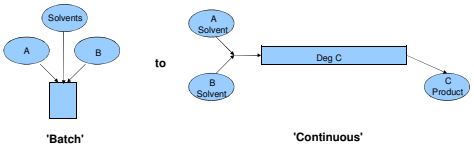
CONTINUOUS REACTION DEVELOPMENT - DEMYSTIFIED

Introduction

The application of **Continuous Processing** and in particular **Continuous Flow Chemistry** is gaining ever increasing interest within the Pharma and Fine Organics sectors of the chemical industry and Academia. However it remains under utilised, in part due to the perception that it is a specialist technology, employed by experts.

This poster helps demystify Continuous Reaction Development by breaking it down into **Six Simple Steps** - **'The Six Simple Steps to Success!'** At the end of which, you will realise that Continuous Reaction Development is nothing more than good Batch Reaction Development!



'Batch' 'Continuous'

To fully exploit the advantages of continuous flow chemistry

In order to achieve this a range of equipment for lab scale evaluation in flow is required, which is **affordable**, can be deployed in every R&D laboratory and is **easily used by every chemist.**

To meet these needs **Cambridge Reactor Design (CRD)** offers a **Mixed - Continuous Stirred Tank Reactor (CSTR) unit – The Chameleon.**

'Chameleon'

And a **Tubular - Plug Flow Reactor (PFR) unit – The Salamander.**

'Salamander'

Why study reactions in flow?

The advantages of continuous flow reactions vs. batch reactions are well documented. Some key examples are:-

- **Consistent quality product** – No batch to batch variations – No/fewer batch failures
- **Safer operation of potentially hazardous chemistry** – Low inventory of materials in process at any instance in time – New, more efficient, cheaper routes
- **No/less scale-up issues** – Reactions run under more controlled conditions – Less issues with changes in impurity/selectivity profile on scale-up
- **Flexible production** – Run for longer/shorter time to match demand
- **Small footprint plant** – Can be cheaper to build and run than batch plant producing the same quantity of material.

Switching from Batch to Continuous The 'Six Simple Steps to Success!'

More detail available from CRD

Steps 1-5 can easily be completed in a working week!

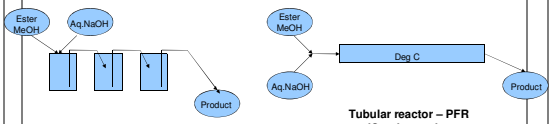
Step 1 - Vision

- Start with the end in mind - What might the process look like in flow?
- Process = Chemistry + Equipment

eg.

$R\text{-}CO_2Me + aq.NaOH \longrightarrow R\text{-}CO_2Na + MeOH$

'2M sodium hydroxide (10mL) is added to a solution of the ester (10mmol) in methanol (10mL) and the mixture stirred at room temperature overnight.'



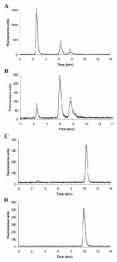
Continuous stirred tank reactor – CSTR 'Continuous'

Tubular reactor – PFR 'Continuous'

Step 2 – Analysis

Whether you are investigating and developing a reaction in batch or flow, a means of comparing and monitoring reactions is required.

eg. HPLC, GC, NMR – standard techniques



Step 3 – Solubility

The presence of solids in flow require special consideration, and are thus best avoided!

- Measure the solubility of all materials in a range of solvents to generate options.
- Record in a traffic light diagram – ongoing process

Solvent	Temp	PhCO2Me	PhCO2H	PhCO2Na	NaOH	Octanol
MeOH	20	Mis	~ 250	~ 125	~ 25	~ 125
H2O	20					
50% aq. MeOH	20					
	50					
Key						
> 100mg/mL						
<100, >50mg/mL						
<50, >10mg/mL						
<10mg/mL						

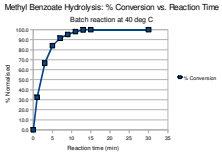
Step 4 – Batch reaction studies

First study your reaction in batch using standard laboratory equipment!

A lot going on here, so start simple and make more complicated as required!

- Determine reaction time
- Check for solids
- Look for impurities
- Understand the critical parameters, and effect on the above

The goal – Define conditions to be trialled in flow - ie ideally, rapid/fast, homogeneous mono-phasic chemistry



Thus,

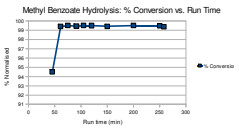
- 1M Aq. NaOH (1vol, 3.079equiv)
- 0.325M methyl benzoate in methanol (1vol, 1equiv) containing 22mg/mL 1-octanol (internal standard)
- 40 deg C

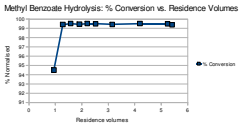
Reaction well stirred and monitored to time.

Step 5 – Flow reaction studies

Trial process in flow at lab scale – have a range of lab scale equipment available (Chameleon, Salamander & pumps)

- **Mixed reactor – CSTR** – Start with a cascade of 4 reactors and a total flow rate that gives a residence time of 3 x the batch reaction time (3 reactors, 5 x the batch reaction time)
- **Tubular reactor – PFR** – Start with a total flow rate that gives a residence time of 2 x the batch reaction time
- Run the process for ideally 10 residence volumes (minimum of 5) to check the process has reached 'steady state', and no unidentified critical parameters identified!
- Adjust/hone process if/as required





NB – Steps 1-5 can typically be completed in a 'working week'!

Step 6 – Technology transfer

What next? What is the end point of your work?

- Scientific point proven – reaction best run in continuous or batch?
- Training in continuous reaction development achieved – knowledge and experience in flow chemistry becoming more important in industry
- Add on additional reactions?
- Add on continuous work-up?

Move on to make/production

- Tens to hundreds of grams – use lab scale equipment for fast make
- 1 to 10kg – use larger, still lab based equipment (kilo-lab makes)
- Tens to hundreds of kilos – pilot plant scale – engineering project
- Tonnes – production plant scale – engineering project

NB - CRD are here to help you through the process

CSTR vs. PFR – Why choose CSTR

PFRs have their place as do CSTRs, but to get started quickly and easily in continuous processing at low cost, existing plant (Stirred Tank Reactors - STR) can be converted to CSTR operation.

- Existing plant and vessels can be used – no new build
- More robust processing – less prone to mixing issues
- Compatible with a wider range of reaction times – CSTRs are more suitable for longer reaction times
- Compatible with solids – CSTRs less prone to blockage by transient solids (can be designed for reactions that produce solids and crystallisations)

Conclusions/recommendations

- Continuous reaction development is nothing more than good batch reaction development.
- The work is never wasted as you will always have a better batch process and greater process understanding.
- Having a range of lab scale continuous flow equipment readily available will allow you to select the best process (chemistry and equipment) for your product.
- The Chameleon and Salamander can also be used for 'make' of modest quantities of product – ten's to hundred's of grams.

Contact CRD for:

- Your **lab scale continuous flow equipment** – it does not have to be expensive
- **Continuous Reaction Development consultancy** – short circuit the learning process
- **Rapid bespoke reactor design**, and build to kilo-lab scale
- **Additional PRD time saving platforms** – extractions, filtrations (and washing and drying)

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