Continuous Flow Chemistry Lab

Flow Chemistry
Planning, Execution and Scale-up

Step by Step Tutorial on how to go about doing
A reaction in flow for the first time and then
How to go about optimization and scaling up

Why Flow from Batch

- **Poor control in batch process (very tight process conditions)**
- **Highly exothermic reaction**
- **Multistep reaction with unstable or hazardous intermediate**
- **Selectivity is an issue in batch**
- **Difficult to prevent side reactions**
- **Particle size need to be controlled**
- **To reduce effluent, improve safety, decrease capex and opex cost**
- **Chemistry in New Space (HTHP)**
- **Chemistry not possible in batch: Ultrafast reactions or intermediates**

Continuous Flow Chemistry Lab

Almost, every type of chemistry

has already been developed via CFP

Please Refer to literature

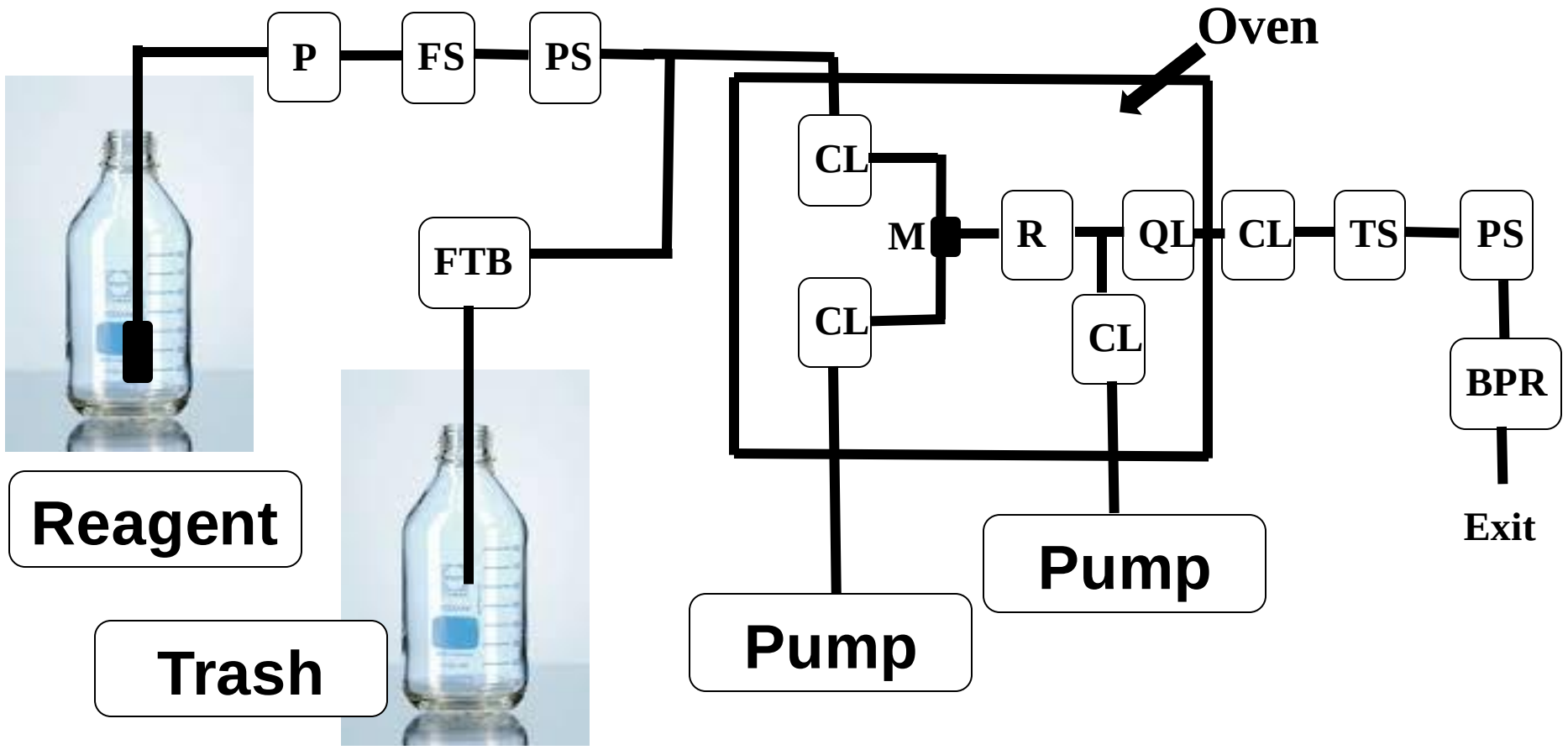
before you start your flow reaction

Why Flow from Batch

Decreasing ease of doing flow reactions:

- **All the reactants are either liquid or Gasses**
- **If some of the reactants are solid but can be dissolved in a suitable solvent**
- **If solid reagents can not be avoided, then Cartridge Type reactors are suited, if possible (by immobilization)**
- **Air Sensitive Reagents need special care in selection of pumps**

Ideal Flow Setup



P = Pump; FS : Flow Sensor; PS : Pressure Sensor;
FTB: Flow through back pressure regulator
CL: Conditioning Loop; R: Reactor; QL: Quenching Loop
BPR: Back Pressure Regulator; M : Micromixer

Flow Reaction Planning: Step A

- Write the reaction scheme
- Make the list of all the reagents and solvents
- Decide the following:
  - Reaction Temperature Range
  - Pressure Range
  - Reaction Times Range
  - Concentration of each reagent
  - Solubility of each reagent in respective solvent at that concentration
  - Solubility of the intermediates/product produced during the reaction

Flow Reaction Planning: Step A

- Check the reaction in batch mode to confirm the absence of any precipitation or surprises.

- Decide the method as how you are going to quench the reaction (to avoid continuation of reaction if it happen at RT also)

- Decide how you are going to work up the reaction mixture for analysis.

- Decide which method you are going to use to analyze (HPLC/GCMS/NMR etc.)

- Develop the method to analyze the reaction wherein the method should clearly distinguish between each reagent as well as well as each product.

Flow Reaction Planning: Step B

Prelim Lab Investigation : Yes and No Only

- Make the final list of all the reagents and solvents.
- Preferably use Syringe Pump, PTFE Tubes and Connectors.
- Oil/Cooling Bath for controlling the temperature.
- In case you have to use metal parts for HT or HP, make sure the compatibility of MOC of all components (including BPRs) with all the reagents used.
- If the reaction is extremely fast, choose the micromixer.
- If the reaction is at high/low temperature, use the preconditioning loops for all reagents and quencher.

Flow Reaction Planning: Step B

Prelim Lab Investigation : Outcomes

- Based on the few prelim results, you should get very good idea of:
  - Is the reaction flow compatible
  - Resident time, Reaction Temperature and Back Pressure
  - Importance of Micromixer, BPR, Quencher and other components

Flow Reaction Planning: Step C

Lab Scale Optimization: Standard Flow Reactor

- Based on the outcome of **STEP A**, setup a standard flow reactor
  - This could be a home made setup or commercial one
  - Make sure to follow the same instructions as for Step A for selection of various components
  - At this stage you will have a good idea if you need the distributive dosing (to improve selectivity or to prevent side reactions or decomposition)
  - Test and calibrate the setup for the flow range you are going to use

Flow Reaction Planning: Step C

Standard Commercial Lab Scale Flow Reactor

- **Vapourtec (Very diverse in terms of capabilities)**
- **Kobelco (Metal)**
- Corning
- **Ehrfeld (Very diverse in terms of capabilities)**
- Nakamura Japan (http://www.nakamura-gp.co.jp/en/product04.html)
- **Labtrix Chemtrix (Very diverse in terms of capabilities)**
- **Synthetron (Kinetichem) (Metal)**
- **ACR (AM Technologies) (Metal)**
- **Autichem (Metal)**
- **Thalesnano (Hydrogenation, Fixed Bed, HTHP)**
- AMAR
- 3D Printed Reactors

Flow Reaction Planning: Step C

Lab Scale Optimization: Standard Flow Reactor

- Run couple of reactions to get feel of the outcome as well as what are the factors which affect the reaction (T, RT, Exo/Endo, Slurry, Quenching, Distributive dosing, concentration etc.)

- **CAUTION:** Make sure to have detailed planning of the complete reaction conditions in terms of temperature, concentration, resident time (since these parameters are easy to change, one land up in increasing concentration or temperature beyond the limit of the tools).

NEVER CHANGE CONDITIONS/RANGE ON FLY

Flow Reaction Planning: Step C

Lab Scale Optimization: Standard Flow Reactor

- It will be highly advantageous to use IN-LINE TOOL for reaction monitoring as this will save lot of time and reagents. It will also help you in understanding kinetics, mechanism and final optimization.

- **If you have the IN-LINE Tool, then best is to USE DOE for Screening and Optimization**

Flow Reaction Planning: Step C

Lab Scale Optimization: Standard Flow Reactor

- Make sure to setup the reactor and test/calibrate it with solvent on first day.
- If possible prepare the reagent solutions also on first day. If not then prepare the next day in the early morning hrs.
- You should calculate the time as well as the amount of reagents required based on the experiments designed.
- Make sure all the experiments can be performed in single day so that you can clean the reactor at the end of the day

NEVER LEAVE THE FLOW REACTOR IN REAGENTS

Flow Reaction Planning: Step C

Lab Scale Optimization: OUTCOMES

- **You will have optimized RT, T, C, P, mode of dosing, mode of quenching, yields, selectivity, effluent volume etc.**

- **This should enable you to take a very informed decision about the advantages (both qualitative and quantitative) of Flow Process**

- **If required, you should be able to have CALORIMETRIC Data for the optimized reaction**

Flow Reaction Planning: Step D

Scale-Up : Standard Interface Flow Reactor

- Ehrfeld (Highly Exhothermic Reactions, LONZA, MIPROVA)
- Corning/LTF (Highly Exhothermic Reactions)
- Chemtrix (Highly Exhothermic and Corrosive Reactions) or Kobelco (Metal)
- Spinpro (FLOWID) (Highly Exhothermic Reactions)
- ATR/Autichem (Plugflow with efficient mixing, slurry, biocatalysis)
- Thelesnano (H-Cube Midi and Pro, Chemistry in new space: HTHP)
- OBR (Crystallization, good heat transfer)
- 3D Printed Reactors
- AMAR 3, 4 and 5

Flow Reaction Planning: Step D

All Reagents Liquid/Solution/Gas with no solid Dosing/formation:

- If the reaction is fast and exothermic, metal compatible : **Spinning Disk, Kobelco**
- If not very fast, exothermic, not metal compatible : **Chemtrix SiC**
- If slow reaction: **ACR/Autichem**
- Cheaper option is **Amar 3 or 4 reactors** if compatible with Metal (issue is the scale up needs again optimization as no interface module or data is available)
- Another Cheaper option is to build your own **LTF Glass Plates** (Scale up need to be optimized).

Flow Reaction Planning: Step D

All Reagents Liquid/Solution/Gas/Slurry and solid/slurry formation:

- If reaction is fast: **Spinning Disk (FLOWID)**
- If reaction is slow : **ATR/Autichem**

Flow Reaction Planning: Step D

Crystallization or Nucleation or Nanoparticle Synthesis or formulations:

- ATR/Autichem
- Spinning Disc if the reaction is very fast
- Oscillatory Baffle Crystallizers (not reactors), so only for crystallization.

Flow Reaction Planning: Step D

Slurry (non Settling) :

- ATR/RTR/Autichem
- Spinning Disc if the reaction is very fast

Flow Reaction Planning: Step D

Heterogeneous Catalysis :

- ATR/RTR/Autichem
- Spinning Disc with coated disc if the reaction is very fast
- Standard Fixed Bed Reactor

Flow Reaction Planning: Step D

Biocatalysis:

- ATR/RTR/Autichem

Flow Reaction Planning: Step D

Hydrogenation, Ozonolysis, Deuterium labelling:

- Thales Nano H-Cube or D-Cube or O-Cube. Scale up is also available upon request

Flow Reaction Planning: Step D

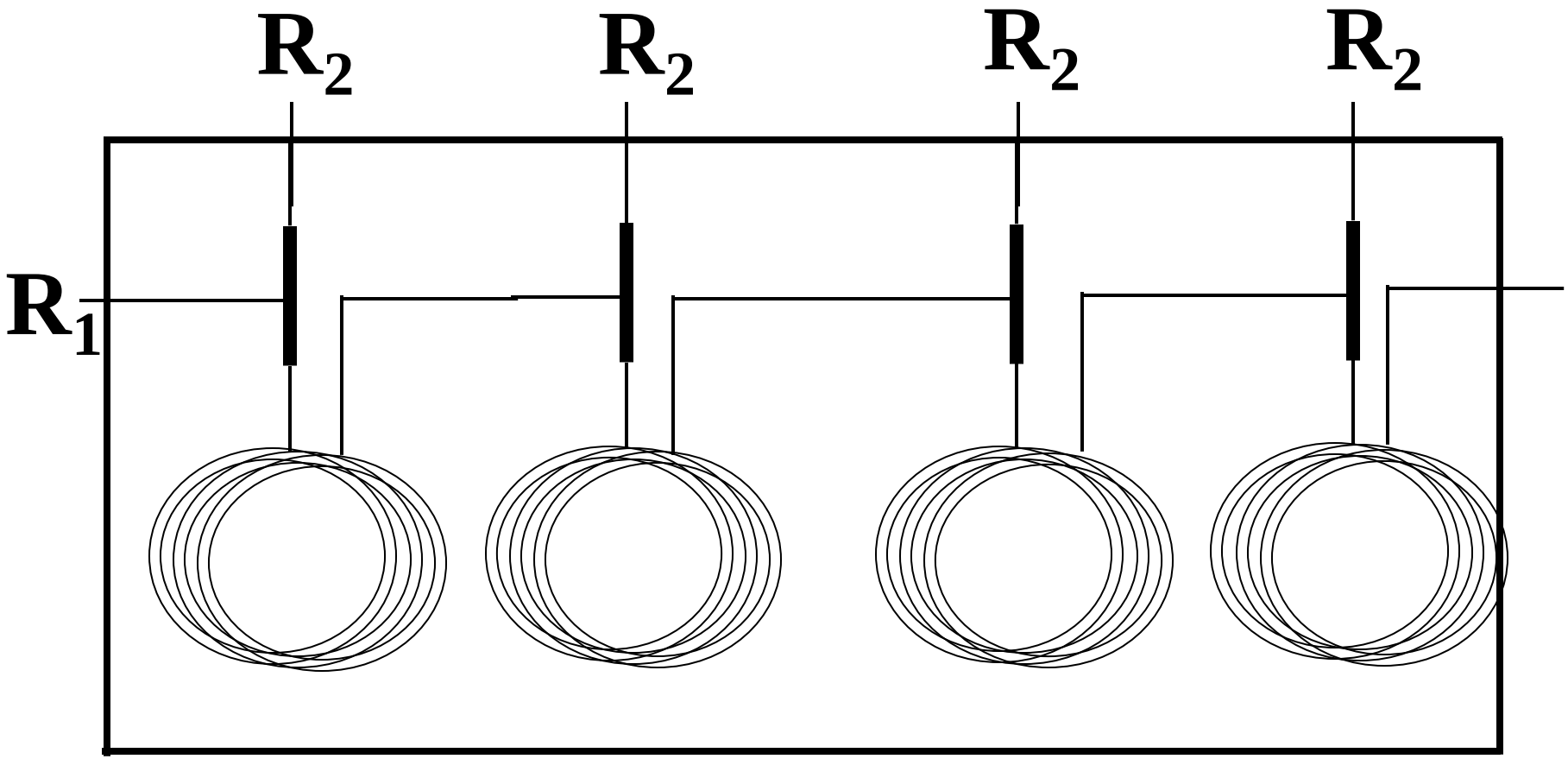
High Temp. High Pressure: Chemistry in New Space:

- Thales Nano Pheonix (450 C)
- Ehrfeld High Temperature Reactor (600 C)

Pumps

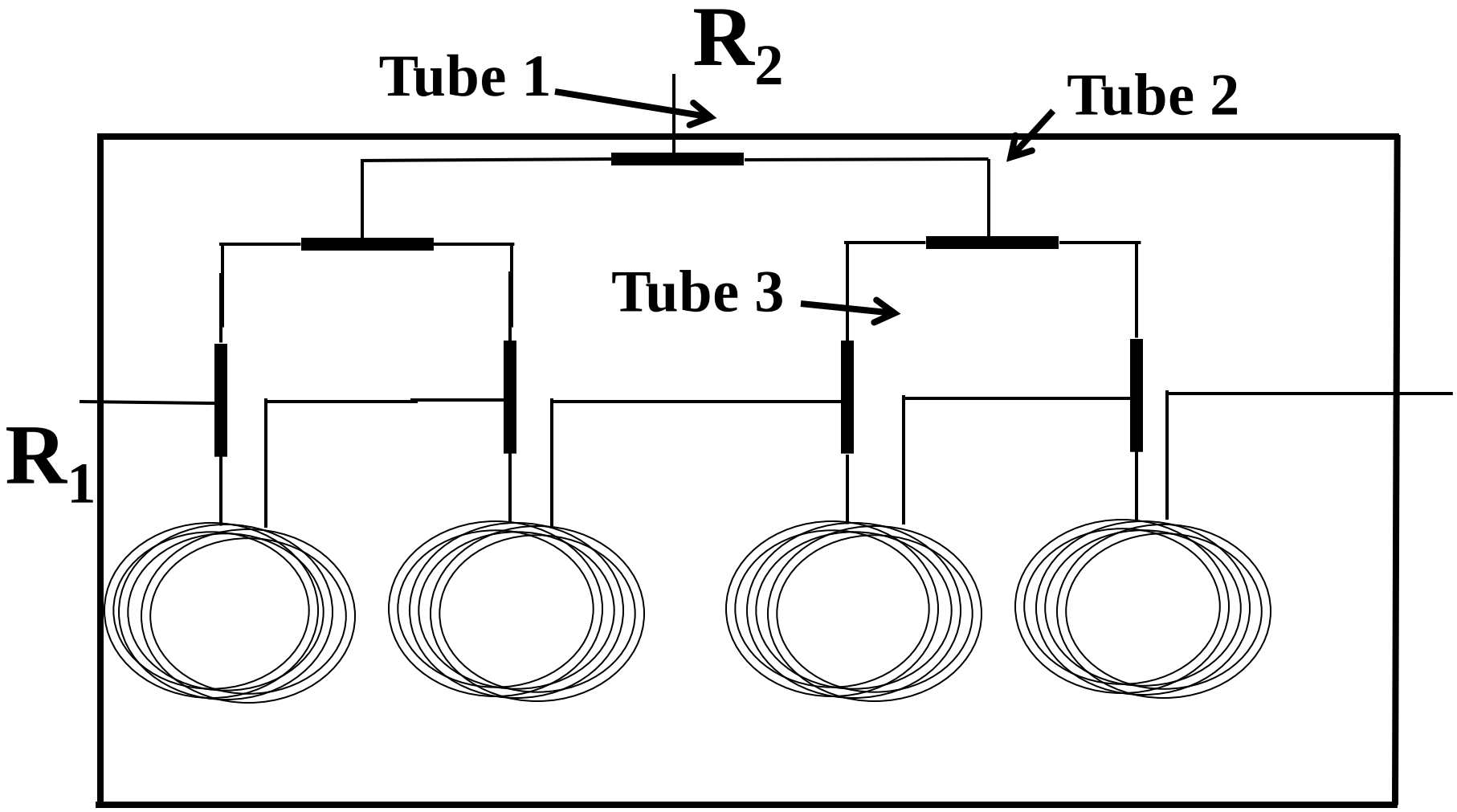
- Air Sensitive Reagents: Magnetically Coupled Gear Pumps with MFC
- For Rest: Many options based on MOC Compatibility

Distributive Dosing



NEED FOUR PUMPS for R_2

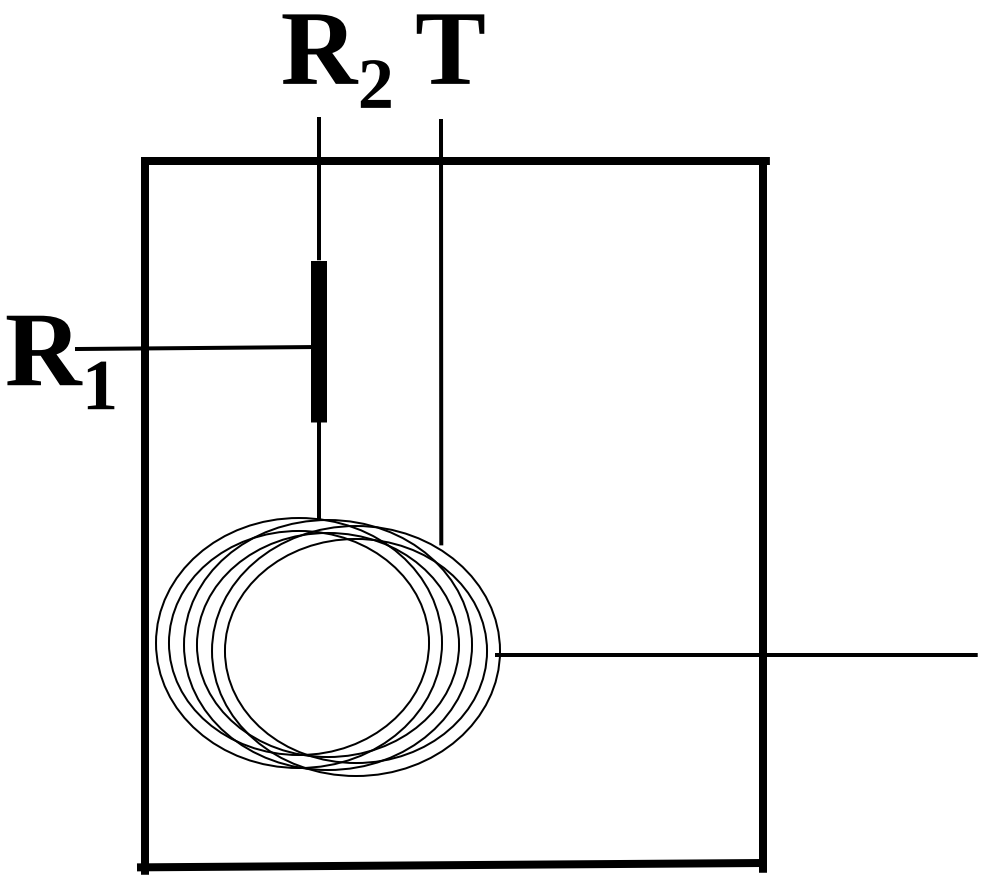
Distributive Dosing



Diameter of Tube 3 ≤ ½ of Tube 2 ≤ ½ of Tube 1

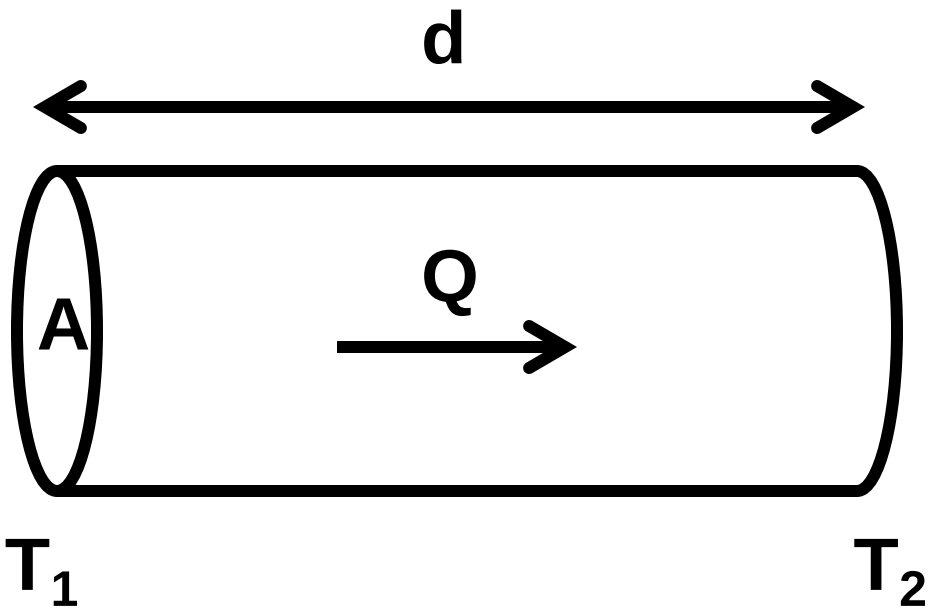
NEED SINGLE PUMP for R_2

Reaction Calorimeter



Measure heat supplied as a function of flow rate to keep T constant

Heat Transfer

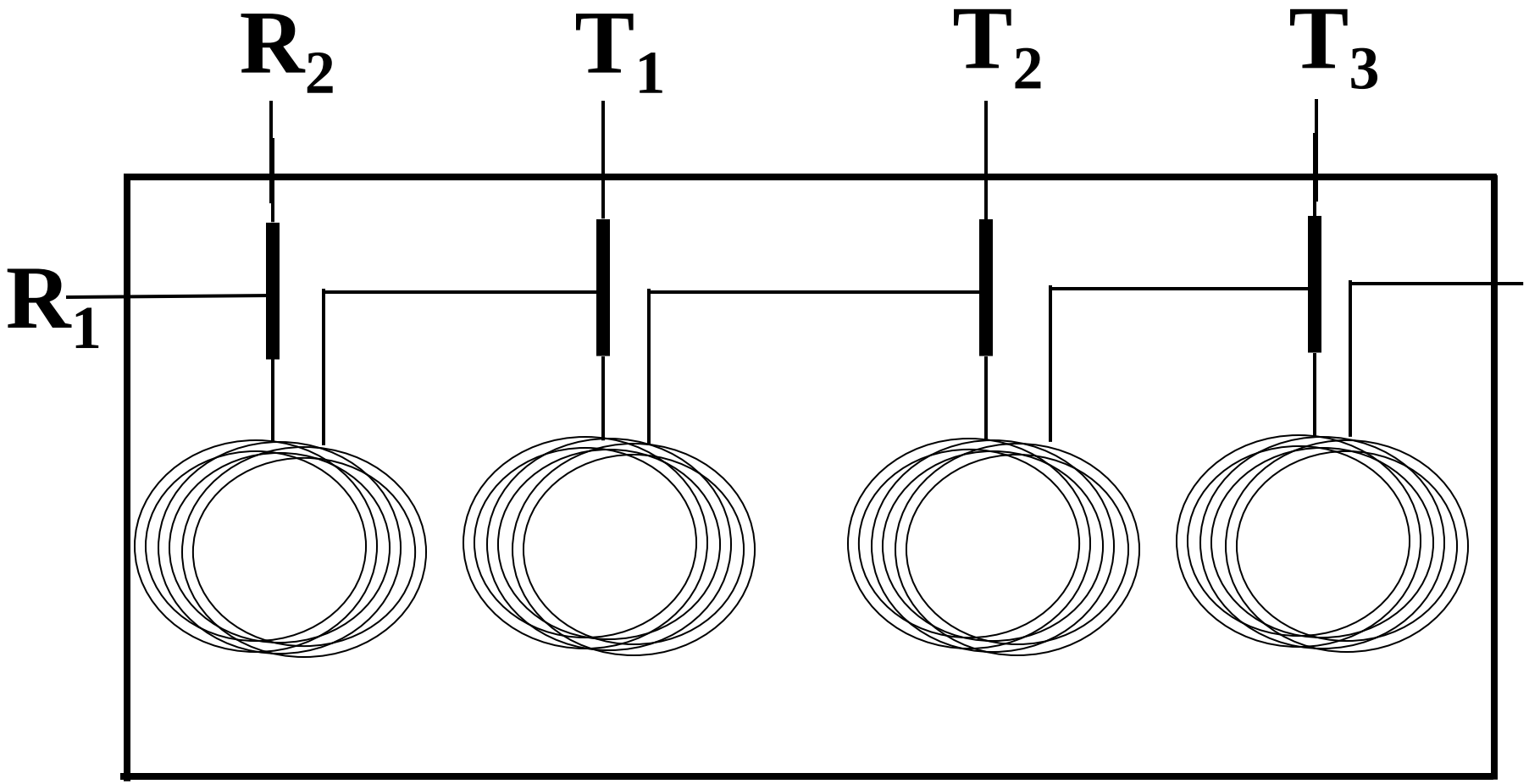


$$\frac{Q}{t} = -kA\frac{T_1-T_2}{d}$$

k is thermal conductivity; d is distance

A is surface area

Reaction Calorimeter



Increase flow rate till T_3 equals to thermal fluid temperature

Continuous Flow Chemistry Lab

SYSTEM (Digital or Analog)

- Pumps
- Tubes (Connections)
- Fittings (for connecting tubes)
- Micromixers and Reactors (tube, chip, disks…)
- Temperature Controller
- BPRs
- Fraction Collector
- Pressure Sensors
- Temperture Sensors
- Flow Sensors

Each Component is also Chemical, T and P sensitive

SYSTEM (Digital or Analog)

MAKE SURE MOC, Temp. and Press. Rating of

Each Component, Each Fitting, Each Connector is

COMPATIBLE WITH REAGETNS/SOLVENTS

&

REACTION CONDITIONS

Ideally one should always use

Preconditioning Loops
&
Micromixer

before the resident time unit

Continuous Flow Chemistry Lab

Preconditioning Loops (for each reagent)

To avoid part of resident time unit for reaching

REACTION TEMPRATURE leading to error in RT

(Function of ID and flow rate)

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System Pressure Drop (Function of Flow Rate)

||| **or Less than**

Pumps Pressure Ratings (Function of Syringe Size)

System Pressure Drop

Sum of Pressure Drop of each component

For Standard Components, it is available directly

For Loops and non standard components, calculate theoretically assuming a pipe of known ID and L

IDEAL SITUATION: connect each component and use HPLC pump

System Pressure Drop

Sum of Pressure Drop is a function of flow rate

Flow Rate:

Typically from few seconds (10) to tens of minutes (30)

IDEAL SITUATION: connect each component and use HPLC pump with varying flow rate

Pumps

Pressure Rating, MOC of wetted parts and Flow Rates are very important for any pump.

For HPLC/Piston Pumps, These are fixed and readily available

For Syringe Pumps, These need to be derived from

- **Linear Force (Kg, Pounds or Newton)**
- **Step Resolution (micrometers or nanometers)**
- **Accuracy and Reproducibility**

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General Thumb Rule

Ignore the 15% of lower and upper flow range

as well as

Operate 20% below the max allowed pressure

Most Important Rule

Ideally connect all the pumps and system components and then calibrate the system at 5-10 different flow range within the allowed range. This can be done by collecting the required volume for few minutes (average of four readings at different times)

IF CORRECT, YOU ARE READY TO GO

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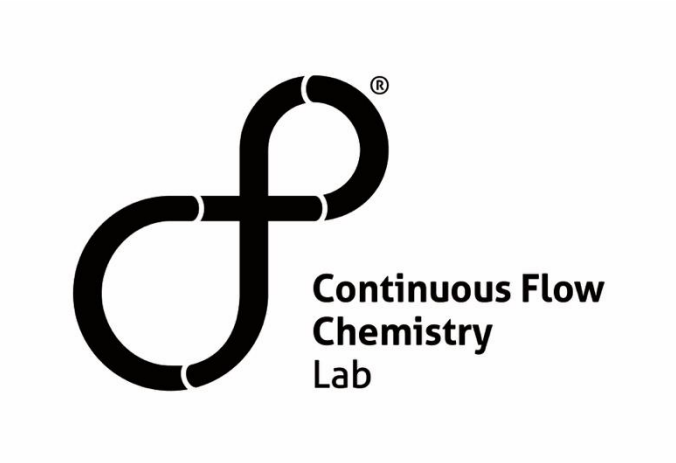
Process Intensification: Tutorial



Process Intensification

How Does one Intensifies a Reaction

↓

Limited by Solubility (for solid reagents)

Temperature

Mixing

Solid-Solid Reaction

Process Intensification

IMPORTANT

Document everything from here in your notebook

Process Intensification

- Write the reaction scheme (Fully Balanced)
- Write down all the possible by-products
- Write down complete mechanism (Product and By-Products)
- Understand the role of each reagent or intermediate
- Understand if any of the product or by-product interact with any reagent or among themselves
- Check maximum solubility of each reagent in various solvents
- Decide which solvent to use (based on precedence or experience)

Process Intensification

- **Identify the limiting reagent and solubility (Balanced Equation)**
- **This will be the ultimate intensified state wrt solubility**
- **Prepare half ml of each reagent, at maximum concentration, based on limiting reagent**
- **Starting point will be trial Reaction using a drop of each reagent**

Process Intensification

Prelim Tests

1. Place an empty vial in fume-hood

2. Add a drop of each reagent (one by one) and observe how the reaction is

↓

Very violent reaction

↓

Dilute the reagents by half
and
repeat until controlled reaction

Process Intensification

No violent reaction

↓

Repeat the experiment
while holding the vial in hand

↓

Vials gets very hot (highly exothermic reaction)

Observe the physical state (ppt etc)

One can do develop a prelim TLC (analytical) method
of monitoring the reaction

Process Intensification

If the vial gets very hot

↓

Dilute the reagents by half
And
Repeat the experiment

↓

Vial is still reasonably hot
Repeat by dilution till its just warm

↓

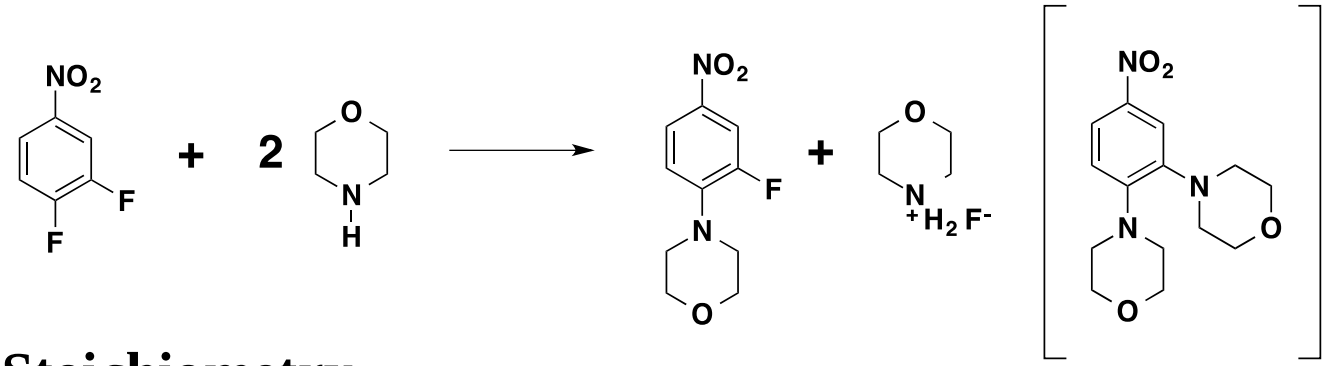
This is the starting point for flow process (room temp or higher)

Process Intensification

If the vial gets hot even at 100 mM,

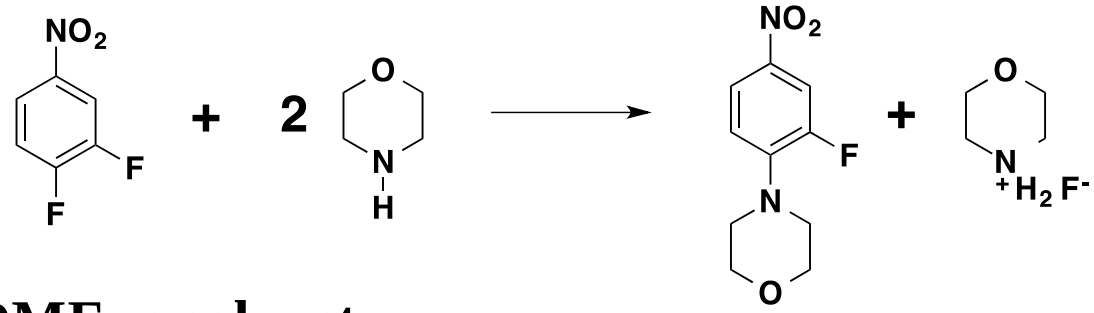
starting point will be a low temperature reaction

Tutorial



- 1:2 Stoichiometry
- Both the starting materials are liquid.
- Di-substitution is a possible side reaction at HT or high concentration
- Molarity of DFNB is 9M (density 1.44, mol wt 159)
- Molarity of Morpholine 11.5M (Density 1.0, mol wt 87)
- As per stoichiometry, one can use 1ml DFNB and 1.56 ml of morpholine
- Since salt is going to ppt out and the product is solid, we need a solvent.
- Another option could be to use morpholine as solvent (di-substitution)
- Best is to use DMF as solvent

Tutorial

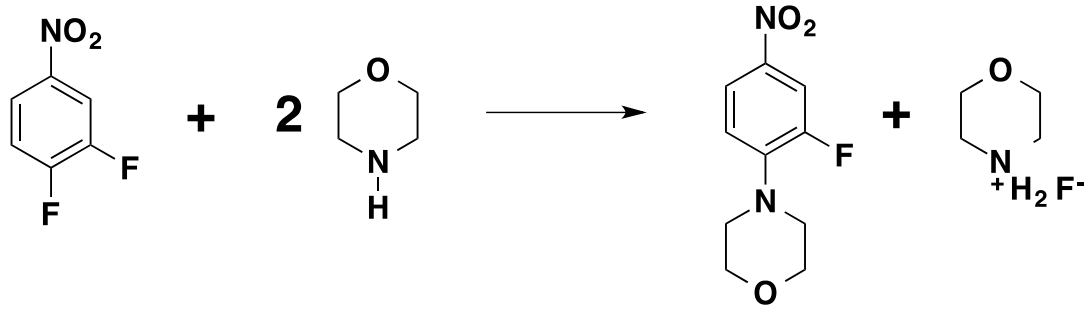


- Let us use DMF as solvent
- To use morpholine as pure, we need to make 5.75M DFNB in DMF
- This will allow us to keep the flow rate of DFNB solution and pure morpholine as equal
- So, our limiting intensification is 5.75M DNFB in DMF and pure morpholine
- Now start the drop test and find out the optimum starting point.

PLEASE DOCUMENT EVERYTHING

PREPARE THE FINAL TABLE SUMMARIZING ALL THE DROP TEST RESULTS

Tutorial

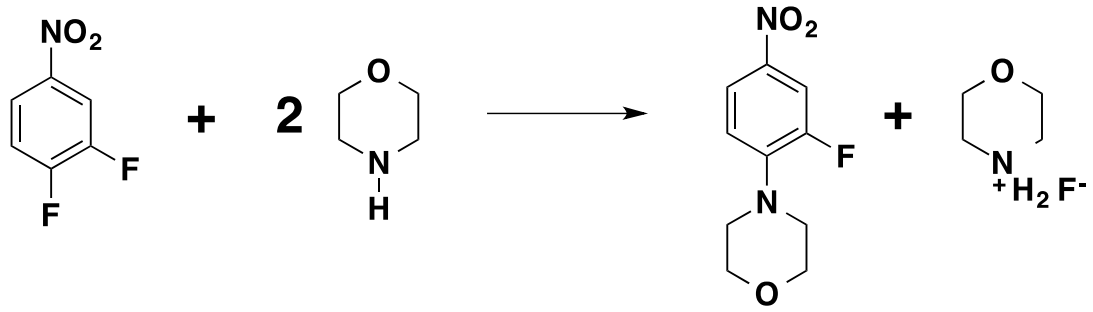


Solvent Selected: DMF

DFNB (M)	Morph (M)	Exothermicity	Observations
5.75 M	11.5 (Pure)		Ppted (thick), color etc
Up to 200 mM			

- **Highlight where the exotherm was small**
- **Highlight where the preciptation (if any) observed or large exotherm**

Tutorial



At this stage you will have documented following:

- **Starting concentration of reagents (~100-200 mM)**
- **Weather you are going to do reaction at High or Low Temp.**
- **What is the maximum intensification possible based on the information wherein precipitation happens.**

Goal is to intensify (highest concentration and lowest time, i.e. highest throughput) as close to this as possible based on the reactor and utility chosen.

Flow Reaction: General Idea

Reaction time, flow rates, stoichiometry in flow reactions

A (1 eq) + B (1.1 Eq) Gives C at 80 degree C and 1 hour, in DMF

Solution 1: 1M A in DMF

Solution 2: 0.8 M B in DMF

Now 1 ml of sol 1 and 1.375 ml of Sol 2 will give 1:1.1 ratio of A:B

Therefore, flow rates will be 1ml/min of sol 1 and 1.375 ml of Sol 2

Total flow rate is 2.375 ml/min

Let us assume that volume of our flow reactor is 10 ml

Therefore, flow rate of 2.375 ml will give reaction time of 4.2 minutes

Reaction time required is 1 hr; total flow rate will be 0.167 ml/min

Ratio of 2.375 to 0.167 is 14.2 times

Actual flow rates will be 1/14.2 (0.07 ml/min) for sol 1 and 1.375/14.2 (0.097 ml/min) for sol 2

Batch to Flow: General Idea

- Check and Confirm that it is a single step reaction
- Calculate Stoichiometry of each reagent
- Calculate the total volume of solvent used
- Now distribute the solvent among each reagent (equal, if possible)
- Prepare separate solution for each reagent
- Calculate molarity of each reagent
- Calculate the flow rate of each reagent for given stoichiometry
- This will be your total flow rate (X1)
- Now calculate the total flow rate (X2) for given reaction time (reactor volume/time)
- Calculate the ratio of X1 to X2
- Divide each reagent flow rate by this ratio to get the final flow rates for the reaction

Batch to Flow: Practice

Take your own batch processes and write it down

Convert it into flow reaction:

Decide how many reagents, how many pumps, reactor volume, flow rates etc.

Share all the details for correctness