Applications of Flow Chemistry in Pharmaceutical Processing: A Flow-Based Synthesis of Telmisartan

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Department of Chemistry
Effecting Change Can Be a Painful Process

PAT

Batch Processing
Research Focus

- Continuous chemical processing
- Catalysis
- Streamlining pharmaceutical processes
**Pharma Batch Process Production Rate (example):**
- Batch Size – 6,000 liter
- Batch Reaction Cycle Time – 10 hours
- Batch Throughput – 10 liters/minute

**Continuous Process Production Rate**
- Throughput – 10 liters/minute
- Void Volume – 60 liters
- **Residence Time** – 6 minutes

Efficient Heating

Catalysis
Carbon-Carbon Bond Forming Reactions

**Importance**
- Strategic assembly of API’s

**Types**
- Suzuki
- Heck
- Sonogashira
- Buchwald-Hartwig
- Stille
- Others

**Issues**
- Homogeneous catalyst
- Product contamination
- Not recyclable

**Needs**
- Heterogeneous catalyst
- Easily isolated
- Recyclable
Graphene Support System for Catalyst Applications

- Thermal stability
- High surface area
- Mechanical stability
- New preparation methods
  - Hydrazine reducing agent
  - Microwave heating

Pd/Graphene

Ligand-Free Heterogeneous Pd/Graphene Suzuki Cross Coupling Reactions

\[
\text{C}_6\text{H}_5\text{Br} + \text{C}_6\text{H}_5\text{B(OH)}_2 \xrightarrow{\text{Pd/Graphene}} \text{C}_6\text{H}_{11}
\]

\[\text{K}_2\text{CO}_3, \text{EtOH-H}_2\text{O}(1:1)\]

Room Temp, 30 min.

94% Isolated yield

<250 ppb in reaction solution by ICP-MS

Turnover Frequency = 108,000 hr\(^{-1}\)

Gupton et. al., *J. Catalysis* 279 (2011) 1-11
Ligand-Free Heterogeneous Pd/Graphene Suzuki Cross Coupling Reactions

Conversion (%)
Time (Min)
Pd/G 0.3 mol%
Pd/G 0.1 mol%
Pd/G 0.02 mol%
Pd/G 0.007 mol%, 80 °C (MWI) - 5 min
Pd/C 0.3 mol%

\[
\text{Br} \xrightarrow{\text{K}_2\text{CO}_3, \text{EtOH- H}_2\text{O}(1:1)} \text{Room Temp} \xrightarrow{} \text{B(OH)}_2
\]

\[ \text{ROCCCH}_2 \text{Br} + \text{PhB(OH)}_2 \rightarrow \text{PhCH}_2 \text{Ph} \]
Ligand-Free Heterogeneous Pd/Graphene Suzuki Cross Coupling Reaction Diversity

Br
\( \text{R}_1 \)
\( \text{R}_2 \)
B(OH)\(_2\)

\[ \text{Pd/Graphene, K}_2\text{CO}_3 \]

ETOH-H\(_2\)O (1:1)
\( 80 \, ^\circ\text{C}(\mu\text{W}), 10 \, \text{Min.} \)

Products

<table>
<thead>
<tr>
<th>Products</th>
<th>90%</th>
<th>92%</th>
<th>85%</th>
<th>90%</th>
<th>94%</th>
<th>95%</th>
<th>90%</th>
</tr>
</thead>
</table>

Isolated Yields

Gupton et. al., J. Catalysis 279 (2011) 1-11
Ligand-Free Heterogeneous Pd/Graphene Suzuki Cross Coupling Reaction Diversity

\[
\begin{align*}
\text{Product} \\
\text{Pd/Graphene, K}_2\text{CO}_3 \\
\text{ETOH-H}_2\text{O (1:1)} \\
80^\circ\text{C} (\mu\text{W}), 10 \text{ Min.}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{B(OH)}_2 \\
R_1 & \quad R_2
\end{align*}
\]

\[
\begin{align*}
\text{Product} \quad 73\% \\
\text{Isolated Yield}
\end{align*}
\]
## Ligand-Free Heterogeneous Pd/Graphene Suzuki Cross Coupling Recycling Studies

<table>
<thead>
<tr>
<th>Run</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>r.t.</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>r.t.</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>r.t.</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>r.t.</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>80</td>
<td>10</td>
<td>58</td>
</tr>
</tbody>
</table>

Gupton et. al., *J. Catalysis* 279 (2011) 1-11
Mode Of Pd/G Catalyst Deactivation
Graphene may be acting to disperse static charge across catalyst surface. Catalysis occurring at the double layer interface.
Telmisartan

**Indication:** Angiotensin II receptor antagonist in the treatment of heart disease, hypertension and renal disorders.

**Annual Sales (2010):** $238,335,000

**Patent Status:** US Patent 6,358,296 (expiration 2014)
Impact of API Process Improvements

**Patented Drug Cost Components**
- Active Ingredient Cost
- Other costs + Profit

**Generic Drug Cost Components**
- Active Ingredient Cost
- Other costs + Profit
Telmisartan: Commercial Process

< 40 % Overall yield
Telmisartan: Commercial Process

< 40 % Overall yield
Retrosynthetic Analysis

Target- Telmisartan

X = Br
A = Nitrile, amide, ester
B = Boronic acid adduct
Preparation of Synthons

2-Bromo-1-methylbenzimidazole

\[
\text{NBS, THF, 30min., reflux} \quad \rightarrow \quad \text{93% yield, 1 step}
\]

4'-bromomethyl-1,1'-biphenyl-2-carboxymethylester

Commercially available
Preparation of Synthons

4-methyl-2-n-6-propylbenzimidazole-6-potassium trifluoroboronate

\[
\begin{align*}
\text{Br} & \quad \text{NO}_2 \\
& \quad \text{NH}_2 \\
\text{NO}_2 & \quad \text{NH}_2 \\
& \quad \text{Cl} \\
& \quad \text{ClBn} \\
& \quad 5\text{ hr., 100 }^\circ\text{C} \\
& \quad \text{H}_2, \text{Pd/C} \\
& \quad 5-15\text{ hr., r.t.}
\end{align*}
\]

82% yield
Screening Studies: Alkylation in Flow

Isolated Yield = 92%
Screening Studies: Suzuki Reaction in Flow

Conversion = 98%

1. Pd/G, MeOH, H₂O

KOH
10 min @ 120 °C
2. Acetic Acid
Alkylation in Flow

Conversion = 94%
Suzuki Cross-Coupling in Flow

Conversion = > 98%

1, Pd/G, MeOH, H₂O
KOH
10 min@120 °C
2. Acetic Acid
Telmisartan in Flow

Corning Low Flow Reactor

X-Cube Flow Reactor

KF₃B, KOH, MeOH

50 °C

Pd/Graphene

MeOH, KOH, H₂O

120 °C

>80% Isolated Yield

KOH, MeOH

Br

CO₂Me

Br
Continuous Catalyst Production

Wavecraft
ArrheniusOne

Up to 100 Barr and 200°C
Flow Chemistry: Impact on Society
Nevirapine: A Clinton Funded Effort
Joint Venture with McQuade Group

Now $170/kg  

Goal <$50/kg

Simple
Inexpensive

Goal <$50/kg

Simple
Inexpensive
An FDA Perspective
Trends in the Pharmaceutical Industry

- Reduced investments in drug discovery
- Increased focus on generic market
- Meeting current and future market requirements
- Movement towards “personalized medicine”

Trends in Drug Discovery

- Fewer FDA drug approvals
- Higher cost to bring new drugs to the market place
- Existing blockbuster drugs coming off patent
- Prospect of government managed health care

Outcome: Fewer new drugs to enhance quality of life for ageing population
Generic Gold Standards for Health Care

- Antihypertensive → Sartans
- Cholesterol → Statins
- Antibiotics → Quinolones
- Antivirals → NRTI’s, NNRTI’s, Purine Nucleosides
- Antiinflamitories → COX-2 Inhibitors

Other Blockbuster Drugs Moving Off Patent
- Plavix (clopidogrel)
- Cymbalta (duloxetine)
- Singular (montelukast)
- Advair (fluticasone)

Patented Drug Cost Components
- Active Ingredient Cost
- Other costs + Profit

Generic Drug Cost Components
- Active Ingredient Cost

Higher volume requirements are driving API production towards continuous processing
Current Health Care Challenges

• Supply
  - Oncology drugs
  - Cardiovascular drugs
  - Parenterals

• Quality
  - Counterfeit drugs
  - Global suppliers (Heparin)
  - Batch to batch variability

• Enforcement
  - International inspections

On demand manufacturing capabilities?

New analytical capabilities
Continuous manufacturing technology

Real time access to production data
E factor = kg Waste per kg Product

Roger Sheldon / “Green Chemistry in the Pharmaceutical Industry”

<table>
<thead>
<tr>
<th>Industrial Segment</th>
<th>E factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk Chemicals</td>
<td>&lt;1-5</td>
</tr>
<tr>
<td>Fine Chemicals</td>
<td>5 to 50</td>
</tr>
<tr>
<td>Pharmaceutical Chemicals</td>
<td>25 to 100</td>
</tr>
</tbody>
</table>

“The ACS Green Chemistry Institute Pharmaceutical Roundtable has ranked continuous processing as the highest priority area for future development”

The challenge is to address process sustainability without compromising product quality
Interdisciplinary Skill Sets Required

**Chemical Synthesis**
- Practical application of process chemistry
- Emphasis on sustainable methods
- Grounded in catalysis

**Analytical Methods Development**
- Broad range of analytical expertise
- Effective sampling
- Experience in commercial applications
- Integration of analytical data with real-time process optimization

**Process Engineering**
- Translational research expertise
- Integration of chemistry and equipment leading to model development and process control
- Practical commercial insights
- Understanding of regulatory boundary conditions
Interdisciplinary Skills Required

Quality By Design

Process Engineering

Chemical Synthesis

Analytical Methods Development
Concluding Thoughts

- The science exists to enable continuous manufacturing of pharmaceuticals
  - Specific scientific considerations related to sampling frequency for continuous manufacturing
- There are no regulatory hurdles for implementing continuous manufacturing
  - However, there is a lack of experience
- FDA supports the implementation of continuous manufacturing using a science and risk-based approach
  - Recommend early and frequent discussion with Agency before implementation
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