FRX Application Note

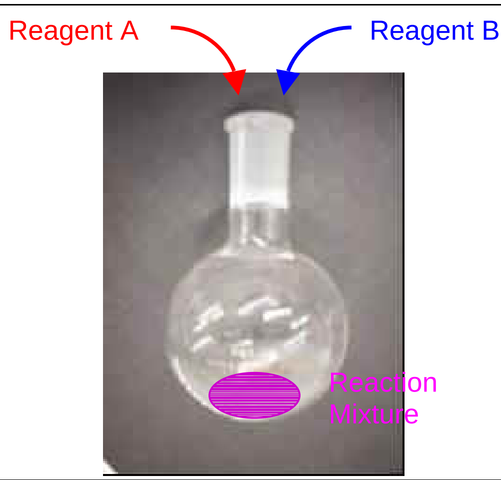
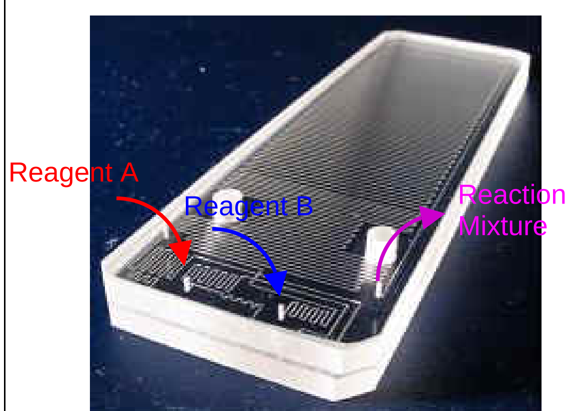
Note Number : 3

The Basics of Flow Chemistry

1 Summary

This application note gives information on the basics of flow chemistry, with particular reference to the FRX system.

2 Batch vs. Flow Reactions

<table>
<tr><td>Batch
Addition of “A” then “B” once</td><td>Flow
Addition of “A” and “B” continuously</td></tr>
<tr><td>
</td><td>
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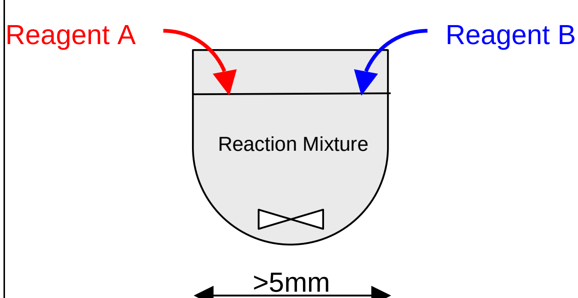
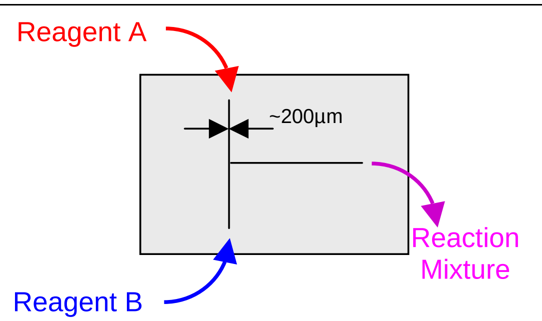
<tr><td>
</td><td>
</td></tr>
<tr><td>Traditional batch reactor e.g. round bottom flask, vial, microtitre plate etc.</td><td>Continuous flow micro reactor</td></tr>
</table>

3 Flow Chemistry

3.1 Flow Rate, Residence Time, Reactor Volume & Production Rate

In a flow reactor, the *residence time* of the reagents in the reactor chip (i.e. the amount of time that the reaction is heated or cooled) is calculated from the *volume of the reactor* and the *flow rate* through it.

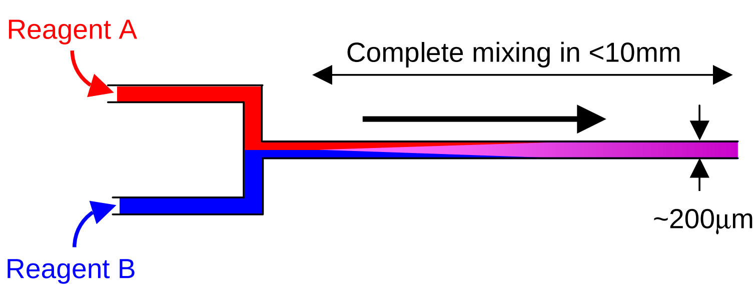
Residence time = Reactor Volume / Flow Rate

Therefore, to achieve a longer residence time, you can either pump more slowly and/or use a reactor with a larger volume. In this way, FRX is able to operate with reaction times from a few tens of seconds to a few hours.

For the same given residence time one can either choose to use a larger reactor (and therefore larger flow rate) or a smaller reactor (and therefore smaller flow rate). The key difference is that with a large reactor, more material will be synthesised in a given time. In practice, this means FRX can be used to synthesise mg to kg quantities in 24hours (depending on reaction time and concentration).

3.2 Diffusional Mixing in Microreactors

In FRX micro reactors, reagents do not mix by turbulence (as in a round bottom flask); instead, the reagents mix by diffusion. Because the distance across the chip reactor channel is ~200µm, the time taken for reagents to completely diffuse is in the order of seconds. At typical FRX flow rates, this corresponds to less than 10mm of flow along reaction channel. Note that the total length of the chip reactors is ~1m.



3.3 Pressure

3.3.1 Back Pressure due to flow

When a liquid (the reaction) flows through a “tube” (the reactor) there is an inherent resistance to its flow. This resistance or backpressure is dependent upon a number of physical factors. Thus smaller reactor cross section, longer reactor length, higher flow rates and more viscous liquids all generate higher backpressure. The reactor chips used by the FRX system are specifically designed to generate low backpressure.

3.3.2 Pressurising & Superheating Reactions

Using the FRX Pressurisation Module it is possible to pressurise a reaction by applying a chosen pressure to the output of the reactor. This allows reactions to be heated to temperatures above the boiling point of the solvent, thereby increasing reaction rates. Examples of the superheating affect that can be achieved include

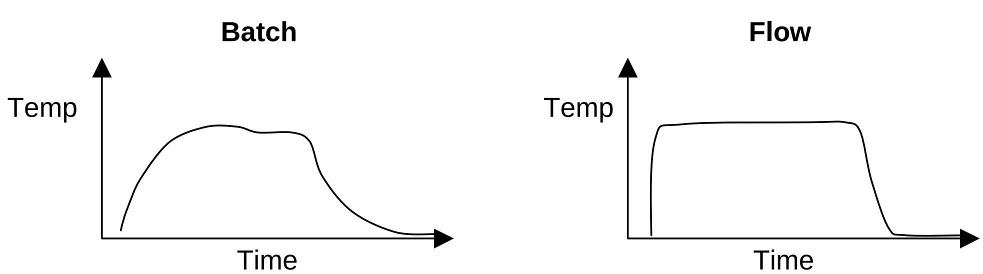
- DCM @ 100°C (vs 40°C at atmos. press.)
- THF @ 140°C (vs 66°C at atmos. press.)
- Dioxane @ 180°C (vs 100°C at atmos. press.)

3.3.3 Pressurising with Gas Evolution

It is also possible to apply pressure to an FRX flow reactor to suppress the evolution of gas. (This is beneficial because if gas bubbles are formed they can propel the reaction mixture out of the reactor leading to uncertain residence times).

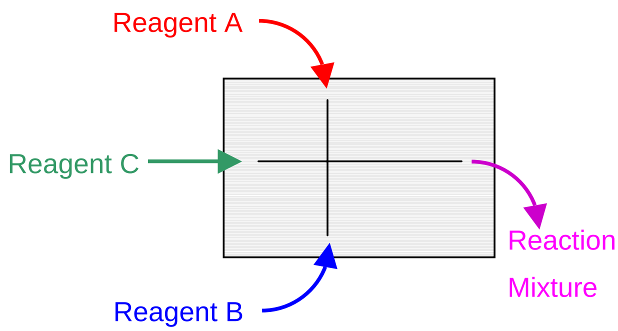
3.4 Heat Transfer

The surface area to volume ratio of the reaction mixture in an FRX flow reactor is very large. This means that heat can be added to or removed from the reaction mixture more rapidly than in a batch reactor. It also means a constant temperature can be maintained for reactions which are exo- or endothermic.



3.5 Order & Timing of Reagent Addition

In a batch reaction, reagents are typically added sequentially, even when it would be advantageous to add all reagents simultaneously. In an FRX reactor up to three reagent streams can be combined simultaneously.



In flow it is possible to achieve exact timing of sequential reagent addition. In this case, more than 1 chip can be used as demonstrated below.