

## **Sustainable Production of Pharmaceutical Drugs Using Continuous Flow Reactors**

The current trend in the pharmaceutical industry is towards continuous flow processes. The objective of this project is to provide the pharmaceutical industry with a technology roadmap to implement continuous flow processes to their manufacturing operations. Reducing economic and environmental costs is the driving force behind this trend. Continuous flow technology can produce a cheaper better quality product at lower energy and environmental costs through efficient mass and heat transfer and the ‘scaling out’ approach (as opposed to the traditional ‘scale up’ approach). Our group is working with industrial partners to develop processes that are both environmentally benign and economically viable.

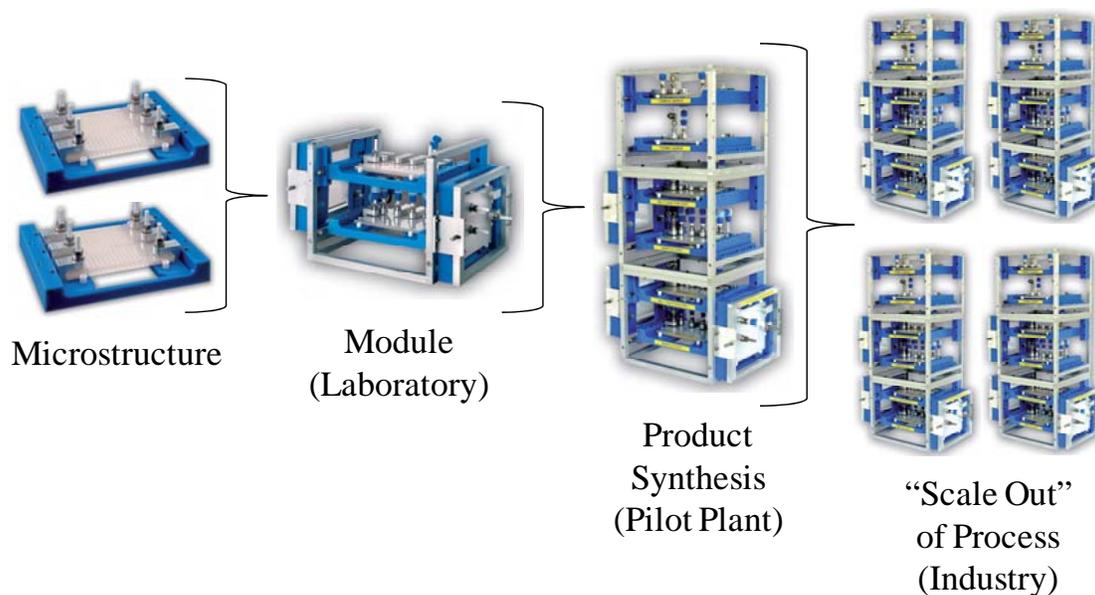
We use a specially designed continuous flow reactor system developed and donated by Corning to run heterogeneous organic reactions. These reactions include substitution, elimination, condensation, addition (chiral), oxidation, and reduction, which are commonly used in pharmaceutical synthesis. In addition to illustrating the feasibility of using continuous flow technology for pharmaceutical synthesis, we are performing economic and environmental analyses. We compare the economic and environmental benefits of our continuous flow process to current non-continuous pharmaceutical processes.

### ***Continuous Flow Reactor Technology***

Continuous flow reactor technology can produce a cheaper better quality product at reduced energy and environmental cost through:

- Optimum mixing (efficient mass transfer)
- Optimum temperature control (efficient heat transfer)
- The application of the ‘scaling out’ approach (as opposed to the traditional ‘scale up’ approach)

Enhanced mixing improves the mass transfer of biphasic systems, which leads to better yields. Temperature influences reaction kinetics and product quality. The ability to accurately control reaction temperature leads to exact control of reaction. This increases product quality and reproducibility by eliminating unfavorable selectivity and by-product formation. Continuous flow reactors can be “scaled-out” to meet high throughput demands by simply multiplying the number of reactors (Figure 1). This “scale-out” strategy facilitates going from microgram to kilogram quantities without chemistry modifications, reactor re-engineering and increased safety hazards that are associated with the traditional “scale-up” approach.

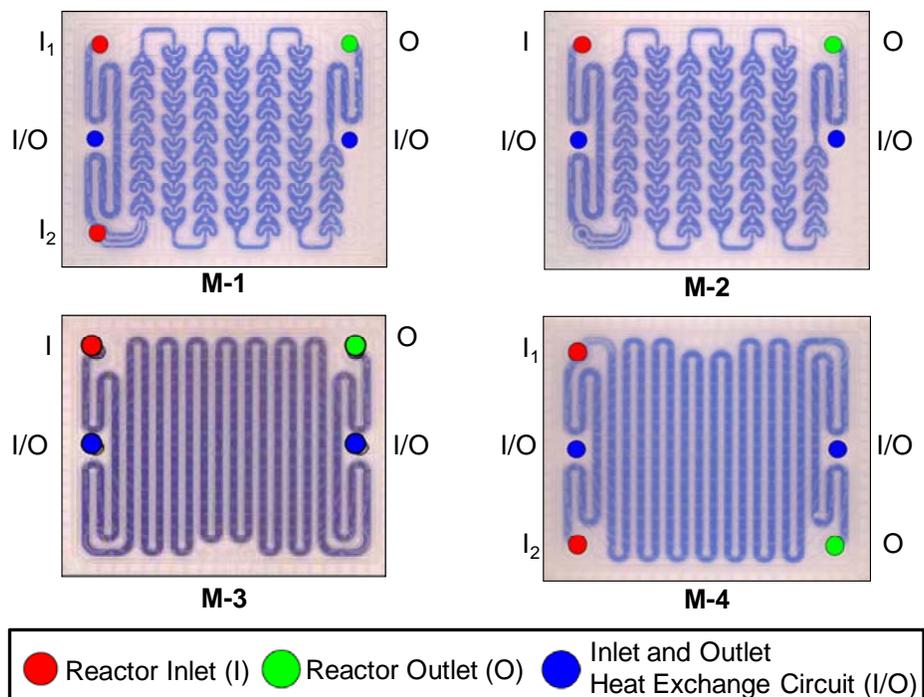


**Figure 1.** The above scheme illustrates the development of a continuous flow reactor process from the laboratory scale to industry scale. The modular scale is easily used in the laboratory. The product synthesis is a fully developed synthetic pathway to the product and is used in pilot-plants. The scaled out product synthesis is used in industry to meet high throughput demands.

### Reactor Microstructure

The Corning continuous flow reactor is an assembly of microstructures (161mm x 131mm x 8mm) made of glass which is compatible with a wide range of chemicals and solvents; and corrosion resistant over a wide range of temperature (-25°C to 200°C) and pressure (up to 18 bar). The Corning microstructures are designed and optimized for specific operations including, but not limited to: injection, mixing, residence time, and heat transfer. Corning has specifically engineered Microstructure-1 (M-1) and M-2 (Figure 2) for heterogeneous processes for our reaction needs. M-3 and M-4 are designed for heating or cooling and residence time.

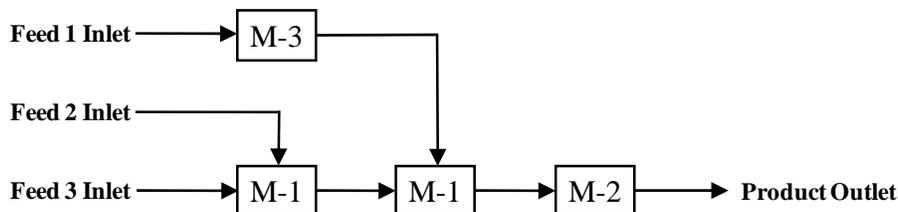
All of the microstructures are equipped with two fluidic layers (-25°C to 200°C, up to 3 bar gauge) for heat exchange on either side of the reaction layer. It is known that the rate of heat transfer is proportional to heat transfer surface area and inversely proportional to volume. These microstructures facilitate an optimum surface-to-volume ratio for improved heat transfer.



**Figure 2.** The four Corning microstructures (161mm x 131mm x 8mm, 8ml) have been designed and optimized for specific operations. M-1(7.5mL vol.) is used for introducing and mixing multiple reagents. M-2 (7.5mL vol.) is used for residence time of immiscible systems (mixing). M-3 (10mL vol.) and M-4 (8.5mL vol.) are used for heating or cooling and residence time. All four microstructures have heating and cooling capabilities.

### Module A

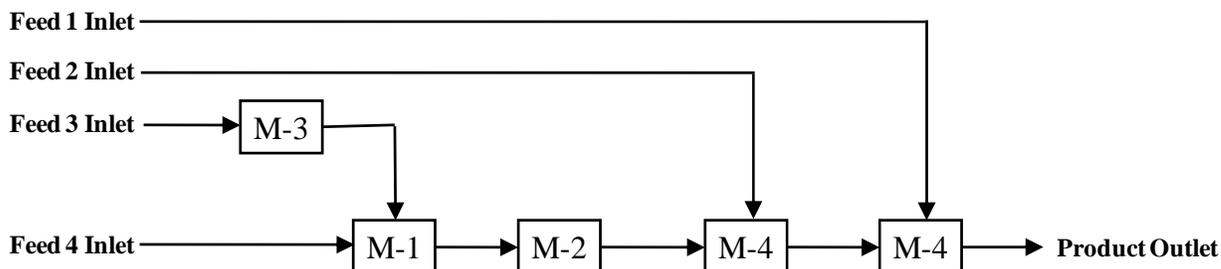
Modular assembly of the Corning microstructures allows for facile reactor design to fit the chemistry being done. Module A (Figure 3) will be used for the liquid/liquid PTC reactions. The PTC reaction is a biphasic system and module A will take advantage of M-1 and M-2 which were specially designed by Corning to optimize mixing of biphasic systems. M-3 and M-4 will be used for heating and cooling of reagents where as M-2 and the second M-1 will be used for mixing and residence time.



**Figure 3.** Module A (340mm x 600mm x 330mm) above represents the proposed microstructure assemblies that will be used for the PTC biphasic reaction. M-3 and M-1 will be used for heating and cooling of reagents where as M-1 and M-2 will be used for mixing and residence time.

## Module B

Module B (Figure 4) will be used for multistep synthesis of [CMK]. M-3 and M-1 will be used as heating and cooling units where as M-2 will be used for residence time and both M-4's will be used for sequential reagent introduction and mixing.



**Figure 4.** Module B (340mm x 600mm x 330mm) above represents the proposed microstructure assemblies that will be used for the multistep synthesis reaction. M-3 and M-1 will be used as heating and cooling units where as M-2 will be used for residence time and both M-4's will be used for sequential reagent introduction and mixing.

### *Economic and Environmental Factor Assessment*

The ratio of waste produced to the product desired, known as the E-factor, is estimated to be between 25 and 100 for pharmaceutical batch based production, creating both a significant disposal cost and an environmental burden. A higher E-factor means more waste and, consequently, greater negative environmental impact. While traditional pharmaceutical synthesis has been incredibly successful, it is inherently wasteful as seen by the E factor. As raw materials become limited, it is essential that we strive to make synthetic pharmaceutical chemistry more efficient.

We are using a combination of ASPEN/HYSYS software and cost tables to estimate and compare the capital and operating costs of the major unit operations for the pharmaceutical production process for both the traditional batch processes of general organic synthesis reactions and multi-step syntheses and our proposed continuous processes using continuous-reactors. We also compare the levels of organic waste, aqueous waste and atmospheric emissions (E-factor) between the traditional batch process and our proposed continuous processes. This allows us to show quantitatively the economic and environmental benefits of switching from the batch to a continuous flow process.