	0.2	6.95
permeate 2	1.0	4.84
permeate 3	0.9	3.82
permeate 4	0.5	1.91
permeate 5	0.6	0.92
permeate 6	0.6	1.05
retentate	8.6	0.76

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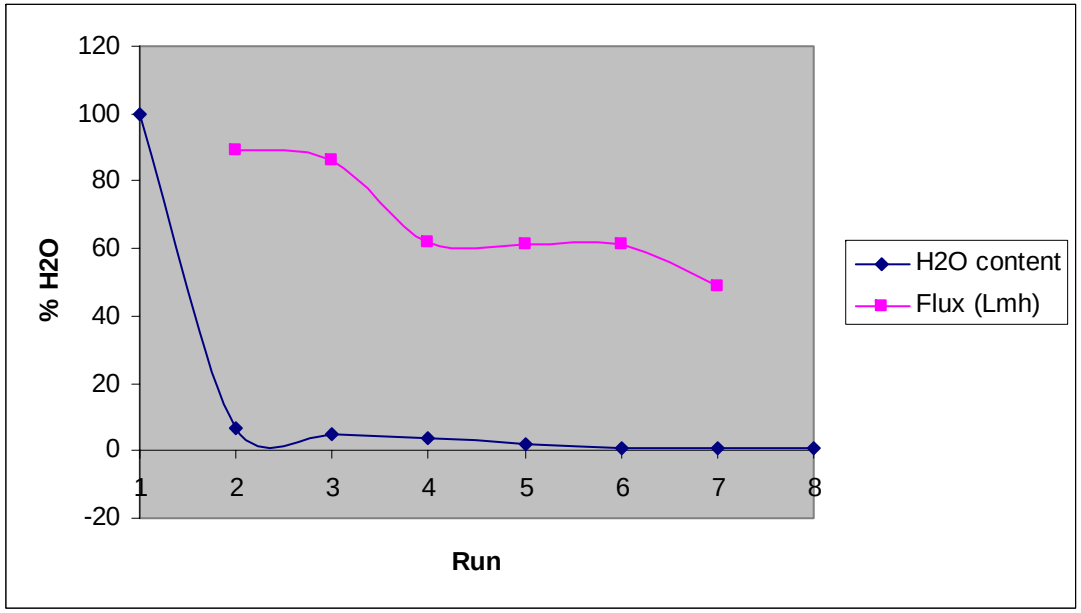

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Example 1 : Non-thermal solvent exchange

•Solvent switch $H_2O \rightarrow$ acetone

+ ve	- ve
- Exchange high boiling point to low boiling point solvent easy	-Long term membrane stability after 6 days in contact with the triethylamine salt of 1 membrane degradation observed
- Yield of 1 is competative with present distillation process	- More stable crosslinked membrane (MWCO = 230) didn't work rejection of 1 was almost 0
- Chemical purity is better with nanofiltration as no dergadation of 1 was observed	- Use of free acid as solute and an RO membrane failed rejection of 1 was 69%

Example 2 : Removal of excess reagents

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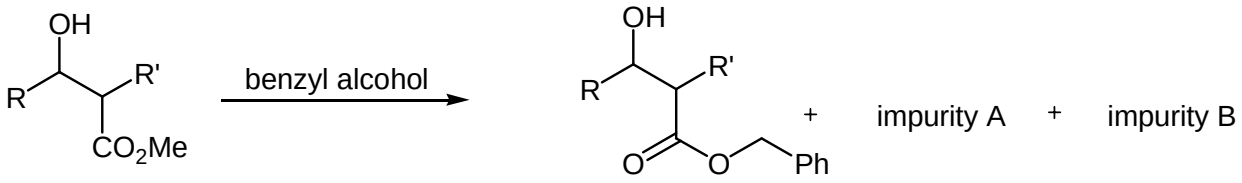
•Transesterification reaction from a methyl ester to a benzyl ester in a molecule whose functionality amongst others includes a secondary alcohol.



M.W =	278	372	354

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.

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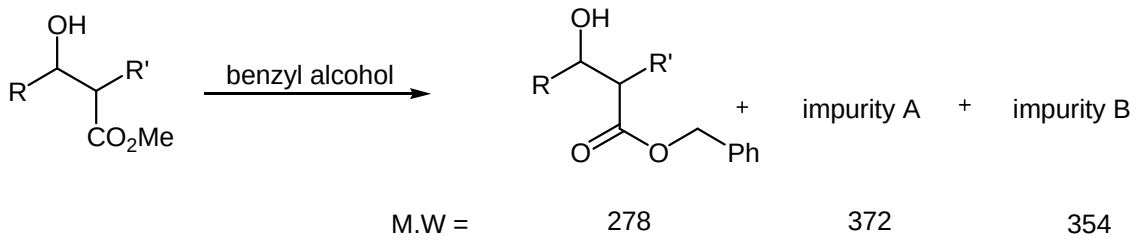
Example 2 : Removal of excess reagents

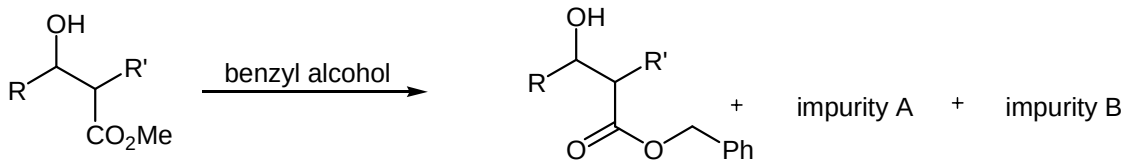
- Options to remove benzyl alcohol.



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

Example 2 : Removal of excess reagents

- Direct OSN of the reaction mixture.



membrane	Pressure (bar)	Flux (L m^{-2} h^{-1})	Rejection (product)	result
Starmem – 120 (MWCO 200)	20	14	50%	Insufficient separation of benzyl alcohol and product

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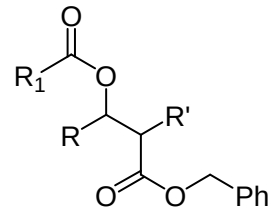
Example 2 : Removal of excess reagents

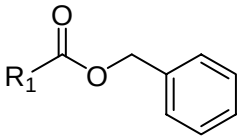
- OSN of reaction mixture after acylation.



M.W = (R_1=CH_3) 320
(R_1=CH_3CH_2) 334

\+ impurity A + impurity B +

372 354



(R_1=CH_3) 150
(R_1=CH_3CH_2) 164

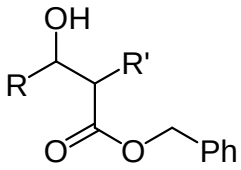
R_1	membrane	Pressure (bar)	Flux (L m^{-2} h^{-1})	Rejection (acylated product)	Result
CH3	Starmem – 120 (MWCO 200)	20	24	85%	Benzyl ester separated from acylated product, impurities remain
CH3CH2	Starmem – 122 (MWCO 220)	20	48	90%	

Yield acyl ester in the retentate (R = CH3CH2-) = 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.



\+ impurity A + impurity B

M.W = 278 372 354

membrane	Pressure (bar)	Flux (L m^{-2} h^{-1})	Rejection (product)	Rejection (impurity A)	Rejection (impurity B)	result
Starmem – 122 (MWCO 220)	20	7	67%	92%	100%	Product obtained in the permeate not 100% pure

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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

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- 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

membrane	Starmem 122 (MWCO 220 Da)	
solvent	Toluene	methanol
Pressure (bar)	20	10
Flux ($L\ m^{-2}\ h^{-1}$)	1.7	3.6
Dimer rejection	96%	87%

	GC area %		
	product	**RRT1.13**	**Dimer**
starting material	56.1	*	36.9
toluene permeate	95.6		1.8
methanol permeate	91.9	1	4.6
retentate	42.8	4.9	47.8

Example 4 : Removal of oligomers from a reaction mixture

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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

membrane	Desal GH (MWCO 1000 Da)
solvent	Acetic acid
Pressure (bar)	22
Flux ($L\ m^{-2}\ h^{-1}$)	7.7
Rejection product	97%
Yield isolated product	30%

Analysis results wt/wt%

purification	product	rest	oligomers
none	63	21.7	15.3
crystallization	78	13.9	8.1
nanofiltration	83	10.1	6.9

Example 4 : Removal of oligomers from a reaction mixture

Membrane-extraction-technology results

Removal of oligomers

membrane	Desal GH (MWCO 1000 Da)	MET-L3431H (MWCO 700 Da)
solvent	Acetic acid	THF
Pressure (bar)	22	30
Flux ($L\ m^{-2}\ h^{-1}$)	7.7	87
Rejection product	97%	89.5
Diafiltration volume	/	35
Yield isolated product	30%	98.5

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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)

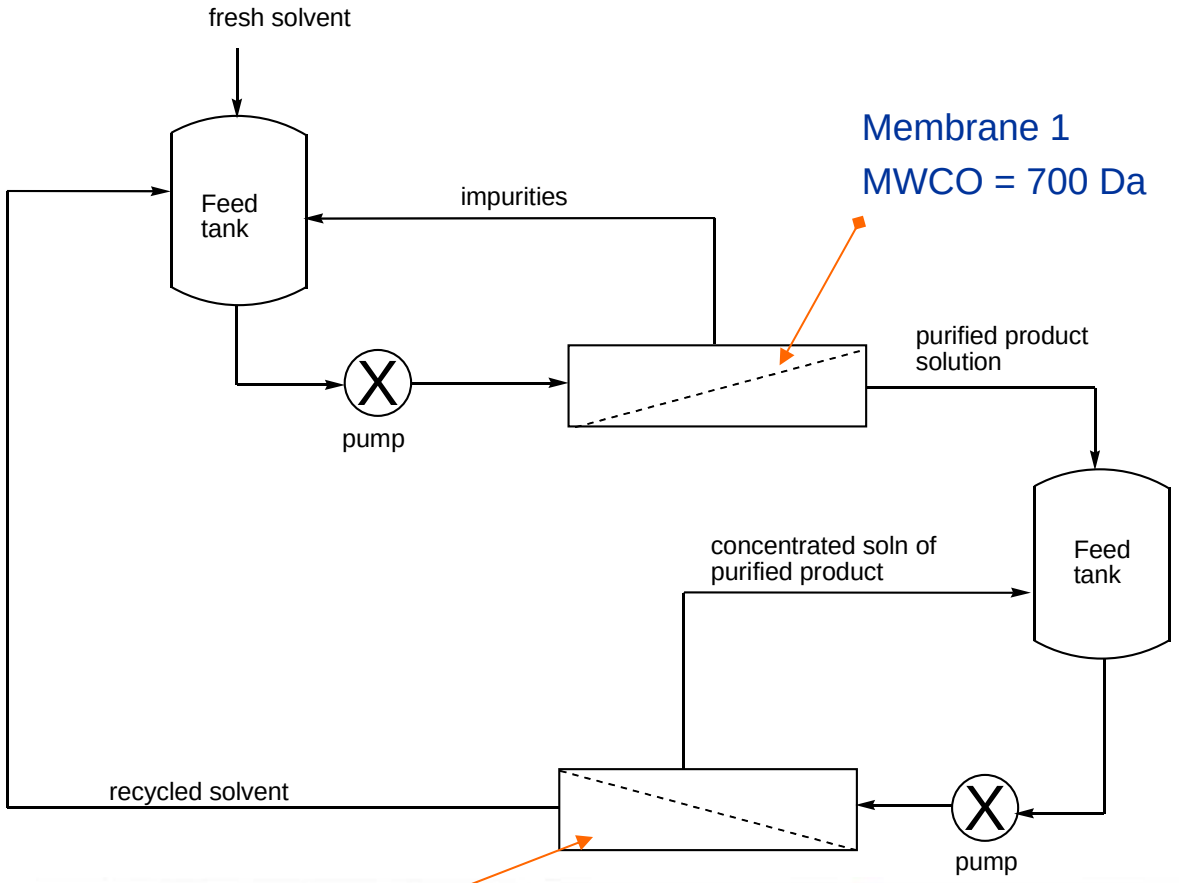
Pressure 60 bar, 30°C

Flux 5 l m^{-2} h^{-1}

Product rejection = 99.6%

Yield product 98.5%

Oligomeric impurity at end process 2%



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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
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- Membrane extraction technology

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