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Flow Chemistry vs. Batch Processes

Chemical development is a time-consuming, expensive and labour-intensive process. This results in a high environmental load and a long time-to-market for a drug molecule. As this could affect the viability and accessibility of the pharmaceutical product, the pharmaceutical companies are increasingly looking for quicker, cost effective and safer process development handles with efficient production platforms. Traditionally new chemicals are developed using batch processing, which fully relies on versatile and qualified equipment to perform different unit operations.

Scaling up of these unit operations require judicious efforts of chemical engineers to implement lab-scale prototyping to bigger scale. The translation of work from laboratory to production environment has its own challenges and dimensions to make process safe, environment friendly and viable for commercial scale.

To address above challenges, Continuous flow chemistry technology1 is currently emerging as an effective tool to conduct chemical synthesis2, both at the micro and mesoscale, providing an improved product quality with safe and environmental conducive process in comparison to traditional batch synthesis.

Flow chemistry is the development and study of chemical processes in continuous flowing streams in tubes, through a controlled pumping mechanism at known rates. These reactions utilize the advantage of rapid mixing of reactants and appropriate surface to volume ratios effects.

The application of this technology has blossomed tremendously due to various advantages it offers – large surface area to volume ratio provide efficient mass and heat transfer rates, use of solvents at elevated temperatures, reduced reaction time, better chemical selectivity and improved yields etc. The most common types of reactors are plug flow reactors and column reactors, whilst for specific chemistries more sophisticated reactor designs might be needed (e.g., photoreactors, electrochemical reactors, etc).

Advantages of Flow Chemistry

From a chemist's view point, flow chemistry offers two distinct advantages over batch processes: control and connectivity. Precise control over reaction conditions, in particularly reaction time, mixing and heat transfer, has explored horizons for a wide range of chemistries which were either not possible or extremely inefficient and difficult in batch process. 3

The merits of continuous flow chemistry in chemical synthesis are numerous over traditional batch processes.

Process intensification

Flow chemistry allows the impact of process intensification as a tool and strategy for plant size reduction. It is being manifested to reduce environmental impact of chemical processes and improve yields, a potential step towards green chemistry.

Process safety

Flow chemistry enables to conduct chemical processes with hazardous reagents in a safe and conducive environment, this is due to small residence time of reactive species and availability of high surface area for exotherm control.

Faster reactions

Continuous flow reaction reduces the amount of reagents required for a chemical process with shorten reaction time. The reduced reaction time is result of efficient mixing in flow, and sometimes allow the solvents to be superheated above its boiling point.

Rapid reaction optimization

Flow chemistry with automation enables the quick variation and control of reaction parameters which are difficult to manage in batch reactors. Reaction conditions such as reaction time, temperature, ratio of reagents, concentration and reagents can be rapidly varied and optimized.

Improved yields and selectivity

The large surface area to volume ratio (1000x greater than a batch reactor) enables almost instantaneous heating or cooling and therefore ultimate temperature control, which accounts for high yields and selectivity in chemical reaction.

Easy scale-up

Translation of chemical process from micro to macro-reactor is easy as physical specifications of equipment remain unchanged. Moreover, similar reaction output (reaction conversion and yield) are attainable on large scale due to unaffected heat, mass and mixing efficiencies from small to large scale.

Integrated synthesis, work-up, and analysis

Reaction products exiting a flow reactor can be flowed into a flow aqueous work up system or solid phase scavenger column and can be analyzed either in line (e.g. FTIR) or manually, using a sampler and diluter to LCMS.

Parameters in Flow Chemistry

Beyond the aforementioned advantages, running a reaction under flow conditions requires knowledge of many reaction parameters such as stoichiometry, reaction time and concept of steady state. Some of the important parameters are discussed below:

Stoichiometry

Whilst under batch conditions the stoichiometry is set by the molar ratio of the reagents used, in a flow process the ratio of parameters such as flow rate and molarity is used to set the specific stoichiometry.

Residence time as "reaction time”

In batch mode synthesis the reaction time is determined by the time a vessel is stirred under fixed conditions, whereas the concept of reaction time in a flow process is expressed by the residence time, i.e., the time reagents spend in the reactor zone. Residence time is given by the ratio of the reactor volume and the reaction flow rate (overall flow rate).

$\tau = V/q$

Where τ is the variable corresponding to the residence time, V is the volume of the system, and q is the flow rate for the system

Flow rates

While in batch mode, the reaction kinetics are controlled essentially by the reagent exposure time under the specified reactions conditions, under flow conditions reactions kinetics are controlled by the flow rates of the reagents streams. The flow rates of the reagents indeed will influence the residence time of the reaction and have an impact on the outcome of the transformation.

$q = dV/dt$

q is usually expressed in units such as mL per min.

Volume vs space (steady state)

When considering a batch reaction, the reagent and product concentrations vary over the time, and mixing becomes a relevant aspect (especially when increasing the scale of the reaction) in order to reduce concentration gradients that affect the kinetics of a reaction. Under flow conditions, each portion of the reactor is defined by specific concentrations of the starting material(s) and product(s): in this sense, the reaction profile within a flow reactor can be defined within space rather than time. A very important parameter in flow chemistry is the steady state that defines a condition where all the parameters are defined and remain unchanged (steady) at a particular point in time.

Mixing and mass transfer

Mixing in a flow process is highly advantageous, compared to batch mode, as it is determined by diffusion within very small volumes of reagents. A high degree of mixing translates into better reaction profiles. Under flow conditions, indeed, mass transfer is considered very effective and determines the specific and enhanced kinetics observed. There are specific aspects of mixing that should be considered (e.g. axial vs. vortex mixing) and are dependent on specific fluid behaviours, namely plug or laminar flow patterns.

Temperature control and heat transfer

The control of temperature in flow processes can be achieved very accurately, due to the high surface area-to-volume ratio. Accordingly, heat transfer can be very efficient although this parameter depends on the specific aforementioned aspects of the fluid behaviour. Indeed, depending on whether the flow is laminar or turbulent, heat transfer can follow different patterns.

Continuous flow chemistry is a growing field with numerous advantages and illustrating excellent translation of batch chemistries into continuous flow processes. This technology is getting tremendous support from regulatory agencies in making drug development process economically and environmental friendly, with plenty of promising opportunities to explore.

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