FlowCAT - continuous flow reactor system for hydrogenation screening and small scale production

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Terminology in catalytic reactions

- Homogeneous catalysis
- Heterogeneous catalysis
- Fixed bed or Plug Flow (continuous) and stirred/Batch reactors

Fixed Bed is special case of continuous flow type.

better chemistry - faster
Terminology in catalytic reactions

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Crude Mathematical equivalence of flow and batch reactors

Residence Time = Volume/flow rate

Equivalence – time in batch reactor equates to position down plug flow. Changing flow rate changes residence time: corresponds to batch time.

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Closer Mathematical equivalence of Reactors

Many CSTRs in series

Co-Current feeds

PFR (plug flow)

Vertical orientation (top-to-bottom)

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Lab-scale flow Systems – Screening and Prep-scale

**Screening**
- Catalyst in small cartridge, very high catalyst loading
- Conversion limited by hydrogen solubility (at high conc.)
- Typical throughput 1+ g/day

H-cube (Thales-nono) well established in this field. Limited to hydrogenations and to screening applications only.

**Prep-scale**
- Traditional “tubular” reactor
- “Trickle flow” mode demonstrated
- High conversion far exceeding solubility limit
- Typical throughput 100+g/day

No fully automated product established up to now.

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FlowCAT Package

• Developed to bridge screening and prep-scale needs
• Not limited to hydrogenations
• Fully software controlled
• Does not require high pressure expert for operation

Trialled at length by Pfizer for hydrogenation applications. Some results to follow.

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flowCAT Feed Section

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flowCAT Product Sampling and Collection
FlowCAT Typical Specification

- Standard lengths: 15cm (6”)
- Two standard int. diameters: ½” (12mm) or ¼” (6mm)
- Volumes: 2.8ml, 12ml (in hot zone, approx).
- Standard ovens: heated lengths 10 cm
- 100bar/300C standard (higher temperature/pressure options)
- One liquid and one gas feed standard, other combinations possible.

Not limited to hydrogenations

Not limited to heterogeneous catalytic reactions

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Flow Capacity of Tubular Reactors

Very wide range of flows are possible, subject to pump range and pressure drop across reactor.

Gas and liquid flow rate determines:
- the “pattern” of flow
- Gas/liquid mixing and contact with catalyst
- Conversion
- Ease of scale up

Flows rates widely selected to favour that “trickle bed” mode.
Trickle Bed Flow Regime

Most common mode of operation for tubular fixed bed reactors

- Fixed bed of inert and catalyst pellets, former occupying large volume (50% or more)
- Co-current downward flow of gas and liquid
- Leads to gas dispersed, liquid continuous phases around solids

General Plot for flow regime prediction

Co-current downflow regimes for a given system (Westerterp and Wammes. 2002)
Hydrogen plus Nitrobenzene/solvent
G/L vol. ratio 20 (100max, gas at NTP)
Hydrogen excess typically 1.83 x stoich.

\[
\text{C}_6\text{H}_5\text{NO}_2 + 3\text{H}_2 \rightarrow \text{C}_6\text{H}_5\text{NH}_2 + 2\text{H}_2\text{O}
\]
Hydrogenation of (4%) nitrobenzene to aniline

0.25” internal dia.
Temperature 30 deg C
1% Pd/C mixed with glass beads
4ml packed volume (30% voids)
Catalyst mass 0.1g (0.2 and 0.4g alternates)

Product (Aniline), analysed by GC

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Trickle Bed Flow – Lab Reactors

Diagram below shows likely position of bench scale flow reactors

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Hydrogen consumption with pressure
Hydrogenation of nitrotoluene to aniline

Hydrogen 1.83 x stoichiometric
(= 20 n ml/min)
Catalyst loading 0.1g
Bed volume 4ml (30% void)
Hydrogen consumption with at different substrate flows

Hydrogenation of nitrotoluene to aniline

- Hydrogen 1.83 x stoichiometric
  (= 20 to 80 n ml/min)
- Catalyst loading 0.1g
- Bed volume 4ml (30% void)
Fractional conversion with pressure
Hydrogenation of nitrotoluene to aniline

Liquid flow = 0.5ml/minute
(residence time approx 2.4 mins)
Hydrogen 1.83 x stoichiometric
(= 20 n ml/min)
Catalyst loading 0.1g
Bed volume 4ml (30% void)
Conversion at different gas flows
Hydrogenation of nitrotoluene to aniline

Hydrogen flow as fraction of stoichiometric

Liquid flow 1ml/minute
Catalyst loading 0.1g
Bed volume 4ml (30% void)
Comparison with Stirred Reactor Data

- **HP Chemscan**
  - 8 x 16ml reactors

- **Auto-MATE**
  - 4 x 100-300ml HP reactors

- **AUTOLAB**
  - 1000ml HP glass reactor

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HYDROGENATION 100ml stirred HP auto-MATE

**Catalyst loading approx 1/100th of flow reactor**

- **10 bara**
- **3.4 bara**

50ml 4% nitrobenzene in decanol, 0.35g Pd/C catalyst – parallel hydrogenations at 40°C, 1500 rpm

Typical residence time in flow tests

- 100 Psi
- 50 Psi
- 75 Psi
- 125 Psi
- 150 Psi
Time to 100% conversion in stirred reactors (5 to 500ml)

Data from three sizes of stirred reactors

4% nitrobenzene Pd/C catalyst, 6.9 bar

Residence time in flow tests

Catalyst concentration (g/l)

Catalyst conc in flow tests
Hydrogenation Screening?

**H-cube**
- Hydrogen generation in situ – safety advantage
- Low flow only, limited to screening at low conc or small scale compound prep (eg med chem)

**flowCAT**
- Needs hydrogen supply – less safe potentially
- Low flow version feasible, cartridge designs being tested
- Already in use for prep-scale work

**Can flowCAT be adapted for screening?**

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Screening with H-cube: Conversion Limited by hydrogen solubility

PhCHO 0.35 M $\rightarrow$ 10% Rh/C $\rightarrow$ PhCH$_2$OH
EtOH, 80°C

(courtesy J Hawkins, Pfizer Inc, August 2010)

Conversion limited by H$_2$ solubility which increases with pressure
Conversion Limited by Solubility - flowCAT

Hydrogenation of nitrotoluene to aniline

Hydrogen added to maintain operating pressure, no excess H2

Gas consumption (mmol/min)
Gas Solubility

Gas feed on pressure
Liquid flow 0.5ml/minute
Catalyst loading 0.1g
Bed volume 4ml (30% void)
**flowCAT in commercial R+D**

- Controlled by commercial, well established software/electronics, fully developed
- Ideal for process development and large enough for prep-scale production
- Possible to integrate with DOE package and optimise totally automatically.

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PAT integration - Real-time monitoring and feed back control

In-line sensor (e.g. FTIR flow cell), almost real-time data

Product from flowCAT

GAS VENT (pressure control)

Gas-liquid separation

Virtually no product hold up (a few ml)

winISO real-time software monitoring and feedback control

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Integrating Process/Analytical Data

process data

schedule

chromatogram
data analyser

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Process Development Examples using DOE

- Samples can be taken at each change of operating condition
- Wide range of conditions can be tested, sequentially, without operator involvement (no need to clean reactor after each change)
- Integrated with Stavex software

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EXAMPLE 2: Conversion of chloronitrobenzene to chloroaniline

\[
\text{NO}_2 \quad \text{Cl} \quad \rightarrow \quad \text{NH}_2 \quad \text{Cl} \quad \rightarrow \quad \text{NH}_2
\]

\[
\text{H}_2 \quad \text{Pd/C} \quad \text{H}_2 \quad \text{Pd/C}
\]

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GC Traces: chloronitrobenzene to chloroaniline

Fractions: 55.8% chloronitrobenzene
15.2% chloroaniline 6.1% aniline
Conditions: P=5bar  T=22°C
Residence time=0.5min

Fractions: 24% chloronitrobenzene
43.4% chloroaniline
24.2% aniline
Conditions: P=10bar  T=61°C
Residence time=1.96min

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Low and high pressures yield the better conversions at medium residence times.
chloronitrobenzene to chloroaniline (Temp – residence time)

- Chloroaniline reacts to yield aniline at high temperatures
- Conversion favoured by low temperatures and high residence times
- Wrong range of conditions selected – go back!

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chloronitrobenzene to chloroaniline (Pressure – residence time)

- mid-range residence time favours chloroaniline
- High or low residence time favours aniline

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chloronitrobenzene to chloroaniline (Temp – Residence time)

- Mid-range residence time and low temperature favours high yield chloraniline
- Aniline favoured by high or low residence time

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Sterioselectivity through flowCAT Process Control

Flow
H₂, Rh/C
1 equiv MsOH
MeOH

90 bar
80 mL/min H₂
1 mL/min solution
20 mL/g substrate

72 g/day throughput
from 1/4" ID column

• 100 g hydrogenated with 1 g of catalyst which was still active

(Example courtesy J. Hawkins, Pfizer Inc, August 2010)

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Diastereoselectivity and Conversion vs. Pressure

Increased diastereoselectivity at the higher pressures easily accessible in flow.

80 mL/min H₂ (STP), 0.5 mL/min solution, 20 mL/g substrate
flowCAT - CONCLUSIONS

• Bench-scale flow system, industrially proven development

• Wide range of operating conditions

• Controls all important variables and reports progress in real time.

• Full integration of third party sensors for PAT

• Low flow version feasible, cartridge designs being tested

• Already in use for prep-scale work

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