Flow chemistry technologies handling solids including crystallisation

Professor Xiong-Wei Ni, BSc, PhD, CEng, CSci, FIChemE

Founder and Technical Director
Email: x.ni@nitechsolutions.co.uk
www.nitechsolutions.co.uk

Hall 9.2, Stand F48

ACHEMA, Frankfurt, 18th June 2012
NiTech® Solutions Ltd

- A spin-out from Heriot-Watt University, Edinburgh, UK

- Innovative provider of product equipment and services including consultancy, design & support joint with our engineering partner, AWL

- IP includes granted patents and patent applications

- Technologies are specially good in handling solids including crystallisation
Structure

1. Brief background
2. NiTech® reactor/crystalliser
3. Cases of continuous manufacturing
4. Forward remarks
1. Background

Mixing is at the heart of chemical and process industries

- Heat transfer
- Mass transfer
- Particle suspension
- Gas dispersion
Traditional routine of scaling up

lab → pilot → full scale

Kinetic controlled e.g. 30 mins

Mass/heat transfer controlled e.g. 30 hrs
What do we know?

• Mixing cannot be scaled linearly
• Specific heat transfer area \( (m^2/m^3) \) reduces with scale
• Mass/heat transfer constraints
How could we create a reactor system that allows kinetic controlled reaction times to be performed at lab scale as well as full scale?
The basis for continuous

From the viewpoint of fluid mechanics

i) consistent product quality can only be achieved in plug flows;

ii) it is very rare to obtain plug flow conditions in batch STR!

iii) Plug flow conditions can only be attained in continuous operation.
How to achieve plug flow?

a) Using a series of CSTRs

Plug flow is achieved when the number of CSTRs approaches to infinite

Conclusions: a) significant increase in inventory, running and capital costs b) far from plug flow
b) Employ a tubular reactor with or without inserts

Operating a tubular reactor at turbulent flow regime in order to obtain near to plug flow

Conclusion: a) significant high flow rates, leading to very long reactor and large capital costs
b) very short residence time
Evolution of Manufacturing Technology for Chemicals Industry

- Little has changed in 450 years
- The stirred tank reactor is the “normal” approach for mixing, reaction and manufacture
  - Particular challenges around the scale-up of processes
  - Expensive, poor control over quality
Supersolubility is thermodynamically not found and kinetically not well defined, depending on:

- Temperature profile
- Rate of generating supersaturation
- Solution history
- Impurities
- Fluid dynamics

How does it affect crystallisation?

MSZW depends on reactor, scale and operating conditions.

Industrial batch crystallisation

Mixing gradient → Concentration gradient → supersaturation gradient → polymorph

Inconsistent morphology
Wide size distribution
Difficult to filter

Temperature gradient → MSZW and Crystallisation path → nucleation & growth → Polymorph & size
2. NiTech® Reactor
Demonstration of radial mixing

Real system

3-D CFD simulation

$Re_o = 1250 \ (x_o = 4 \text{ mm}, \ f = 1 \text{ Hz})$
NiTech® Continuous Reactor/Crystalliser

No. of CSTR = 550 for a RT of 60 mins
D ~ 10^{-3} – 10^{-4} m^2/s

Probe 1
3.7 meters away from injection

Probe 2
7.9 meters away from injection

Probe 3
10.1 meters away from injection
Key differences from traditional tubular devices on the market

- Mixing is not controlled by net flow
- Plug flow achieved at laminar flows
- Good with solids
- Excellent heat & mass transfers
- No concentration gradients
## Heat Transfer on Scale-Up

<table>
<thead>
<tr>
<th></th>
<th>Volume (m³)</th>
<th>Area (m²)</th>
<th>Area / unit Volume (m²/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical 90 litre STR</td>
<td>0.09</td>
<td>0.9</td>
<td>10</td>
</tr>
<tr>
<td>Typical 6500 litre STR</td>
<td>6.82</td>
<td>15.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Typical 72m long 100mm diameter NiTech® Reactor</td>
<td>0.56</td>
<td>22.6</td>
<td>40</td>
</tr>
</tbody>
</table>

NiTech® Reactor/Crystalliser has larger specific surface area for HT
Control over cooling profile

Any cooling profile, e.g. linear, parabolic, non-continuous, step-wise and etc, can be obtained along NiTech® Crystalliser.

Any lab monitoring tools can directly be implemented along NiTech® Crystalliser without modification.
Many reactions fall into the band of exotherm against reaction time.

- Micro reactors
- Spinning disc reactors
- Compact reactors
- Static mixer reactors
- Oscillating flow reactors
- CSTR

Exotherm

Reaction time

ms  secs  mins  hrs
3. Case studies

Handling Solids
Manufacture of a pharmaceutical API involving a liquid-solid slurry with gas

NiTech® Reactor gives consistent gas absorption rate resulting in consistent product

Reaction time reduced from >60 mins to 2 mins
Continuous API Manufacture

The world’s largest patent-protected continuous pharma API plant is at Genzyme, Haverhill, where NiTech® continuous reactor is used as part of key synthesis step handling three phases since April 2007.

Reactor volume reduced by 99.6% against traditional approach of 2 off 150 m³ STRs

Batch production of a photochemical (L-L-S)
Acetylation

Continuous temperature control

Continuous pH control
The residence time in the NiTech® Crystalliser translates to 12 minutes, compared to a batch cycle time of 9 hours 40 mins, demonstrating a significant potential improvement in throughput relative to a batch manufacturing facility.
Filtration index for a pharma product

NiTech® Crystalliser delivered

- Product characteristics/performance
- Consistent filtration index of 25
Crystal moisture contents

Moisture content:

50%     73%

Crystallisation achieved in 1/8\textsuperscript{th} of the time
Fractionation of edible oils

- Two stage cooling (17 and 0.3 °C/min)
- Consistent IV achieved
  - Significant reduction of crystallisation time
  - Improved filtration time
Some interesting findings

a) How did nucleation take place in NiTech® crystalliser without seeding, while seeding was essential in benchmarking cases?

b) Why did NiTech® crystalliser have higher nucleation temperature & narrower MSZW than other traditional crystallisers?

c) Why/how did NiTech® crystalliser allow consistent crystal morphology?

d) Why/how did NiTech® crystalliser achieve the same/better purities while using faster cooling rates than benchmark cases?
CMaC (Continuous Manufacturing and Crystallisation)

a) GSK led consortium (~£40M) based at Strathclyde University focusing on continuous manufacturing with initial aims at continuous crystallisation

b) Joint by major UK universities, e.g. Bath, Cambridge, Edinburgh, Glasgow, Heriot-Watt, Loughborough, Strathclyde

c) Customers orientated real projects as well as PhD projects on finding the scientific explanations to these questions

d) NiTech® crystalliser/reactor is the core technology

www.cmac.ac.uk
Liquid-liquid
Comparison of traditional methods (above) with NiTech® reactor (below)

Improved uniformity with reduced energy usage
Biodiesel Plant (15 L/min)
Processing Slow Reacting, Non-Aqueous and Viscous Materials Under Pressure

<table>
<thead>
<tr>
<th></th>
<th>Incremental Flowrate (L/min)</th>
<th>Total Flowrate (L/min)</th>
<th>Residence Time (min)</th>
<th>Tube Length (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat Up A</td>
<td></td>
<td>0.157</td>
<td>16</td>
<td>6.3</td>
</tr>
<tr>
<td>1st adding B</td>
<td>0.024</td>
<td>0.181</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>2nd adding B</td>
<td>0.037</td>
<td>0.218</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>3rd adding B</td>
<td>0.061</td>
<td>0.279</td>
<td>9.5</td>
<td>6</td>
</tr>
<tr>
<td>4th adding B</td>
<td>0.123</td>
<td>0.402</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Adding oil &amp; cooling</td>
<td>0.277</td>
<td>0.679</td>
<td>1.8</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>65.3</td>
<td>36.3</td>
<td></td>
</tr>
</tbody>
</table>

European Process Intensification Conference, 21st June 2011, Manchester
Gas-liquid

Air bubbles in a baffled column
Gas dispersion into liquid

- Bubble retention time considerably improved
- Bubble sizes are smaller and more uniform
- Gas holdup is significantly increased
- Higher mass transfer rates

Fermentation of a biopolymer
Continuous Small Scale Hydrogenation

HPLC Data for batch hydrogenation of aromatic nitroso compound

\[
\text{ArNO} + 2\text{H}_2 \rightarrow \text{ArNH}_2 + \text{H}_2\text{O}
\]

Table 1: Kinetic Study showing batch conversion of Nitroso to Amine vs time

<table>
<thead>
<tr>
<th>Time/minutes</th>
<th>ArNH2 (%)</th>
<th>ArNO/ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>35.2</td>
<td>64.8</td>
</tr>
<tr>
<td>30</td>
<td>59.8</td>
<td>40.2</td>
</tr>
<tr>
<td>45</td>
<td>77.8</td>
<td>22.2</td>
</tr>
<tr>
<td>60</td>
<td>91.7</td>
<td>8.3</td>
</tr>
<tr>
<td>75 (batch complete)</td>
<td>99.6</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

Data for continuous hydrogenation

Table 2: Typical results for continuous hydrogenation of an aromatic nitroso to amine

<table>
<thead>
<tr>
<th>Run Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in continuous mode/minutes</td>
<td>-</td>
<td>360</td>
<td>240</td>
<td>180</td>
<td>240</td>
<td>160</td>
<td>120</td>
</tr>
<tr>
<td>Number of elutions</td>
<td>-</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Weight screened solution/g</td>
<td>-</td>
<td>5288</td>
<td>4783</td>
<td>5120</td>
<td>4817</td>
<td>3129</td>
<td>3532</td>
</tr>
<tr>
<td>Weight product returned/g</td>
<td>-</td>
<td>1308</td>
<td>1221</td>
<td>1339</td>
<td>1232</td>
<td>803</td>
<td>854</td>
</tr>
<tr>
<td>Weight yield/%</td>
<td>-</td>
<td>73</td>
<td>76</td>
<td>78</td>
<td>76</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>Assay/%</td>
<td>-</td>
<td>100.1</td>
<td>99.1</td>
<td>98.5</td>
<td>100.4</td>
<td>99.8</td>
<td>99.0</td>
</tr>
<tr>
<td>Purity%</td>
<td>-</td>
<td>&gt;99.9</td>
<td>&gt;99.9</td>
<td>&gt;99.9</td>
<td>&gt;99.9</td>
<td>&gt;99.9</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>Indicated product yield/day</td>
<td>-</td>
<td>5.2</td>
<td>7.3</td>
<td>10.7</td>
<td>7.4</td>
<td>7.1</td>
<td>10.2</td>
</tr>
</tbody>
</table>

The table above shows that when operating in continuous mode the reactor produced consistent yields and quality in both assay and purity.

Courtesy of Dennis Wray, CPI
## Applications

<table>
<thead>
<tr>
<th>Phases</th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NiTech® Tubular Reactor</strong></td>
<td></td>
</tr>
<tr>
<td>Liquid-Solid-Gas</td>
<td>Carbonation</td>
</tr>
<tr>
<td>Liquid-Liquid-Solid</td>
<td>Hyaluronic Acid</td>
</tr>
<tr>
<td>Liquid-Solid</td>
<td>Blending /Formulation</td>
</tr>
<tr>
<td>Liquid-Liquid</td>
<td>Acetylation</td>
</tr>
<tr>
<td><strong>NiTech® Continuous Reactor</strong></td>
<td></td>
</tr>
<tr>
<td>Liquid-Solid-Gas</td>
<td>Hydrogenation</td>
</tr>
<tr>
<td>Liquid-Solid</td>
<td>Wetting</td>
</tr>
<tr>
<td></td>
<td>Diazotisation</td>
</tr>
<tr>
<td></td>
<td>Cyclisation</td>
</tr>
<tr>
<td></td>
<td>Drug Encapsulation</td>
</tr>
<tr>
<td>Liquid-Liquid</td>
<td>Acetylation</td>
</tr>
<tr>
<td></td>
<td>Bromination</td>
</tr>
<tr>
<td></td>
<td>Enzymatic reactions</td>
</tr>
<tr>
<td></td>
<td>Polymer dissolution</td>
</tr>
<tr>
<td>Liquid-Liquid Separation</td>
<td>In-Line phase separation</td>
</tr>
<tr>
<td><strong>NiTech® Continuous Crystalliser</strong></td>
<td></td>
</tr>
<tr>
<td>Liquid-Solid Crystallisation</td>
<td>L-Glutamic Acid</td>
</tr>
<tr>
<td>Liquid-Liquid-Solid Fractionation</td>
<td>Pharma APIs</td>
</tr>
<tr>
<td></td>
<td>Palm/Sunflower oil</td>
</tr>
</tbody>
</table>

© NiTech Solutions Ltd, 2008
4. Key messages

- STR/CSTR has been the work horse over 450 years, NiTech® reactor/crystalliser is the only real challenger to STR/CSTR in the R&D and manufacturing spaces

- NiTech® Reactor/Crystalliser work well with solids

- NiTech® Reactor allows reactions with their intrinsic reaction times to be performed in lab/pilot/full scales, facilitating smooth scale up operation

- Any lab scale monitoring tools can directly be fitted along NiTech® Crystalliser/Reactor without modification, enabling direct use of knowledge/knowhow learnt from batch to full scale
NiTech® batch evaluation reactor (0.1/0.3 L) @ £25K (left)

NiTech® R&D continuous reactor/crystalliser (1.5 L) @ £75K (right)

Come to see us in Hall 9.2, Stand F48