Unlocking the full potential of flow chemistry

Hannes Gemoets of Creaflow looks at how new flow reactors are pushing the boundaries of flow chemistry in terms of scalability, customisation and specific chemistries

DUE TO ITS proven advantages, flow chemistry is continuing to cement its position in industry, with the full support of the regulatory agencies. However, despite over a decade of R&D efforts and investments, some challenges remain in the areas of scale-up, customisation, handling of multi-phase processes and alternative energy input.

To address these unmet needs, EcoSynth and Ajinomoto Bio-Pharma Services have recently developed the Costa* technology, which is the cornerstone of a range of flow reactors. The name originates from its three distinct features: Continuous processing in a linear plate flow reactor; the use of a superimposed OScillatory flow regime; and the STAtic mixing elements located in the process channel.

This combination creates a pulsating split-and-recombine flow pattern, which results in an intense and tunable mixing, independent of the net flow rate. Critical process characteristics, such as mass- and energy-transfer, residence time distribution and pressure drop, are not influenced by the broadening of the linear process channel, so processes can easily be scaled. In addition, process conditions can be further optimised using two new process parameters: oscillation frequency and amplitude.

The assembled reactors can be customised and tailored to the reaction kinetics and physicochemical properties of the reaction mixture, such as corrosion resistance and viscosity. As such, specific chemistries that are traditionally difficult to scale come into the picture.

Scalable photochemistry

Photochemistry is particularly interesting for the pharmaceutical and chemical industries, since photoactivated transformations allow access to new chemical space and shortcuts in synthetic routes. However, it is still a rather 'forgotten' discipline, because industry is reluctant to pick it up, due to the lack of suitable multi-purpose and scalable photoreactors.

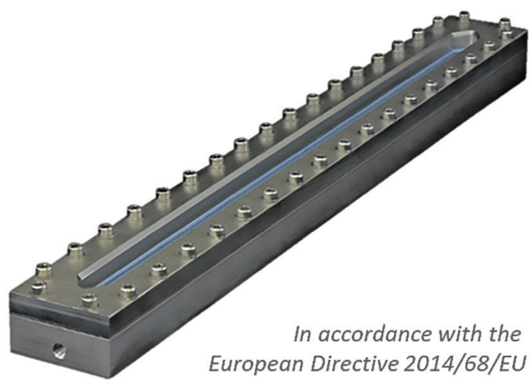
By definition, when scaling up photochemical processes, enlarging the reactor dimensions hampers efficient photon input, due to the well-known light attenuation effect stated in the Bouguer-Lambert-Beer law. When scaled up via traditional batch vessel methods, this effect rapidly leads to processes that run in a photon-limited regime.

In order to ensure productive conversions, engineers basically have to run their processes in recirculation vessels – side-loop and falling film reactors – at highly diluted concentrations and equipped with energy-intensive light source units, such as mercury lamps, for prolonged irradiation times. These inherent scale-up restrictions often render the process uneconomic.

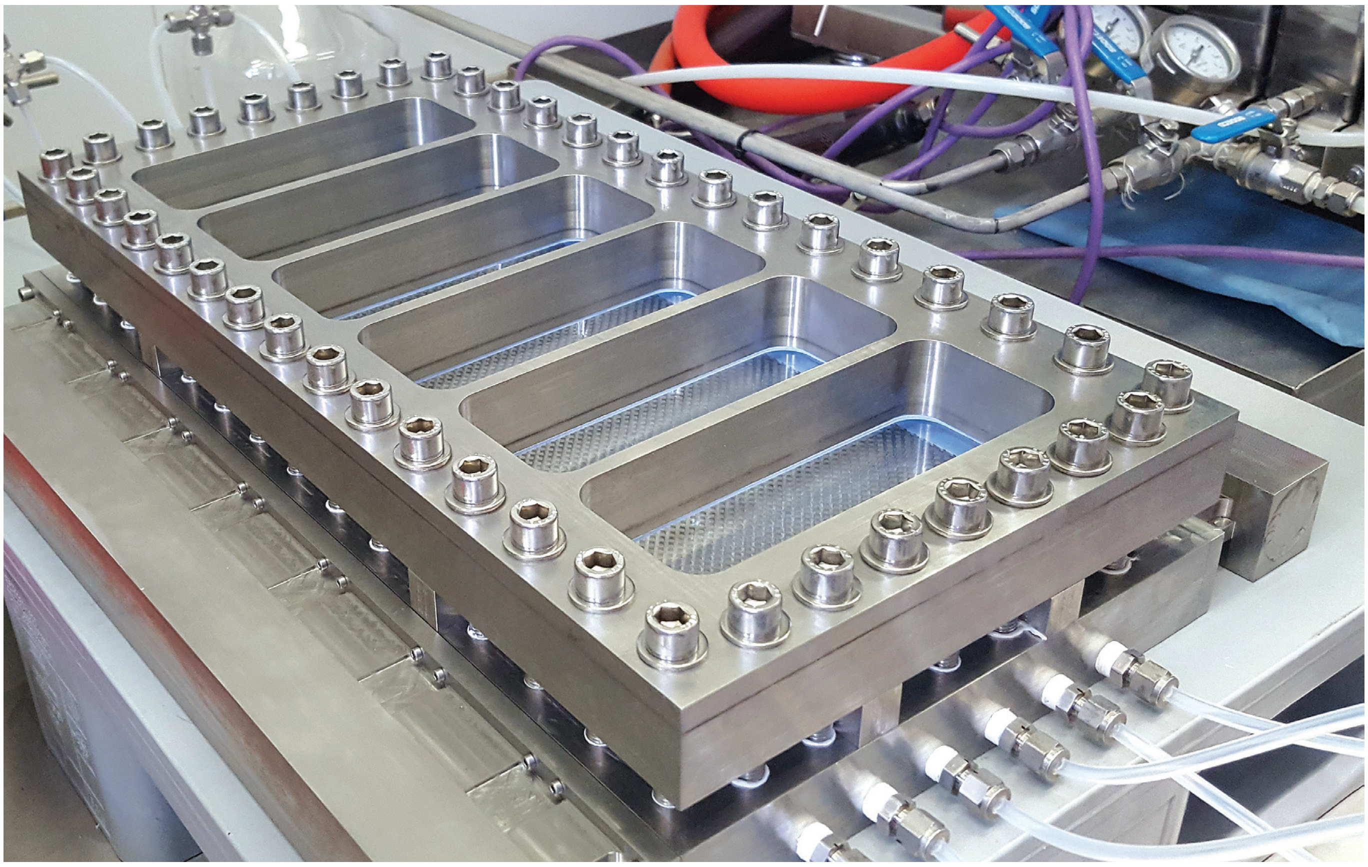
As a result, only a handful of photochemical processes, notably the synthesis of vitamins D3 and A (by BASF and Hoffmann-LaRoche), rose oxide (Symrise), caprolactam (Toray) and artemisinin (Sanofi and Huvepharma), have been applied commercially. However, recent developments in continuous-flow chemistry and efficient monochromatic light sources, like LEDs, spark opportunities for

Figure 1 – Lab-scale HANU reactor characteristics

HANU 15 & **HANU HX 15** lab reactor series for scalable photochemistry



Parameter	Description
Internal volume	15 mL
Transparent window	Borosilicate (> 325 nm) Quartz (> 200 nm)
Temperature range	-20 to 80 °C
Pressure rating	10 bar
Reactor material	Stainless steel 316L, Hastelloy C276 or customised
Heat exchange	Heat transfer fluid



HANU 150 reactor at the Ajinomoto Bio-Pharma Services' pilot plant in Belgium

photochemical applications in the chemical industry.

Figure 2 – [2+2]-photocycloaddition leading to Cookson's diketone

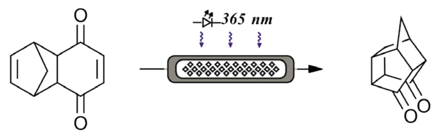


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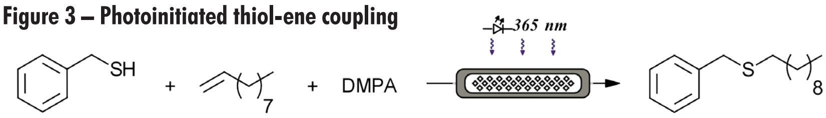
Figure 3 – Photoinitiated thiol-ene coupling



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HANU reactor

Based on the Costa technology, Creaflow recently introduced its HANU reactors. These have a large, transparent window and can be operated in temperature (-20 to +80°C) and pressure (10 bar) ranges that are typically used for photochemical reactions.

Of particular interest is the excellent temperature management of the system. This parameter is often overlooked at the R&D stage and is traditionally hard to control at a larger scale, due to the excessive heat irradiated (i.e. infrared) from the light source.

Heat is effectively dissipated through-metal via an internal fluid heat transfer system located in close proximity of the surface of the process channel, in which the static mixing elements add to the heat exchange surface (Figure 1).

Intense mixing ensures adequate film refreshment of the irradiated zone and the independency of the mixing from the flow rate allows continuous one-pass operations with no need for recirculation. The HANU reactor can accommodate both UV and visible light photochemistry, since the reactor can accommodate both a borosilicate or quartz window. In addition, the effective handling of suspensions containing, for example, heterogeneous catalysts, insoluble APIs or inorganic bases truly opens new avenues in flow photochemistry.

In terms of process scale-up, pilot reactors were developed by simply widening the process channel, thus increasing the internal volume ten-fold to 150 ml. The fact that all process characteristics – process path length, irradiation properties, mass and heat exchange, residence time distribution and so on – remain equal allows scale-up with minimal process development when going from R&D to the production level.

Ajinomoto Bio-Pharma Services will soon have a scaled-up HANU 150 reactor in operation at its GMP pilot plant in Wetteren, Belgium (*pictured*). As light sources are an essential part of a photochemical set-up, dedicated LED modules for the HANU reactor, at laboratory and pilot scale, have been developed in collaboration with Peschl Ultraviolet, an industrial partner in the field of photochemical irradiation source units.

The NovaLight FLED75 systems include high-power water-cooled LED arrays that can be exchanged via a plug-and-play method. Nine different LED arrays are available, covering the range from UVA to the visible light spectrum (365-625 nm). The LED modules are designed for direct implementation in a GMP environment, as they are built ATEX certification-ready.

Applications in photochemistry

In order to demonstrate the capabilities of the HANU reactor, several application notes are being published online at **www.creaflow.be/applications**. A first example describes a typical benchmark reaction used to compare photoreactor productivity: the intramolecular [2+2]-photocycloaddition of a Diels-Alder product, leading to a cage compound also known as Cookson's diketone (Figure 2, **2**).

An EtOAc-solution of 1 (9 wt%) was irradiated for 45 seconds in the HANU reactor by means of 365 nm LEDs. Under optimised conditions, productivity reached 2.3 kg/day of **2** in a single-pass continuous operation using a single 15 mL lab reactor. This example clearly demonstrates that it is possible to make kilogram quantities in a laboratory setting and the effectiveness of the working principle, since the system outperforms other advanced flow photoreactors.

In a second example, the capacity of the HANU reactor was pushed to its limits. The photoinitiated thiol-ene reaction between benzyl mercaptan (Figure 3, **3**) and 1-decene (**4**) was selected as model. Performed in neat conditions and in the presence of 2 mol% Irgacure 651 (DMPA, **5**) as photoinitiator, productivity culminated in 46 kg/day sulfide (**6**), again using just a single lab-scale HANU reactor.

Beyond photochemistry

Apart from enabling scalable photochemistry, the Costa technology can be applied to the scale-up of demanding multi-phases processes, as it allows the effective mixing of immiscible liquids and guarantees the processing of solid particles in suspension at any flow rate. In addition, when no irradiation source is required for the chemistry or during cleaning validation, the large transparent glass can be used as an inspection window.

Since the HANU reactor is an 'open-shell' system, disassembly allows straightforward physical cleaning of the process channel. In terms of process development, kinetic data can be generated and plotted rapidly by means of through-glass PAT methods, such as Raman and near infrared spectroscopic monitoring of the process stream. ●

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