Wolf & Lamb
Multicatalyst - Sequential One-Pot Reactions

Roozbeh Yousefi

January 9, 2008
Incompatibility
Incompatibility
Synthesis of LYRICA (pregabalin)

\[ \text{AcO} + \text{CN} \xrightarrow{\text{DABCO, H}_2\text{O}} \xrightarrow{2,6\text{-ditert-butyl-4-methylphenol}} \text{CN} \xrightarrow{\text{ClCO}_2\text{Et, pyridine}} \text{CN} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt}} \text{CN} \]

\[ \xrightarrow{\text{Pd(OAc)}_2, \text{PPh}_3, \text{EtOH}} \xrightarrow{\text{CO (300psi), 50 °C}} \text{CN} \xrightarrow{1. \text{LiOH, H}_2\text{O, THF, rt; 2. HCl}} \xrightarrow{3. \text{tert-BuNH}_2, \text{EtOAc}} \text{CN} \xrightarrow{M= \text{t-BuNH}_3^+} \]

\[ \xrightarrow{\text{Rh Catalyst H}_2 (45 \text{ psi})} \xrightarrow{\text{MeOH, 55 °C}} \text{CN} \xrightarrow{99\%} \xrightarrow{1. \text{Ni, KOH, H}_2 (50 \text{ psi})} \xrightarrow{\text{H}_2\text{O, EtOH; 2. AcOH}} \text{NH}_2 \xrightarrow{60\%} \]

Lyrica Pain Relief
$465 \text{ M third quarter 2007}$

Hazardous Operational Waste in Pharmaceutical & Chemical Industry

- Organic waste
- Inorganic waste
- Halogenated solvents
- Non-Halogenated solvents
- Hazardous packaging
- Others


www.corporatecitizenship.novartis.com
The Commercial Route for the Synthesis of Viagra

**Route A**

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O}_2\text{N} \\
\text{N} & \quad \text{Pr} \\
\text{N} & \quad \text{Me} \\
\end{align*}
\]

\[
\text{H}_2, \text{Pd/C} \\
\text{EtOAc}
\]

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{N} \\
\text{N} & \quad \text{Pr} \\
\text{N} & \quad \text{Me} \\
\end{align*}
\]

**Route B**

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O}_2\text{N} \\
\text{N} & \quad \text{Pr} \\
\text{N} & \quad \text{Me} \\
\end{align*}
\]

\[
\text{H}_2, \text{Pd/C} \\
\text{EtOAc}
\]

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{N} \\
\text{N} & \quad \text{Pr} \\
\text{N} & \quad \text{Me} \\
\end{align*}
\]

There is a continued drive for improved environmental performance and butanol will be switched to another reaction solvent that can be recovered. This new process was developed and optimised in Ringaskiddy and has been demonstrated in the production plant in Ireland. When fully implemented this will give the final optimised solvent usage of 4 L Kg⁻¹.

A more detailed environmental analysis of the optimised medicinal chemistry synthesis (1994), the 1997 commercial route and the future target follows, using such measures as atom economy, reaction mass efficiency, chemical yield, organic waste, aqueous waste, atmospheric emissions, energy usage and the E-factor. The original medicinal chemistry process (1990) is not analysed here, since it was only ever intended for laboratory scale synthesis.

Atom economy, reaction mass efficiency and chemical yield

The concept of atom economy was first introduced by Barry Trost as a prompt to synthetic chemists to pursue "greener chemistry". The method of calculating atom economy was kept deliberately simple and is a percentage of how much of the reactants remain in the final product. Hence, atom economy ignores reaction yield and reagent excess. It also does not account for solvent usage. Further information on how to calculate atom economy can be found in Green Chemistry.

Reaction Mass Efficiency (RME)

is a more sophisticated measure of "greenness" which allows for the effect of yield and the excesses of reagent used. RME does not account for solvent usage.

For a generic reaction $A + B = C$

The atom economy, reaction mass efficiency and chemical yields for the sildenafil citrate processes in 1994 (optimised medicinal chemistry route), 1997 (commercial route) and the future target (commercial route following solvent recovery) are shown in Tables 2 to 4.

As can be seen from the data, the atom economy of the process has remained essentially constant over time. Improvements have been made in yield and through a greater degree of convergency in the synthesis, but these are not measured by atom economy. In contrast, there was a substantial improvement in both RME and chemical yield between 1994 and 1997 when the new route was introduced. There has been a further significant incremental improvement since 1997. A summary of the data in Tables 2–4 is given in Fig. 2.

**Table 2**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Step No</th>
<th>RME</th>
<th>Atom econ.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amide formation</td>
<td>1</td>
<td>25%</td>
<td>61%</td>
<td>92%</td>
</tr>
<tr>
<td>Reduction (nitro to amine)</td>
<td>2a</td>
<td>83%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>Activation/acylation</td>
<td>2b</td>
<td>48%</td>
<td>71%</td>
<td>84% from (2)</td>
</tr>
<tr>
<td>Cyclisation</td>
<td>3</td>
<td>61%</td>
<td>65%</td>
<td>100%</td>
</tr>
<tr>
<td>Chlorosulfonation/sulfonamide formation</td>
<td>4 Reaction</td>
<td>73%</td>
<td>90%</td>
<td>71%</td>
</tr>
<tr>
<td>Salt formation</td>
<td>5 Reaction</td>
<td>91%</td>
<td>100%</td>
<td>91%</td>
</tr>
<tr>
<td>Purification</td>
<td>5 Purification</td>
<td>90%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Overall process</td>
<td></td>
<td>10%</td>
<td>56%</td>
<td>36% from (1)</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Step number</th>
<th>RME</th>
<th>Atom econ.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amide formation</td>
<td>1</td>
<td>40%</td>
<td>61%</td>
<td>92%</td>
</tr>
<tr>
<td>Chlorosulfonation/sulfonamide formation</td>
<td>2</td>
<td>30%</td>
<td>74%</td>
<td>68%</td>
</tr>
<tr>
<td>Reduction (nitro to amine)</td>
<td>3a</td>
<td>83%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>Activation/acylation</td>
<td>3b</td>
<td>61%</td>
<td>73%</td>
<td>90% from (2)</td>
</tr>
<tr>
<td>Cyclisation</td>
<td>4</td>
<td>65%</td>
<td>83%</td>
<td>92%</td>
</tr>
<tr>
<td>Salt formation</td>
<td>5</td>
<td>98%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>Overall process</td>
<td></td>
<td>26%</td>
<td>54%</td>
<td>75% from (1)</td>
</tr>
</tbody>
</table>

**Fig. 1**

The amount of organic waste produced by the sildenafil citrate processes at various time points.

**Table 4**

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Step number</th>
<th>RME</th>
<th>Atom econ.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amide formation</td>
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<td>92%</td>
</tr>
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<td>83%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
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<td>84% from (2)</td>
</tr>
<tr>
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<td>3</td>
<td>61%</td>
<td>65%</td>
<td>100%</td>
</tr>
<tr>
<td>Chlorosulfonation/sulfonamide formation</td>
<td>4 Reaction</td>
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<td>71%</td>
</tr>
<tr>
<td>Salt formation</td>
<td>5 Reaction</td>
<td>91%</td>
<td>100%</td>
<td>91%</td>
</tr>
<tr>
<td>Purification</td>
<td>5 Purification</td>
<td>90%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Overall process</td>
<td></td>
<td>10%</td>
<td>56%</td>
<td>36% from (1)</td>
</tr>
</tbody>
</table>

**Fig. 2**

The amount of solvent waste produced in different routes.
Multicatalyst Sequential Reactions are the Solution

1. Flow process synthesis

2. One pot multicatalyst synthesis
A Flow Process Synthesis of Oxomaritidin

PIFA: (ditrifluoroacetoxyiodo)benzene

Multicatalyst Sequential Reactions are the Solution

1. Flow process synthesis

2. One pot multicatalyst synthesis
Wolf & Lamb Multicatalyst Sequential One-Pot (cell) Reaction in Nature

Selectivity & Site Isolation in Nature

- Substrates
- Intermediate A
- Intermediate B
- Product
Wolf & Lamb Reactions

\[ S + A \quad \overset{\text{\textbullet}}{\longrightarrow} \quad SA + B \quad \overset{\text{\textbullet}}{\longrightarrow} \quad SAB \quad \text{desired product} \]

Wolf: A + Lamb: B \quad \rightarrow \quad \text{Undesired Product}

\[ \text{Wolf: } A \quad + \quad \text{Lamb: } B \quad \rightarrow \quad \text{no reaction} \]

\[ \text{Wolf: } A \quad + \quad S \quad \rightarrow \quad SA \]

\[ \text{Lamb: } B \quad + \quad SA \quad \rightarrow \quad SAB \]

Acylation of a Carbon Acid

Acylation of Carbon Acid: Wolf & Lamb Approach

www.lpb.org/kids
<table>
<thead>
<tr>
<th>Starting material</th>
<th>Acylating reagent</th>
<th>Product</th>
<th>Wolf &amp; lamb Yield %</th>
<th>Yield % reaction in solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-CN</td>
<td>( \text{NO}_2 \text{O}_2 \text{C}_2 \text{H}_5 \text{O}_2 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_4 \text{NO}_2 \text{C}_2 \text{H}_4 \text{C}_2 \text{H}_5 \text{Ph} )</td>
<td>Ph-CN</td>
<td>91%</td>
<td>37%</td>
</tr>
<tr>
<td>H\textsubscript{3}C-CN</td>
<td>( \text{NO}_2 \text{O}_2 \text{C}_2 \text{H}_5 \text{O}_2 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_4 \text{NO}_2 \text{C}_2 \text{H}_4 \text{C}_2 \text{H}_5 \text{Ph} )</td>
<td>NC-\text{C}=\text{Ph}</td>
<td>90%</td>
<td>27%</td>
</tr>
<tr>
<td>Ph-CO</td>
<td>( \text{NO}_2 \text{O}_2 \text{C}_2 \text{H}_5 \text{O}_2 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_4 \text{NO}_2 \text{C}_2 \text{H}_4 \text{C}_2 \text{H}_5 \text{Ph} )</td>
<td>Ph-CO</td>
<td>96%</td>
<td>48%</td>
</tr>
<tr>
<td>Ph-CO</td>
<td>( \text{NO}_2 \text{O}_2 \text{C}_2 \text{H}_5 \text{O}_2 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_4 \text{NO}_2 \text{C}_2 \text{H}_4 \text{C}_2 \text{H}_5 \text{Ph} )</td>
<td>Ph-CO</td>
<td>92%</td>
<td>40%</td>
</tr>
<tr>
<td>Ph-CON\textsubscript{3}</td>
<td>( \text{NO}_2 \text{O}_2 \text{C}_2 \text{H}_5 \text{O}_2 \text{C}_2 \text{H}_5 \text{C}_6 \text{H}_4 \text{NO}_2 \text{C}_2 \text{H}_4 \text{C}_2 \text{H}_5 \text{Ph} )</td>
<td>Ph-CON\textsubscript{3}</td>
<td>92%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Multicatalyst Sequential Reactions are the Solution

1. Flow process synthesis

2. One pot multicatalyst synthesis
Wolf & Lamb Catalyst Immobilization

**Immobilization on Solid support**

1. Solid polymeric acid and nanoparticle base
2. Solid polymeric acid and base
3. Layered Clay Acid and Base

**Immobilization in Microcapsule**

1. Polyurea Microcapsules
2. Star polymer capsule
3. Polymersome
Site Isolated & Recoverable Catalyst

Super paramagnetic spinel ferrite nanoparticle functionalized with base

Sulfonic acid polymer resin (amberlyst A15)

Gill, C. S.; Jones, W. C. Angew. Chem. Int. Ed. 2007, 45, 2209
Tandem Deacetalization- Knoevenagel & Hydrogenation

Solvent: Toluene

<table>
<thead>
<tr>
<th>catalyst</th>
<th>conv [%] first step</th>
<th>conv [%] second step</th>
<th>conv [%] third step</th>
</tr>
</thead>
<tbody>
<tr>
<td>solid acid, solid base</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>solid acid</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>solid base</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>solid acid, liquid base</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>solid base, liquid acid</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Gill, C. S.; Jones, W. C. Angew. Chem. Int. Ed. 2007, 45, 2209
Wolf & Lamb Catalyst Immobilization

**Immobilization on Solid support**

1. Solid polymeric acid and nanoparticle base
2. Solid polymeric acid and base
3. Layered Clay Acid and Base

**Immobilization in Microcapsules**

1. Polyurea Microcapsule
2. Star polymer capsule
3. Polymersome
One-Pot Complex Heterocycle Synthesis

One-Pot Complex Heterocycle Synthesis

Pilling, A. W.; Dixon, D. J. Angew. Chem. Int. Ed. 2007, 46, 5428
Base Mediated Catalytic Cycle

Amberlyst A15 N-acyl iminium ion formation

Nucleophilic ring closure

Product

pKa: 16.2

Amberlyst A15
Wolf & Lamb
Catalyst Immobilization

Immobilation on Solid support
1. Solid polymeric acid and nanoparticle base
2. Solid polymeric acid and base
3. Layered Clay Acid and Base

Immobilation in Microcapsules
1. Polyurea Microcapsule
2. Star polymer capsule
3. Polymersome
Combination of Acidic & Basic Layered Clay

- Hydrotalcites are layered, mixed hydroxides of Mg and Al which can act as solid base catalysts.

- Ti\(^{4+}\)-mont acts as strong acid associated with the chain-like Ti domains within the interlayer.

- In organic solvents, the interlayer space is effectively expanded, allowing access of the substrates to the catalytic site of the Ti species.

The Longest Sequential Multicatalyst Reactions

Wolf & Lamb
Catalyst Immobilization

Immobilization on Solid support

1. Solid polymeric acid and nanoparticle base
2. Solid polymeric acid and base
3. Layered Clay Acid and Base

Immobilization in Microcapsules

1. Polyurea Microcapsule
2. Star polymer capsule
3. Polymersome
Enantioselective Michael Addition of 1,3 Dicarbonyl to Conjugated Nitroalkenes

\[
\text{CH}_3\text{NO}_2 + \text{RCHO} \xrightarrow{10\text{M NaOH, } 0^\circ\text{C, EtOH}} \text{RCH(OH)NO}_2 \xrightarrow{(\text{CF}_3\text{CO})_2\text{O, Et}_3\text{N}} \text{RCH(\text{CO}_2\text{Et})NO}_2
\]


\[
\text{PhCH(=NO}_2) + \text{MeO}\text{CH(OOC)O}_2\text{Me} \xrightarrow{2\text{ mol\%}} \text{MeO}\text{CH(}\text{CO}_2\text{Me})(\text{S})\text{NO}_2
\]

yield(%) = 94  ee(%) = 88

yield(%) = 99  ee(%) = 94

yield(%) = 99  ee(%) = 95

Enantioselective Michael Addition of 1,3 Dicarbonyl to Conjugated Nitroalkenes

Is it Possible to Mix two Catalysts Together?

```
\begin{align*}
\text{O} & \text{H} \\
\text{CH}_3\text{NO}_2 & \rightarrow \text{CH}_3\text{NO}_2
\end{align*}
```

```
\begin{align*}
\text{Cat 1} & \rightarrow \\
\text{Cat 1} & \rightarrow
\end{align*}
```

```
\begin{align*}
\text{DMM} & \text{Cat 1} \\
\text{CH}_3\text{NO}_2 & \text{Cat 2}
\end{align*}
```

```
\begin{align*}
\text{Cat 1} & \text{DMM} \\
\text{Cat 2} & \text{Cat 1}
\end{align*}
```

```
\begin{align*}
\text{Cat 1} & \text{Cat 2}
\end{align*}
```
Wolf & Lamb Catalyst

Inactive Dual Catalyst System

Active Dual Catalyst System

Microcapsule Enabled Multicatalyst System

\[
\text{CH}_3\text{NO}_2 + \text{PhCHO} + \text{MeO\text{C\text{O\text{C\text{O\text{Me}}}}} \rightarrow \text{MeO\text{C\text{O\text{C\text{O\text{Me}}}}} Ph_{\text{NO}_2}} 80.2\% \\
\text{Conversion of Benzaldehyde: 95%}
\]

Synthesis of LYRICA (pregabalin)

\[
\begin{align*}
&\text{AcO} + \text{CN} \xrightarrow{\text{DABCO, H}_2\text{O}, 2,6\text{-ditert-butyl-4-methylphenol}} \text{CN} \xrightarrow{97\%} \\
&\text{CO (300psi), 50 }^\circ\text{C} \xrightarrow{\text{Pd(OAc)}_2, \text{PPh}_3, \text{EtOH}} \text{CN} \xrightarrow{83\%} \\
&\text{EtOH} \xrightarrow{1. \text{LiOH, H}_2\text{O, THF, rt; 2. HCl}} \text{CN} \xrightarrow{88\%} \\
&\text{3. tert-BuNH}_2, \text{EtOAc} \xrightarrow{\text{M} = \text{t-BuNH}_3^+} \\
&\text{H}_2 \xrightarrow{\text{Rh Catalyst, H}_2 (45 \text{ psi})} \text{CN} \xrightarrow{99\%, 99.7\% e.e.} \\
&\text{MeOH, 55 }^\circ\text{C} \xrightarrow{1. \text{Ni, KOH, H}_2 (50 \text{ psi})} \text{NH}_2 \xrightarrow{60\%} \\
&\text{H}_2\text{O, EtOH; 2. AcOH, Lyrica Pain Relief} \\
&$465 \text{ M third quarter 2007}$
\end{align*}
\]

Synthesis of LYRICA (pregabalin)

\[
\text{Cat 1, Cat 2} \quad \text{Toluene, MeOH} \quad \text{r.t. 48h}
\]

\[
(\text{S}) \quad \text{94\%} \quad \text{72\% e.e}
\]

\[
\text{Raney Ni, H}_2 (45\text{psi}) \quad \text{EtOH, r.t. 18h}
\]

\[
(\text{S}) \quad \text{95\%} \quad \text{72\% e.e}
\]

Micro-Encapsulation through Oil in Oil Interfacial Polymerization

Wolf & Lamb Catalyst Immobilization

Immobilization on Solid support

1. Solid polymeric acid and nanoparticle base
2. Solid polymeric acid and base
3. Layered Clay Acid and Base

Immobilization in Microcapsules

1. Polyurea Microcapsule
2. Star polymer capsule
3. Polymersome
Star Polymers

Library 1:
- Hydrophobic
- Hydrophilic
- Fluorinated

Library 2:
- Solubility
- Functionality
- End group

Library 3:
- Acidic
- Basic
- H-Bonding

End group
- Synthon
- Ligand

Set of stars:

Star Polymer Acid & Base Synthesis

1. Styrene, DMF 125°C
2. KOH
3. H⁺

Star Polymer Wolf & Lamb Catalyst

# One Pot Cascade Reaction
(Acetal Hydrolysis & Baylis Hillman)

![Chemical reaction diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid Catalyst</th>
<th>Base Catalyst</th>
<th>Deprotection Yield [%]</th>
<th>Baylis Hillman Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>star polymer</td>
<td>star polymer</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>star polymer</td>
<td>DMAP</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PTSA</td>
<td>star polymer</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>PTSA</td>
<td>DMAP</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>star polymer</td>
<td>linear polymer</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>linear polymer</td>
<td>star polymer</td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

Star Polymer Wolf & Lamb Catalyst

\[
\text{MeO} \quad \text{OMe} \quad \text{acid Cat.} \quad 10 \text{ mol \%} \quad \text{DMF, H}_2\text{O} \quad \text{O}_2\text{N} \quad \text{OH} \quad \text{amine Cat.} \quad 10 \text{ mol \%} \\
\text{O}_2\text{N} \quad \text{O}_2\text{N} \quad \text{MeO} \quad \text{OMe} \quad \text{H} \quad \text{O} \quad \text{O}_2\text{N} \quad \text{OH} \quad \text{O} \quad \text{H}
\]

Arm: \[
\begin{array}{c}
\text{Ar} \\
\text{HO} \\
\text{OH}
\end{array}
\]

Arm: \[
\begin{array}{c}
\text{Ar} \\
\text{HO} \\
\text{OH}
\end{array}
\]
Wolf & Lamb Catalyst Immobilization

Immobilization on Solid support

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Liposome and Its Structure

Cell Membrane

Outside cell

Protein Molecule

Carbohydrate chain

Protein Molecule

Bilayer lipid

Inside cell

Liposome

http://www.bioteach.ubc.ca/Bio-industry/Inex
http://library.thinkquest.org
Liposome & Its Application

- Vitamin C
- Vitamin E
- Drug

http://www.nanopharmaceuticals.org
**Block Copolymers & Polymersomes**

**Block copolymers:**
1. Comprised of two or more homopolymer subunits linked by covalent bonds.

2. They have the same architecture as lipids, in that they possess a hydrophilic head group and hydrophobic tail.

**Polymerosome:**
1. More tunable because of unlimited variety in block copolymer and polymerization method.

2. Less dynamic because of the larger dimension of the amphiphilic block copolymers

3. Diffusion is slower as a result of thicker shell

---

Discher, D. E; Eisenberg, A. *Science*, **2002**, *297*, 967
PS-PIAT a *Rod-Coil* Type Diblock Copolymer

**PS-PIAT**: polystyrene$_{40}$-b-poly(L-isocynoalanine (2-thiophen-3-yl-ethyl)amide)$_{50}$

**PS-PIAT polymersome:**

1. They are stable polymersomes
2. Sufficiently porous by themselves to allow diffusion of small molecules while large molecules such as enzymes, remain trapped inside

Putting Enzymes in Membrane & Internal Water Pool of Polymersome

Vriezema, D. M.; Rowan, A. E.  
Proof of Principle of Enzymatic Encapsulation

**CALB**: Candida antarctica lipase B

![Chemical structure of CALB reaction](image)

**GOX**: Glucose oxidase

![Chemical structure of GOX reaction](image)

**HRP**: Horseradish peroxidase

![Chemical structure of HRP reaction](image)

Polymerosome Efficiency in Enzymes Site Isolation

Conversion (%) vs. time (min)

- Complete system
- Enzyme in solution

Conclusions

- Wolf and lamb multicatalyst sequential one-pot reactions can decrease the number of purification steps.

- Site isolation of wolf and lamb catalyst is essential.

- The catalysts can be site isolated on solid polymer, nanoparticles or microcapsules.

- Site isolated catalysts should be porous enough for reagent diffusion.

- Site Isolation has to be efficient enough to keep catalysts trapped inside itself.
Acknowledgements

Dr. Borhan

Dr. Baker  Dr. Jackson

Chrysoula, Marina, Dan, Xiaofei, Stewart, Sing, Xiaoyong, Aman, Toyin, Calvin, Wenjing, Atefeh, Mercy, Arvind, Camille, Carmin, Sarah

Afra, Aman, Behnaz, Behrooz, Dima, Luis, Maryam, Rafida, Ramin