Converting Batch to Continuous for Profit as well as Fun

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Summary

• Batch and continuous processing
• How can continuous make money?
• Examples
• The hidden gaps
Why we have batch

• It does most things... badly, but it does them
• It is immensely tolerant of ignorance
• I already have a lot of pots and think I understand them
  • I can clean the pots and use them again
  • My friends have pots I can use in case I don’t have enough
• It fits my business model
  • Short time to market
  • Short product life
• I’m still in business – why risk change?
So continuous is better?

• Well of course
  – It’s smaller
  – Cheaper
  – Faster
  – Safer
  – Cleaner
  – More efficient
  – Scales up more easily
• How could anybody not see the benefit?

DSM using Corning Microreactors
So continuous wants to compete?

• Of course there’s a catch
• Yes, there may well be benefits
  BUT
  – Lots of exaggerated claims have been made based on selective data
  – Need to deliver at whole process level not just one magical item
  – Need to provide benefit for a sufficient proportion of processes to warrant the resource overhead
  – Need to demonstrate a clear business case for each investment
Things that a business might want

• Fast time to market;
• Low development effort (as can’t afford a large effort with high attrition and margin pressures);
• Low cost exposure if product fails or market prediction is wrong;
• Transferability to contract manufacture;
• A need to use a range of chemistries and complex multistage processes to make products;
• Work under high degrees of regulation of product;
• ie Ability to implement robust processes quickly and cost-effectively using flexible resources
Mythbusters

• There is a lot of misunderstanding around...
• Reactions/crystallisations care about flow...
• Microchannels mix fast
• Continuous is inherently safe
  • Remember Bhopal and Flixborough
• All reactions can go fast
• Not many reactions use solids
• The capabilities of continuous automatically align with business need
• etc

BEWARE OF THE BULL
Making a business case

• The business case for continuous spans a continuum....
  – “No Brainer” – why aren’t we doing this already?
    • Perhaps 10% of cases
  – “No Way” – glad I still have some batch vessels!
    • Perhaps 10-30% of cases
  – “The Middle Ground” – maybe... and the battleground is here
EXAMPLES... THE TECHNICAL BIT
Skids and infrastructure at ICES

Integrated Modular skids

Continuous Oscillatory Baffled Reactor

Wiped Film Evaporator
Co-located with batch plant

- 60L standard batch plant
- Equivalent continuous scale
  20L/h nominal capacity
- And batch vessels can be used as continuous stirred tanks

Batch Reactor Systems
Development tools

- Tools as for batch development
- Calorimetry, batch small-scale Reactions, individual behaviour assessment (eg settling velocity)
- Use of PAT tools in development

APTAC

RC1 with Raman
4,6-erythronolactone

Facile

Solids/gas

And product recovery is horrific
Process development

- Developed and ran full scale batch process (60L) for comparison
- Carried out minimal additional development for continuous
- Hybrid processing adopted as back end problematic
The oxidation reaction

- Batch calorimetry indicates instantaneous reaction
But *in situ* Raman tells a different story

Start of salt formation

Sodium isoascorbate level falling

7.5 minutes

Sodium isoascorbate concentration

Erythronic acid sodium salt concentration

Erythronic acid sodium salt level rises
Skid 1

Ascorbic Acid

Mixing Ascorbic acid with sodium carbonate to pH 8.5-9.5 at amb via flow control.

Skid 2

Hydrogen Peroxide

- Acidification of mixture ex SM90201 to pH 3.5.
- Temp is not controlled.
- Pre-set flow rates

Hydrochloric Acid

- Heat Sodium ascorbate solution ex R3000 & mix with hydrogen peroxide at 40°C.
- If pH transmitter is available, pH can be controlled at 8.5 with Na₂CO₃ from Skid 1. Else preset the flow rates.

Continuous evolution of gases from R3000

Product in aqueous solution discharges into VE1100 for storage

Maintain temp @ 40°C

External pump

Skip cooling to amb step prior to acidification
## Some results

<table>
<thead>
<tr>
<th>Stage</th>
<th>Species</th>
<th>%w/w solution</th>
<th>Flowrate (kg/hr)</th>
<th>Flowrate (g/s)</th>
<th>Flowrate (mol/s)</th>
<th>Mol eq</th>
<th>Total mass (kg)</th>
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</thead>
<tbody>
<tr>
<td><strong>Salt formation (Phases 1 and 3)</strong></td>
<td>D-isoascorbic acid</td>
<td>7.7</td>
<td>9.60</td>
<td>2.67</td>
<td>0.21</td>
<td>0.0012</td>
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<tr>
<td></td>
<td>sodium carbonate</td>
<td>15</td>
<td>3.30</td>
<td>0.92</td>
<td>0.13</td>
<td>0.0013</td>
<td>6.6</td>
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<tr>
<td><strong>Oxidation (Phases 2 and 3)</strong></td>
<td>Hydrogen peroxide</td>
<td>30</td>
<td>1.05</td>
<td>0.29</td>
<td>0.09</td>
<td>0.0026</td>
<td>2.09</td>
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<tr>
<td></td>
<td>sodium carbonate</td>
<td>15</td>
<td>6.38</td>
<td>1.77</td>
<td>0.27</td>
<td>0.0025</td>
<td>12.76</td>
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<tr>
<td>*<em>Acidification <em>Batch Phase 4</em></em></td>
<td>HCl</td>
<td>18</td>
<td>4.17</td>
<td>1.16</td>
<td>0.21</td>
<td>0.0057</td>
<td>8.34</td>
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</tbody>
</table>
4DEL learning

• The first part of the process could readily be run continuously and with ease

• The appearance of solids and a solvent swap indicated batch for the back end...
  – We think there is a way, but it’s speculative

• Without end-to-end continuous there is no business case
3 stage process

Stage 1 – Reformatsky reagent formation

Stage 2 – Reformatsky reaction

Stage 3 – Aqueous quench using citric acid

Reformatsky Chemistry

Why continuous processing?

1. Reduced inventory – Inherently safer
2. Increased heat and mass transfer, allowing higher heat removal rate and mixing efficiency
3. Higher thermal inertia of the equipment due to higher mass/volume ratio of equipment including cooling/heating system to reactive mass.
4. Smaller equipment footprint, possible lower capital cost

This one is almost a “no brainer”
The data showed a rapid increase in both temperature and pressure of about 700°C/min and 50kPa/min respectively.
Example issue – insufficient cooling following benzaldehyde addition would give temperature excursion (even in continuous)

Two reactors in series provide:

1. Better distribution of heat across reactors
2. Better heat control
3. Higher surface area to mass ratio
4. Higher thermal inertia
Bench Scale Reactor System

- 400kg/yr throughput
Bench Scale Reactor System

Zinc Activation

Reagent Formation

Phase separation
Results – a Happy Surprise

Continuous (10ml/min)

Batch 40ml
Benefits of continuous Reformatsky process:

1. Reduced inventory – Inherently safer
2. Increased volumetric heat transfer, giving more robust safety case
3. High throughput - bench scale throughput is comparable to a small/medium size batch plant
4. Higher selectivity and purity
Reformatsky learning

• Give or take some solids control issues the process could readily be run continuously and with ease
• It allowed us to run a process we would not have taken on at 60L scale and to produce at a comparable rate
• There is a good business case – and encouraged, we are now close to running continuous Grignard including making the reagent
What we learned about implementation and skills

• While at first the problems seemed daunting, with a little determination they were resolvable
  – Inexperienced technologists delivered successful outcomes in realistic times and without excessive effort.
  – Didn’t need to draw on advanced modeling or simulation.
  – Good quality (standard) experimental and sound chemistry/engineering sufficient.

• The set of equipment and skills we have are flexible enough to take on a good range of processing problems
  – Continuous processing is within the capabilities of many organisations

• Benefits are not automatic from “going continuous”. 
SO WHAT ARE THE BROADER IMPLICATIONS TO DEVELOPMENT?
Things could be better. I can see what might be done. I need a demo. I can do, but need a business case. I have the skill base to do regularly. This is the way I do things.

Effort vs. Innovation progress. Facilties innovation is about here. Intensive / innovative / continuous processing is about here. Progress since 06.
Things could be better. I can see what might be done. I need a demo. I can do, but need a business case. I have the skill base to do regularly. This is the way I do things.

Effort

Facilities innovation is about here
Intensive / innovative / continuous processing is about here
That was fun, could we do it again?

- Delivery of a one-off project by specialists is relatively easy with plenty of time
- Learning from them is harder
- Embedding as a way of working is difficult
  - Skill set changes – adopting new skills where needed (modeling? PAT for control?)
  - Decision making process modifications
  - Laboratory and pilot plant resources and capabilities
  - Integration with other activities – SHE assessment, purchasing and supply
  - Cutting across organisational boundaries
Two key Gaps

• Process understanding
  – How much is enough?
  – How to capture and exploit?

• Design methodology
  – Organising the design activity to be fast and efficient
  – Minimising rework and cost
Gathering and processing understanding

• Mathematical modelling / simulation
  • Viable but very expensive in primary, reliant on good experimental data
  • Tools weak for secondary

• Statistics / OR techniques
  • Links well to experimentation BUT
  • Not understanding based and not design-friendly
  • Too many variables (especially in secondary)

• Structured qualitative approaches
  • Various in house and proprietary methods eg BRITEST
  • Used to capture and exploit understanding in primary and secondary processing
Design methodology

• The Unit Operation approach?
  – Represent (and even optimise) process as a set of well-defined equipment-based operations. SUMS
  – Much less effective for processes where the properties that define a stream are complex and even undefined

• The way chemists put together a process
  – Recipe-based, quite like cookery. LAB
  – Overly experiential and experimental so likely to miss non-obvious opportunities

• The “A Team” approach
  – Put the best guys on it. LAB+SUMS+SMARTS
  – Not feasible if you want to design a lot of processes
Conclusions

• The battle now is moving from the business case to having an embedable, teachable method

• Much underpinning work remains to be done to provide the required understanding
  – But it’s not seen as sexy

• There are still massive challenges in allowing all developers to “see the big picture”
  – But it is a massively difficult problem
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