Microreactors: Using the Very Small to Make the Very Large
New Technology in Pharmaceutical Development

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Outline

• Introduction

• Continuous Flow Reactions

• Lab Style Applications; Yield improvements, ee improvements, time improvements, etc.

• Process Scale Applications; Access to different chemistry, process development improvement, potential cost savings

• Two Real Life Applications

• Conclusions
Definitions

• Batch chemistry
  • Basically what we do everyday
  • Add all reactants, stir for x hours, work-up and analyze.

• Combinatorial chemistry
  • What robots do
  • Batch scale chemistry in parallel with automation

• Continuous flow chemistry
  • Less Common
  • Add reactants to pot A; allow to flow into pot B for work-up; never stop flow

• Microreactor chemistry – Continuous flow chemistry using specialized equipment
What is a Microreactor

- An extension of µTotal Analysis (µTAS), i.e., Lab-on-a-Chip
  - 1st example a GC from Stanford

- Recent example
  - DNA Analyzer – Available commercially from Agilent Technologies
  - Can detect 1 ng/L
  - Only need 1 µL of sample
µReactors: Why Should You Care?

- Cleaner reactions

- A wider variety of reactions possible

- Potentially faster scale-up

Definitely has the potential to spend less time on development and scale up and more time selling. i.e. More money for company (and hopefully you)

- Currently a “hot” topic in pharmaceuticals and fine chemicals

- Potential (partial) paradigm shift

Advantages of μReactors to “Normal Chemistry”

- Possibility to “number up” instead of scale up reactions
- Reduced reaction time in many cases
- Vastly improved heat transfer
- Ability to perform “dangerous” chemistries

“The technology offers an efficient, safe scale-up, shorter process research times and eventually a reduction in drug development times. Microreactor technology shows promise as an innovative tool to help us fulfill our mission to move new medicines from discovery into patients as quickly as possible.” J & J

What is a µReactor

It is not a nano-reactor

Both reasonable scale and technologies applied

Example of nano-reactor

Characteristics of \( \mu \)Reactors

- Channels 50 to 500 \( \mu \)m wide
- Wall between reaction and heat exchanger 20 to 50 \( \mu \)m
- Laminar flow, opposed to turbulent mixing
Manufacture of µReactors

- Bulk machining using wet chemical etching of silicon
- Dry etching using plasma or ion beams
- Micromolding
- Wet chemical etching of glass
- Isotropic wet chemical etching
- Laser ablation
- Buy from commercial sources

Commercially Available

- Cellular Process Chemistry
- Mgt mikroglas
- FZK
- IMM

One drawback is lack of standardized interfaces.

Appears as if academic labs usually make their own system

Reactions Performed in µReactors

- 1,3 Dipolar cycloadditions
- Suzuki Coupling
- Michaelis-Arbuzov Rearrangement
- NaBH₄ Reduction
- Intramolecular Diels-Alder Reaction
- Nef Reaction
- Ketalization
- Aminolysis
- BuLi Add’n to Cyclohexanone
- BuLi Add’n to Benzaldehyde
- Wittig-Horner Reaction
- Wagner-Meerwein Rearrangement
- Beckmann Rearrangement
- Paal-Knorr Pyrrole Synthesis
- Guaresky-Thrope-Pyridone Synthesis
- Red-Al Reduction Synthesis of THP-Ether
- Synthesis of α-Hydroxyacetals
- Synthesis of 2-Amino-Pyridine-N-Oxide
- Pd-Catalyzed Cross Coupling
- Wittig Reaction
- Favorskii Rearrangement
- Oxidation of Sulfide
- Mitsunobu Reaction
- Nucleophilic Aromatic Substitution

Route A was optimized and proceeded well on scale, however, the overall yield was 12%.

Yields for the eight individual steps were not reported, but avg. yield per step is 77%.

Amount needed not specified, but eventually 10 kg of intermediate was obtained.

Foulkes, J. A., Hutton, J. Synthetic Comm., 1979, 9, 625-630
An Early Example of Continuous Flow Chemistry

Route B

\[
\begin{align*}
\text{R} \quad \text{H} & \quad \text{1} & \quad \text{R} \quad \text{Cl} & \quad \text{10} & \quad \text{R} \quad \text{CH}_3 \quad \text{OH} & \quad \text{9} \\
1. \text{MeMgI} & \quad 2. \text{SOCl}_2 & \quad 1. \text{NaCN} & \quad 2. \text{NaOH, EtOH} & \\
\end{align*}
\]

\[t_{1/2} = 20 \text{ min @ 30 - 35 } ^\circ\text{C}\]

On small scale reaction worked decently, 20-30 % yield over 4 steps

Average yield of 67 % - 74 % per step

Yield on large scale, 100 - 200 g was "unacceptably low"

Foulkes, J. A., Hutton, J.  *Synthetic Comm.*, **1979**, 9, 625-630
Using above set-up with 10 mL flasks over 10 kg of the nitrile was obtained in one week.

Average lifetime of the chloride was 1 min

Yield of nitrile was 90 - 92 %, average per step of 97 %

Foulkes, J. A., Hutton, J.  *Synthetic Comm.*, **1979**, 9, 625-630
Continuous Flow for Catalyst Stability

Continuous Flow for Catalyst Stability

- Both ee and yield are remarkably stable
- Catalytic ability (ee and yield) barely decreases from theoretical over 9 days
- <1 % Ru leaching
- CF yield is 15 g L⁻¹ h⁻¹, batch yield is 5.7 g L⁻¹ h⁻¹

Entry 8 run without base, gave best results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow (µL h⁻¹)</th>
<th>Conv %</th>
<th>ee %</th>
<th>Ru leaching</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>95</td>
<td>63</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>240</td>
<td>95</td>
<td>77</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>350</td>
<td>95</td>
<td>83</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>700</td>
<td>90</td>
<td>89</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>1400</td>
<td>81</td>
<td>90</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>1400</td>
<td>95</td>
<td>89</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7</td>
<td>1400</td>
<td>95</td>
<td>89</td>
<td>&lt;1</td>
</tr>
<tr>
<td>8</td>
<td>1400</td>
<td>95</td>
<td>90</td>
<td>&lt;1</td>
</tr>
<tr>
<td>9</td>
<td>1400</td>
<td>53</td>
<td>88</td>
<td>&lt;1</td>
</tr>
<tr>
<td>10</td>
<td>1400</td>
<td>29</td>
<td>88</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Continuous Flow: Improvement in ee:
A Good Candidate for µReactor Technology

At various ligand concentrations ee's ranged from 74 to 85 % for 5 and 7 in batch-wise operations

10 in a flow-through system gave 99 % ee
Flow through system was re-usable at least 4 times

Hydrogenation Reactions

- No Pd leaching
- Product clean after solvent removal
- Scale-up should be easy, just add reactors
- Some yields (benzyl ether deprotection) much higher than batch reactions

Hydrogenation Reactions

Palladium Catalyzed Reactions in μReactors

\[
\text{Ar}^\text{I} + \text{H} \equiv \text{R} \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2} \text{Ar} \equiv \text{R}
\]

Batch Yields 88 - 97 %; Rxn time 2 h
Micromixer yield was 93 % and 83 %; Residence time 10 min

• Necessary to start with recycled catalysts for solubility issues
• Upon further recycling of the ionic liquid the yield dropped to 83 %
• More proof of concept than an improvement
• At least one Suzuki coupling has been reported as well, but yield was very low.


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β-peptide Synthesis

Coupling

FmocHN\_CONH\_CONH\_ODmap

DCC (5 eq)

NH\_CONH\_ODmap

FmocHN\_CONH\_ODmap

93 %

Deprotection, then Coupling

FmocHN\_CONH\_ODmap

DBU

Boc\_CONH\_CONH\_ODmap

96 %

Tripeptide Synthesis

- Reactions faster than batch reactions
- One of only a few examples of two or more reactions in a µreactor

Better Phase Transfer Characteristics

\[
\text{\begin{align*}
\text{O} & \text{O} \\
\text{+} & \text{Br} \\
\end{align*}}
\]

5 mol % TBAB

CH\(_2\text{Cl}_2\):0.5 N NaOH (1:1)

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\mu\text{Reactor} ) (60 s)</td>
<td>57 %</td>
</tr>
<tr>
<td>(\mu\text{Reactor} ) (300 s)</td>
<td>&gt; 90 %</td>
</tr>
<tr>
<td>rbf (1350 rpm, 60 s)</td>
<td>37 %</td>
</tr>
<tr>
<td>rbf (400 rpm, 60 s)</td>
<td>(~ 20 %)</td>
</tr>
</tbody>
</table>

Generality of Reaction

**Fig. 3** The effect of the width of the reactors.

Photochemistry on Process Scale

- Problems on large scale
  - Formation of insoluble aggregates
  - Rapid loss of light intensity
  - Explosive nature of \( \text{O}_2 \) saturated solvents

- Appears that photochemistry is done on scale, but health and safety concerns still exist.

- Ideal case for miniaturization
Proof of Concept

- Chip was 5 cm $\times$ 2 cm, channel 50 $\mu$m deep by 150 $\mu$m wide
- $\sim 95$ % of the light is transmitted
- Light bulb is only 20 W, 6 V.
- Solution is immediately degassed, basically no explosion hazard
- $> 80$ % conversion in 5 s rxn time

Heat Control in Reaction Vessels

- Heat transfer rate is proportional to surface area of vessel
- Surface to volume ratio thus becomes key

<table>
<thead>
<tr>
<th>Reaction Vessel</th>
<th>Ratio (cm²/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>μReactor</td>
<td>200</td>
</tr>
<tr>
<td>100 mL rbf</td>
<td>1</td>
</tr>
<tr>
<td>50 gal (190 L)</td>
<td>0.084</td>
</tr>
<tr>
<td>1000 L</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Heat Control in Reaction Vessels

- Hot spots are minimized (e.g., 3 K versus 60 K rise)
- Entire rxn mixture can be kept at optimal temperature

Reactions at Low Temperature

\[
\begin{align*}
\text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{Bu} & + N= & \text{N} \\
\text{MeO} & \quad \text{OMe} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} & \quad \text{OMe} \\
\end{align*}
\]

-78 °C, CH₂Cl₂

<table>
<thead>
<tr>
<th>Reactor</th>
<th>4 (%)</th>
<th>5 (%)</th>
<th>4:5</th>
</tr>
</thead>
<tbody>
<tr>
<td>batch</td>
<td>37</td>
<td>32</td>
<td>54:46</td>
</tr>
<tr>
<td>T-shaped tube</td>
<td>36</td>
<td>31</td>
<td>54:46</td>
</tr>
<tr>
<td>Micromixer</td>
<td>92</td>
<td>4</td>
<td>96:4</td>
</tr>
</tbody>
</table>

5 increases with temp, improved heat transfer credited with improved selectivity

Reactions at Low Temperature:
Ability to Raise the Temperature

![Reactions at Low Temperature: Ability to Raise the Temperature](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>T, stage 1 (°C)</th>
<th>T, stage 2 (°C)</th>
<th>Ratio R−M/C₂F₅I /17</th>
<th>t, Stage 1 (min)</th>
<th>t, Stage 2 (min)</th>
<th>17 (%)</th>
<th>18a (%)</th>
<th>18b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 batch</td>
<td>MeMgCl</td>
<td>-30</td>
<td>0</td>
<td>2.5:2.8:1</td>
<td>10</td>
<td>&gt;60</td>
<td>84</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>MeMgCl</td>
<td>2</td>
<td>-4</td>
<td>3.9:4.3:1</td>
<td>0.9</td>
<td>&lt;10</td>
<td>65</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>MeMgCl</td>
<td>1</td>
<td>-4</td>
<td>3.9:2.7:1</td>
<td>0.9</td>
<td>&lt;10</td>
<td>13</td>
<td>80</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>MeMgCl</td>
<td>-6</td>
<td>-4</td>
<td>3.9:2.7:1</td>
<td>0.9</td>
<td>8</td>
<td>9</td>
<td>86</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>MeMgCl</td>
<td>-8</td>
<td>-6</td>
<td>5.4:2.7:1</td>
<td>0.7</td>
<td>&lt;10</td>
<td>7</td>
<td>82</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>MeMgCl</td>
<td>-6</td>
<td>-4</td>
<td>7.8:7.8:1</td>
<td>0.8</td>
<td>&lt;10</td>
<td>28</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>


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Application of µReactor Minimize Addition Concerns

Heat release upon addition of methyl chloroformate

Slow addition is sufficient to control heat, except in loss of cooling or stirring

Direct transfer to µReactor at 35 ºC provided 91 % yield

Residence time of 7 min, > 1 kg produced in 1 h

Application of $\mu$Reactor to “Unscaleable” Chemistry

- Addition of BF$_3$ Et$_2$O very exothermic
- Heat release not feed controlled, initiation period is observed
- Solvent reflux temperature could be reached with loss of cooling
- Evolution of large amounts of N$_2$

“Scaling this reaction to kilogram scales safely in a conventional reactor is not recommended”


```
\begin{align*}
\text{N} & \quad \text{O} \\
& \quad \text{OEt}
\end{align*}
\begin{align*}
\text{N} & \quad \text{H} \\
& \quad \text{OEt}
\end{align*}
```

Literature: Et$_2$O, -25 °C, 90 % crude

Process (70 mg scale): CH$_2$Cl$_2$/MTBE (1:4), 0.2 eq BF$_3$Et$_2$O, < 15 °C, 81 %
Application of µReactor to “Unscaleable” Chemistry

- 70 mg batch conditions directly transferred to micro-reactor
- Yield increased to 89 % with precise control
- Rxn time of 1.8 min
- 91 g/h obtained, potentially 2.2 kg per day
- “… we were able to reduce the time-consuming process research to find optimal safe conditions.”


Literature: Et₂O, -25 °C, 90 % crude
Process (70 mg scale): CH₂Cl₂/MTBE (1:4), 0.2 eq BF₃Et₂O, < 15 °C, 81 %
Are µReactors Green?

- Time for addition of reagents quite significant on process scale
- Reaction can be done without solvent in µReactor
- 91 % yield (after distillation)
- 260 g/h (6.2 kg/day)
- 10 min clean-up (flush with EtOH)

Application to a Blockbuster Drug: Medicinal Chemistry Route

7.5 % over nine linear steps (75 % avg/step)

Unsuitable for commercial development
  a. Linear
  b. Multiple recrystallizations of final product
  c. Chlorosulphonation on scale is difficult (quench)

Application to a Blockbuster Drug: Commercial Route

Yield is vastly improved (75 %)
Synthesis is convergent
Waste is minimized


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Application to Commercial Drug: Safety Issues

- Nitropyrazole decarboxylates at 100 °C under reaction conditions

- Mixing of H₂SO₄ and HNO₃ generates 249 kJ/mol (59.5 kcal/mol)
  - Reaction starts at 50 °C and could easily reach 127 °C

- Procedure modified to minimize heat release
  - SM dissolved in H₂SO₄
  - HNO₃ and H₂SO₄ separately mixed
  - SM and 1/3 of nitrating mixture mixed
  - HPLC analysis was performed and another 1/3 added, etc.

- Process is safe and robust, but time consuming and labor intensive

Application to Commercial Drug: An Advertisement

- Interested in proving concept
- Reaction was run at 90 °C – the “ideal” reaction temperature
- Residence time of 35 min
- 5.5 g/h (132 g/day), 46 g/L, 73 % yield
  Commercial scale, 1.93 kg/10h, 2400 g/L
- Direct scale up of medicinal chemistry route (75 %) yield
- Further optimization of concentration, time and temperature should quickly raise yield.

µReactors: Not A Replacement for Process Chemists

Figure 4. Comparison of organic waste from medicinal chemistry and commercial routes. The cyclisation solvent, tert-butyl alcohol, ends up in the aqueous waste (for treatment) in both medicinal chemistry and commercial routes.
μReactors in series for Hazardous Materials

- On academic scale reaction proceeded to 52 % conversion

Azo Coupling on Large Scale

- Application of CPC reactors to dye formation extensively studies by Clariant: Pigments and Additives Division.

- No dye given, no yields

- Explored differences between traditional batch processing for one red and one yellow dye

- Chemistry is basically:

\[
\begin{align*}
\text{NH}_2 \quad & \xrightarrow{\text{NaNO}_2, \text{HCl}} \quad \text{N}_2^+\text{Cl}^- \\
\text{H}_2\text{O}, \text{DMF} \quad & \quad \text{Explosive, thermally unstable} \\
\text{H}_2\text{O}, \text{DMF} \quad & \quad \text{Chem. Eng. Jour., 2004, 101, 179.}
\end{align*}
\]
Results of Study

- **Output**
  - 80 kg per batch operation and hour
  - 1 kg/h for $\mu$ Reactor
  - Both reproducible to ±3%

- **Quality**

![Color Shade Graph](image1)

<table>
<thead>
<tr>
<th></th>
<th>Lab</th>
<th>Pilot</th>
<th>Prod. Plant</th>
<th>MRT Lab</th>
<th>MRT Pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shade</td>
<td>5.5</td>
<td>5.5</td>
<td>4.6</td>
<td>5.5</td>
<td>5.8</td>
</tr>
</tbody>
</table>

![Color Strength Graph](image2)

<table>
<thead>
<tr>
<th></th>
<th>Lab</th>
<th>Pilot</th>
<th>Prod. Plant</th>
<th>MRT Lab</th>
<th>MRT Pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>150</td>
<td>125</td>
<td>135</td>
<td>140</td>
<td>145</td>
</tr>
</tbody>
</table>

µReactor Reproducibility

- Quality improves because of better dosing at strong flow rates
- Particle size and distribution stayed consistent
- Process transfer from lab to plant took 1 week, 2-3 for batch

<table>
<thead>
<tr>
<th>Property</th>
<th>MRT-lab</th>
<th>MRT-pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color dC</td>
<td>1.58</td>
<td>1.52</td>
</tr>
<tr>
<td>Color strength (%)</td>
<td>111</td>
<td>118</td>
</tr>
<tr>
<td>Color shade dH</td>
<td>0.40</td>
<td>0.38</td>
</tr>
<tr>
<td>Color lightness dL</td>
<td>0.42</td>
<td>0.4</td>
</tr>
</tbody>
</table>

- Only example I could find of a published scale-up
- Pilot plant has been ordered from CPC

Combinatorial Chemistry on Chips

- **Method A: Parallel Synthesis**
  - Complicated chip patterns
  - Multiple pumps and outlets
  - Efficacy demonstrated

Combinatorial Chemistry on Chips

- “Slug” Injection
  - Less Hardware and complicated chip design needed
  - Possibility of direct analysis of product either with \( \mu \)TAS or conventional methods
  - Amounts obtained are relatively small

Limitations of System

- Will the process be cGMP compliant??
- May not be (is not?) suitable for all reactions.
- NO SOLIDS
- Lack of knowledge about the “art” may hinder and slow usage
- Quality of the commercially available systems has to be improved

Conclusions

- Intriguing way of performing reactions
- Definite possibility for commercial use
- Most likely a medicinal chemist will never see one in his or her lab
- Could be useful first in small scale, on site, manufacture of toxic chemicals in bulk
- Someone needs to use it first:
  - "Nobody wants to take the lead on his own; thus, the situation can be described as wait and see."
  - "Finally, all this information must be used to build plants with µflow devices and to profit from the new technology. Otherwise the technology will stay at a level of an ‘innovation,’ ‘plaything’ or whatever."

Impact of Chemical Weapon Proliferation

- Small, easily hidden

- Problems of “good” toxic chemicals same as “bad” toxic chemicals

- Microreactors will likely be easily manufactured in the near future

- Could possibly be used for reliable “onsite” generation


- Much the same could be said of “batch” chemistry and existing technology

- Should be aware of the problem, but not overly concerned.