The Development of a Scalable Continuous-Flow Photoreactor

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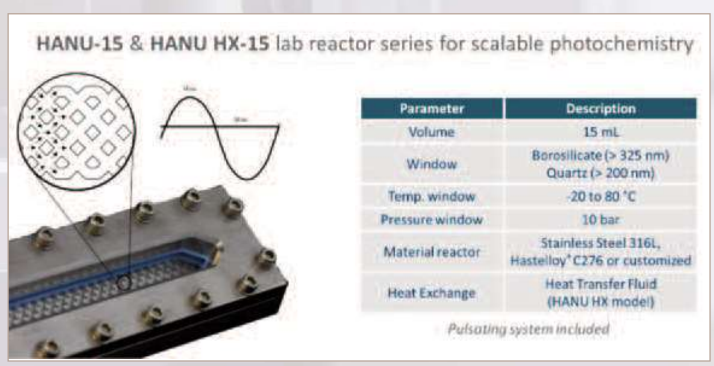
Hannes Gemoets, head of R&D at Creaflow, explains how the HANU™ reactor offers a solution towards scalable photochemistry.

On December 13th 2016, president Obama signed the 21st Century Cures Act In order to expedite drug development. The act encompassed the strong advocacy to transition the pharma industry towards continuous manufacturing. Following this incentive, the Food and Drug Association (FDA) expressed common belief and recently published their first guidelines regarding the quality aspects in continuous manufacturing of medicinal products.

However, to accelerate the delivery of new drug entities via continuous production methods, disruptive technologies that are capable of replacing the existing batch-wise production strategies are required. In this respect, the advent of continuous-flow technology has enabled chemists and engineers to radically redesign their chemical processes by tapping into formerly considered 'forbidden' and 'forgotten' chemistry toolboxes. Because of their intrinsic high surface-to-volume ratios (up to 20.000 m^{-1}), flow reactors excel in terms of control over the critical process parameters. This results in minimized waste and energy consumption and enhanced overall process safety and reliability. In addition, effortless automation incorporation and production volume flexibility (amount product = amount time) make it possible to respond better to today's fluctuating market needs.

FLOW CHEMISTRY AS ENABLING TOOL FOR SCALABLE PHOTOCHEMISTRY

A particular interesting outcome is the renewed interest in photochemistry. The main reason why photochemistry persisted to be a rather 'forgotten' discipline till the last decade is principally due to deficiency of available multi-purpose and scalable reactor technologies.



Parameter	Description
Volume	15 mL
Window	Borosilicate (> 325 nm) Quartz (> 200 nm)
Temp. window	-20 to 80 °C
Pressure window	10 bar
Material reactor	Stainless Steel 316L, Hastelloy® C276 or customized
Heat Exchange	Heat Transfer Fluid (HANU HX model)

Figure 1. Lab-scale HANU™ reactor characteristics.

By definition, when scaling up photochemical processes, reactor dimension enlargement hampers efficient photon input due to the light attenuation effect as described in the Bouguer-Lambert-Beer law. When scaled via traditional batch vessel methods, this effect rapidly leads to processes that run at a photon-limited regime. In order to ensure productive conversions, engineers are basically obliged to run their processes in recirculation vessels (e.g. side-loop and falling film reactors) at highly diluted concentrations and at prolonged irradiation times. In addition, reactors were usually equipped with polychromatic energy-demanding light sources such as mercury lamps. As a result, only a handful of photochemical processes, including synthesis of vitamins D3 and A, rose oxide, caprolactam, and artemisinin, have been applied commercially.

Figure 2. Lab-scale HANU™ LED Module Characteristics.

However, recent development in continuous-flow photoreactor and Light Emitting Diode (LED) technology spark opportunities for this former 'niche field' and is therefore gaining substantial momentum. Via the implementation of smart scale-up protocols (i.e. novel photoreactor form factor designs, scale-out and numbering-up strategies), reliable and effortless amplification of the process output can be obtained using a fully continuous operation mode.

COSTA™ TECHNOLOGY AND THE HANU™ REACTOR

At the heart of this paradigm shift, EcoSynth and Ajinomoto Bio-Pharma Services recently developed the COSTA™ technology as a platform for a portfolio of innovative continuous-flow reactors. The name originates from its three distinct features: the Continuous processing in a linear plate flow reactor, operated in a superimposed Oscillatory flow regime, and in combination with the STAtic mixing elements located within the process channel.

In operation, the synergistic combination of these three features generates a pulsating split-and-recombine plug flow behavior, which results in an intense and tunable mixing, independent of the net flow rate. Essential 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 without further process optimization. In addition, process conditions can be further optimized using two novel process parameters, namely the pulsation frequency and amplitude.

Built on the COSTA™ technology, Creaflow recently developed the HANU™ reactor for scalable photochemistry. This assembled unit consists of a reactor base which embodies the process channel and the integrated heat exchanger system. On top of the process channel, a large transparent window is fitted and held in place by a lid. The reactor can be operated in temperatures from -20 to +80°C and pressures up to 10 bar, covering an operational window which is generally used for over 95% of the described photochemical reactions (Figure 1).

The 'open-shell' configuration of the HANU™ reactor opens up perspectives for reactor customization. Reactor material, window and static mixing elements' size and shape can be tailored to fit the reactor to both the reaction kinetics and physicochemical properties (including corrosiveness) of the reaction mixture. As such, specific chemistries such as multi-phase processes, that are traditionally difficult to scale, come into the picture.

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 the larger scale, due to the excessive heat emitted by the light source via infrared irradiation. Heat is effectively dissipated via an internal fluid heat transfer system located which is located in close proximity of the surface of the process channel, while the static mixing elements add to the heat exchange surface as well.

The pulsatile flow in combination with the static mixing element in the process channel develop vortices that improve mixing in all directions which ensures adequate film refreshment of the irradiated zone. Because of the superimposed pulse effect, mixing intensity is decoupled from the net flow rate, thus allowing slower (photo)chemical transformations to be operated at continuous one-pass operations, without the need for recirculation. In addition, the effective handling of suspensions containing, for example, heterogeneous catalysts, insoluble starting compounds or inorganic bases truly opens new avenues for preparative flow photochemistry.

As light sources are an essential part of a photochemical set-up, dedicated light source modules for the HANU™ reactor, have been developed in collaboration with Peschl Ultraviolet. These systems include high-power water-cooled LED arrays that can be exchanged via a plug-and-play method. Currently, 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 (Figure 2).

In terms of process scale-up, pilot reactors were developed by simply widening the process channel, thereby increasing the internal volume ten-fold to 150 ml, while critical process characteristics remain unaffected. As such, Ajinomoto Bio-Pharma Services will soon have a scaled-up HANU™ 150 reactor in operation at its GMP pilot plant in Wetteren, Belgium.

APPLICATIONS ON SCALABLE PHOTOCHEMISTRY

The capability of the HANU™ reactor has been demonstrated via several application notes which are available online. A first example describes a typical benchmark

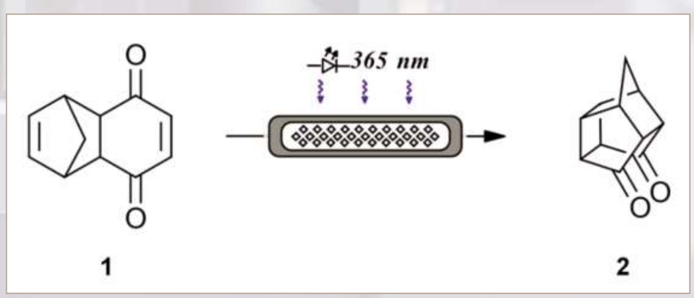


Figure 3. [2+2]-photocycloaddition reaction leading to Cookson's diketone.

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 3).

An EtOAc-solution of 1 (9 wt%) was irradiated for 45 seconds in the HANU™ reactor by 365 nm LEDs. Under optimised conditions, productivity reached 2.3 kg/day 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 its working principle, since the system outperforms other state-of-the-art 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 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 a single lab-scale HANU™ reactor (Figure 4).

The scale-up of demanding multi-phases processes becomes attainable as this technology allows the effective mixing of immiscible phases. The processing of solid particles in suspension was recently described in a publication (Reaction Chemistry & Engineering 2020,5, 597-604) by the Kappe group. The use of the HANU™ reactor facilitated an industrially relevant heterogeneous dual nickel/carbon nitride photocatalytic C–N coupling, showcasing its applicability for preparative scale production of medicinally relevant compounds.

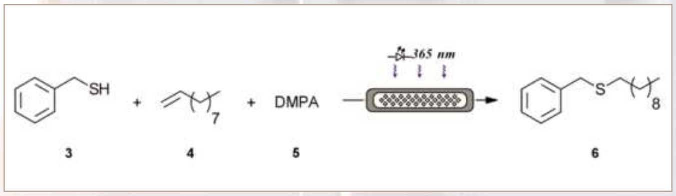


Figure 4. Photoinitiated thiol-ene coupling reaction.

The above examples clearly demonstrate the production capabilities and scale-up potential of photochemistry by the implementation of the COSTA™ technology.

Apart from enabling scalable photochemistry, the COSTA™ technology excels in other fields as well. Besides its unique processing of multi-phase process streams which are of interest beyond photochemical applications, visual inspection or non-invasive PAT through the glass window add to its unique set of reactor characteristics.

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