Why Microfluidic Synthesis?

NanoTek: A Microfluidic Flow-Chemistry System by Advion

SNM
San Antonio 2011
Little has changed in 150+ yrs

18F
Incorporation
References

• Quantitative Spatial Mapping of Mixing in Microfluidic Systems.
  Steven W. Magennis, Emmelyn M. Graham, and Anita C. Jones

• Greener Approaches to Organic Synthesis Using Microreactor Technology
  Brian P. Mason, Kristin E. Price, Jeremy L. Steinbacher, Andrew R. Bogdan,
  and D. Tyler McQuade*
  Published on Web 03/21/2007 American Chemical Society

• Miniaturized continuous flow reaction vessels: influence on chemical reactions
  Monica Brivio, Willem Verboom and David N. Reinhoudt
  Lab Chip, 2006, 6, 329–344
Key Microfluidic Differences

• Mixing is by diffusion
  – A reproducible and rapid process under laminar flow.
  – Vial based mixing is turbulent and stochastic.

• Precise temperature control
  – High surface area to volume eliminates temperature gradients
  – Vial based systems exhibit considerable temperature variations within the vial.

• Short residence times
  – Incorporation typically undertaken in seconds.
Laminar Flow and Diffusion
Fluorescence Lifetime Imaging Microscopy (FLIM)

Red = Fluorescent dye 1,8-anilinonaphthalene sulfonate (ANS) in pure methanol.
Blue = ANS in water/methanol mixture (1:1 molar ratio, which corresponds to water at 30.8% v/v)

- The compositional variation observed is indicative of two fluids under laminar flow there is no sign of turbulent mixing.
- The input streams are well-behaved. The two streams stay completely separate, except for the mixing region that results from diffusion as the fluids move further downstream.
Precise Temperature Control
Potential Improvements Utilizing Microfluidics

- Speed
- Reproducibility
- Yield
- Purity
- Versatility
- Conservation of reagents
Mode of Operation

E-mail info@advion.com to request a copy of the animation.
Short Reaction Times: Proprietary Precursor Optimization

• Over a day and a half, 20 experiments were conducted along with Radio TLC and HPLC analysis.
• Three solvents were evaluated at temperatures ranging from 70°C to 170°C along with an initial evaluation of precursor concentration and reaction time.
• Reducing precursor concentration to 20% of initial experiments had little effect on overall labeling efficiency.

% RCY Radio TLC

DMSO

DMF

Reaction times 45 sec
Reproducibility

• Intra-system example
  – UT, FLT the yield (uncorrected) starting with up to 1 Ci of [18F]fluoride was 22 ± 3% (n=20).

• Inter-system examples: Fallypride

<table>
<thead>
<tr>
<th>Temp</th>
<th>Reactor</th>
<th>%Yield</th>
<th>Activity</th>
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<tbody>
<tr>
<td>170</td>
<td>2 x 2M</td>
<td>88</td>
<td>15.4mCi NIH</td>
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<tr>
<td>160</td>
<td>4M</td>
<td>88</td>
<td>NA Wolfson</td>
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<tr>
<td>170</td>
<td>4M</td>
<td>93</td>
<td>4mCi Yale</td>
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### Examples of Incorporation Yield

<table>
<thead>
<tr>
<th>18F Tracers</th>
<th>Incorporation % RCP</th>
<th>% TCY</th>
<th>Source</th>
<th>Reference</th>
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<tbody>
<tr>
<td>FDG</td>
<td>&gt;95</td>
<td>62.5±3 (n=12)</td>
<td>Advion System Validation project</td>
<td>NA</td>
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<tr>
<td>Fallypride</td>
<td>88</td>
<td></td>
<td>NIH, V Pike, Shuiyu Lu</td>
<td>Current Radiopharmaceuticals, 2009, 2, 49-55</td>
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<tr>
<td>FMISO</td>
<td>91</td>
<td>&gt;97</td>
<td>UT</td>
<td>J Nucl Med. 2010; 51 (Supplement 2):1462</td>
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<td>Altanserin</td>
<td>&gt;50</td>
<td></td>
<td>Advion App Note</td>
<td>Preparation of [F-18]Altanserin using the NanoTek® LF</td>
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<tr>
<td>2FA</td>
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<td>8</td>
<td>Internal communication</td>
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<td>PBR 06</td>
<td>&gt;95</td>
<td>&gt;50</td>
<td>Evaluation at UT</td>
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<td>DPA 714</td>
<td>&gt;95</td>
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<tr>
<td>EtDT</td>
<td>67±3 (n=8)</td>
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<td>Pascali at Pisa</td>
<td>Nuclear Medicine and Biology 37 (2010) 547–556</td>
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<tr>
<td>PrDT</td>
<td>78±3 (n=5)</td>
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<td>Pascali at Pisa</td>
<td>Nuclear Medicine and Biology 37 (2010) 547–557</td>
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<tr>
<td>FTHA</td>
<td>74</td>
<td>&gt;40</td>
<td>UT</td>
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<tr>
<td>FE@SUPPY</td>
<td>79.2±10.9 (n=6)</td>
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<td>Vienna</td>
<td>Comparison of “conventional” radiosynthesis and microfluidic preparation of [18F]FE@SUPPY EANM 2010-Vienna</td>
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<tr>
<td>FE@SUPPY 2</td>
<td>95.3±1.9</td>
<td></td>
<td>Vienna</td>
<td>RAPID RADIOSYNTHESIS OF [18F]FE@SUPPY:2 USING THE NANOtek® MICROFLUIDIC DEVICE <a href="http://www.radiopharmaceutical-sciences.net">www.radiopharmaceutical-sciences.net</a></td>
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<tr>
<td>FAZA</td>
<td>80</td>
<td>&gt;95</td>
<td>&gt;20(n=3)</td>
<td>Elsinga Groningen</td>
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<td>FBA</td>
<td>&gt;85</td>
<td>&gt;95</td>
<td>GSK and UC Davis with Lee</td>
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<td>FDG Peptide</td>
<td>87</td>
<td></td>
<td>Alberta</td>
<td>2-[18F]-2-DEOXY-D-GLUCOSE ([18F]-FDG) LABELING OF PEPTIDES USING A MICRO-FLUIDIC REACTOR</td>
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Flow Synthesis Incorporation Experiment
170C No By-product Formation

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<tr>
<th>Peak No.</th>
<th>Peak Name</th>
<th>Result (°)</th>
<th>Ret. Time (min)</th>
<th>Time Offset (min)</th>
<th>Area (counts)</th>
<th>Sep. 1/2 (sec)</th>
<th>Status Codes</th>
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<td>0.000</td>
<td>379222</td>
<td>BB</td>
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<td>Totals:</td>
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<td></td>
<td>0.000</td>
<td>9064719</td>
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</table>
Reaction at 180°C vs. 170°C

By-product Formed and Desired Product Yield Drops from 80% to 1%
Temperature, Solvent, Pressure

• Calculated variation of boiling point of common solvents with pressure
  - Acceleration of reaction rates in flow vs. batch reactors may be achieved by routinely operating at elevated pressures and temperatures.

<table>
<thead>
<tr>
<th></th>
<th>Boiling point °C @</th>
<th>1 bar</th>
<th>6.9 bar</th>
<th>17.0 bar</th>
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<tbody>
<tr>
<td>CH₂Cl₂</td>
<td>41</td>
<td>109</td>
<td>153</td>
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<tr>
<td>MeOH</td>
<td>65</td>
<td>138</td>
<td>185</td>
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<tr>
<td>THF</td>
<td>66</td>
<td>140</td>
<td>186</td>
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<tr>
<td>iPrOH</td>
<td>82</td>
<td>159</td>
<td>207</td>
<td></td>
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<tr>
<td>MeCN</td>
<td>82</td>
<td>159</td>
<td>207</td>
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<tr>
<td>H₂O</td>
<td>100</td>
<td>181</td>
<td>231</td>
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<tr>
<td>Dioxane</td>
<td>101</td>
<td>182</td>
<td>234</td>
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<tr>
<td>DMF</td>
<td>153</td>
<td>244</td>
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<tr>
<td>DMA</td>
<td>165</td>
<td>259</td>
<td>318</td>
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</table>

- Useful solvents for flow with bp exceeding 150°C @ 7 bar
  • NanoTek back-pressure upper operating limit is 400 psi (28 bar).
  • Reactor upper temperature limit is 220°C.
Future Potential

Reacting mixture
Stable product mixture
Separation
By-product Product

Dilute (~10^3)

Assays

Conditions
Chemistry

Decision software

Reagents

Biology
Flow
Well-based
• Single
• Multiplex

Advion
Versatility

- 40+ optimization reactions possible in one day.
- Operating range of activities μCi to Ci.
  - No observed changes in yield as scale increases.

SNM 2010 Poster:

**Microfluidic Synthesis of [18F]FLT**
Murthy R. Akula1, Thomas L. Collier4, George W. Kabalka2, Jonathan S. Wall3, Steve Kennel4, Alan Stuckey3 and Amy K. LeBlanc2
1 Department of Radiology, University of Tennessee, Knoxville, TN, United States.
2 Departments of Radiology and Chemistry, University of Tennessee, Knoxville, TN, United States.
3 Department of Medicine, University of Tennessee, Knoxville, TN, United States.
4 Advion BioSystems, Inc., Ithaca, NY, United States

- Dose-on-demand capability published

**Dose-on-demand of diverse 18F-fluorocholine derivatives through a two-step microfluidic approach**
Giancarlo Pascalia!, Giovanni Nannavecchiaa,b, Sabrina Pitziantia,c, Piero A. Salvadoria
Nuclear Medicine and Biology (March 2011) doi:10.1016/j.nucmedbio.2011.01.005

- Back to back production
  
  Tuesday morning presentation 8:48 AM to 9:00 AM
  Location: 213AB Publication number: 289

**Sequential preparation of two different PET radiotracers employing the Advion NanoTek synthesis system**
Sequential preparation of two different PET radiotracers employing the Advion NanoTek synthesis system

Authors shown: Murthy R. Akula and T. Lee Collier