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A pharma perspective on sustainability advantages through adoption of continuous flow

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Abstract

The pharmaceutical sector is increasingly employing sustainable strategies to combat its environmental impact through the implementation of green chemistry and engineering practices. As regulatory requirements become more stringent and the drive towards sustainable chemical manufacture continues, new process methods and technologies are rapidly being developed with continuous flow at the forefront. This review highlights recent publications where continuous flow was adopted as a driver for sustainability with green metrics discussed.

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Continuous flow, Sustainability, High-throughput experimentation, Self-optimizing, Process analytical technology, Green metrics, Green chemistry.

Introduction

Continuous flow has historically dominated in the petrochemical and commodity industry driven by the high volumes of material required. Over the last decade, it has expanded into the pharmaceutical realm as a green, enabling technology, being named one of IUPAC's top 10 chemical innovations that could change the world [1]. The efficient mass and heat transfer, broader process windows, and precise reaction control offered by continuous flow facilitate reduced reaction times, together with improved yields, selectivity, safety, and scalability. Many of these attributes align with the 12 principles of Green Chemistry as coined by Warner and Anastas [2].

The 12 principles act as a guideline for developing and enhancing the sustainability of a chemical process and should be used in tandem with green metrics to quantifiably assess the environmental impact of the process. These green metrics include the E-factor, process mass intensity (PMI), and atom economy [3,4]. An in-depth analysis of the lineage between the advantages associated with continuous flow and the 12 principles has been documented previously and therefore will not be discussed here [5–9].

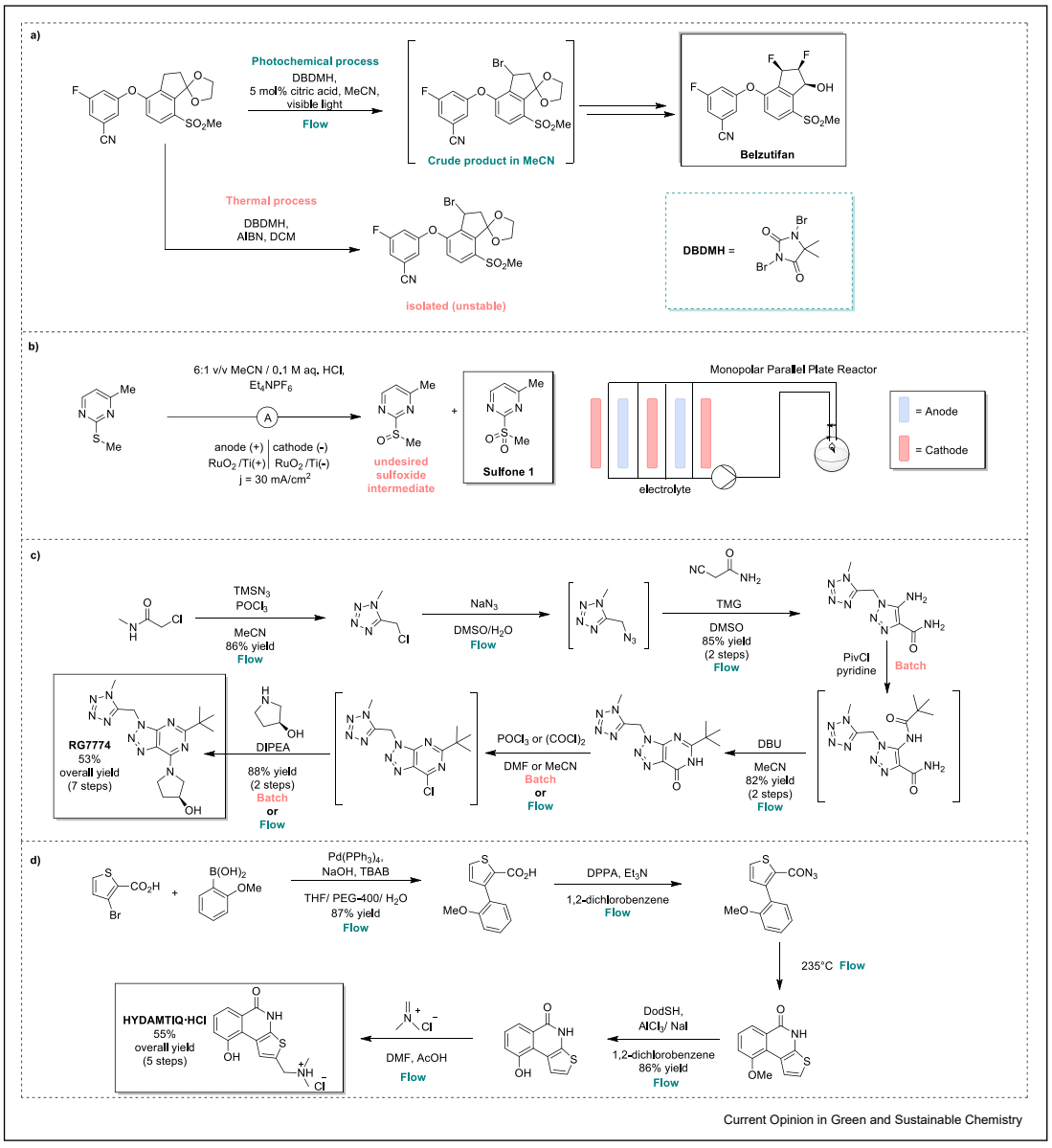
Numerous regulatory bodies champion the implementation of continuous-flow manufacturing within the pharmaceutical industry to improve product quality, consistency, and sustainability [10]. Consequently, adaption of manufacturing processes to continuous flow is on the rise. Despite this, there are still significant hurdles associated with its uptake, including aggressive timelines often experienced within the pharmaceutical industry, the need for operator training, support of regulatory bodies for current Good Manufacturing Practice (cGMP) documentation, and access to equipment within suitable timelines.

This brief perspective will provide a review of some of the most recent innovations in sustainable continuous flow processes. The following sections highlight the myriad of process advantages realized through the implementation of continuous flow for reaction screening, optimization, and manufacture, and its associated environmental benefits.

Sustainable continuous chemical synthesis

The drive towards sustainable manufacture through the development of photochemical processes has greatly benefited from the parallel developments in continuous flow microreactor technology. With light already considered a clean, traceless reagent, small-scale reactor designs further enhance its benefits by providing superior mass transport kinetics to maximize chemoselectivity when compared to traditional batch reactors [11–15]. The utility of continuous flow photochemistry was exemplified in the commercial manufacturing process of Belzutifan (MK-6482), where a key transformation featuring a radical bromination flourished under microfluidic flow conditions (Scheme 1a) [16]. Beyond reducing side-product formation, telescoping

Scheme 1



Continuous flow-enabled synthesis of a) Belzutifan [13], b) Sulfone 1 [21], c) RG7774 [23–25], and d) HYDAMTIQ·HCl [26].

the bromination step into a subsequent oxidation reaction overcame challenges associated with isolation of the brominated intermediate and reduced the process' auxiliary waste. Scalability was demonstrated through the implementation of a numbering up strategy, where a cGMP-qualified flow reactor was developed achieving >100 kg/day output.

Synthetic electrochemistry provides analogous benefits to photochemistry, with redox chemistry realized without the use of stoichiometric hazardous reducing and/or oxidizing agents [17–19]. Microfluidic flow reactors again promote enhanced mass transfer between the electrodes providing more energy-efficient transformations, whilst simultaneously providing a more uniform current distribution [20–22]. Electrochemistry comes with its fair share of unique scalability challenges for a flow system. Electrode choices are limited, not only by reaction performance but also through availability, cost, and durability considerations. Furthermore, hydrogen, a common by-product of electrochemical reactions, can become trapped within the cell reducing the effective reactor volume and raising safety concerns [23].

In 2022, Merck reported the development of a continuous flow electrochemical oxidation for the transformation of a thioether to a sulfone on kilo-scale (Scheme 1b) [24]. Initial investigations were conducted in batch mode on the milligram scale identifying suitable electrolyte, Et_4NPF_6, and electrode, RuO_2 on Ti. An excellent yield of the desired sulfone and Faradaic efficiency (5 F/mol of charge) were observed on employing these reactants. The combined use of online flow ^1H NMR, cyclic voltammetry, density functional theory (DFT), and ion chromatography delivered critical insights into the reaction mechanism and competing pathways, providing guidance for reaction scalability. Further developments were conducted under continuous flow operation with key parameters identified as the total charge, current density, and linear velocity. The electrochemical oxidation was conducted in a continuous recirculatory mode to ensure efficient mixing and removal of H_2, allowing high flow rates to be employed. The oxidation was successfully scaled using parallel plate reactors offering a productivity of 1 kg within a 24 h period. This work provides a useful guide for the development and scale-up of electrochemical reactions.

One key advantage of continuous flow is realized through its utilization in scaling hazardous chemistries [25]. Highly energetic, toxic, or explosive reagents are regularly employed under continuous flow mode owing to its small reactor dimensions and the precise reaction control offered. In 2021, Kappe and co-workers developed the flow-assisted synthesis of RG7774, a cannabinoid receptor type 2 agonist (Scheme 1c) [26–28]. The previous synthetic strategy relied on an 8-step synthesis with a low overall yield of 27% due to the poor regioselectivity observed in the final alkylation step. Continuous flow enabled alkylation to be conducted at the start of the process through the incorporation of hazardous azide transformations averting downstream regioselectivity issues. The process productivity was also enhanced during the [3 + 2] cycloaddition reaction through a combination of plug flow reactors and continuous stirred tank reactors to circumvent the solubility limitations of the product. Furthermore, employing continuous flow for the cyclization reaction enabled a temperature of up to 200 °C to be deployed which was significantly higher than the solvent boiling point. Through a combination of intensified batch and flow protocols, a scalable synthesis of receptor RG7774 was successfully developed with an overall yield of 53%.

Gioiello and co-workers reported the multi-step continuous synthesis of 2-((Dimethylamino)methyl)-9-hydroxythieno[2,3-*c*]isoquinolin-5(*4H*)-one (HYDAMTIQ), a Poly(ADP-ribose)polymerase-1/2 (PARP-1/2) inhibitor [29]. The prior synthetic route offered a low overall yield (23%), employing hazardous reagents, and requiring tedious purification processes [30]. Adoption of a continuous flow approach enabled a five-step synthesis to be conducted sequentially, along with *inline* purification techniques such as a liquid/liquid (l/l) separator and a silica-packed column affording the final product HYDAMTIQ·HCl in an overall yield of 55%, with >97% purity on multigram scale (Scheme 1d). A detailed assessment of the key green metrics, the process cost, and productivity revealed the significant benefits of the flow process over the prior batch approach, with a 10-fold increase in the reaction mass efficiency observed and the mass recovery parameter was improved by 200%.

Automated flow for reaction screening and optimization

Quality by Design (QbD) is a strategic method emphasized by the FDA to ensure the delivery of high-quality products [31]. This is achieved using risk assessments, experimental methods such as design of experiment (DoE), process analytical technology (PAT), and the automation of chemical processes. In recent years, continuous flow technology has matured into the field of automated chemical synthesis enabling sets of experiments to be conducted without human intervention thus greatly reducing optimization timelines, experimental error, and costs, whilst relieving chemists of labor-intensive tasks. Additionally, incorporation of PAT, and predictive computational methods can expedite reaction development and optimization whilst simultaneously improving product quality, process safety, and promoting sustainable manufacturing.

Self-optimizing flow reactors

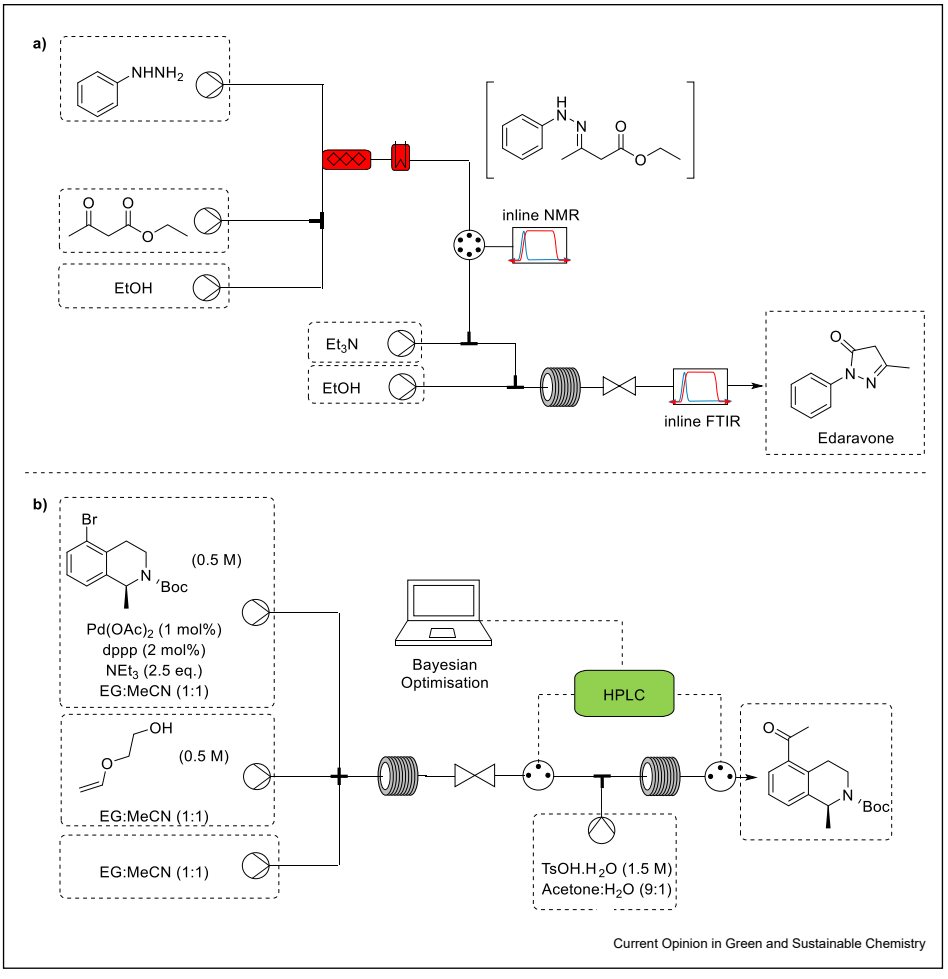
The precise reaction control achieved using a flow reactor makes it well suited to statistical and algorithm-based optimization. Combined with real-time feedback presented by PAT, the use of continuous flow platforms in tandem with statistical modeling software enables autonomous self-optimization, whereby a feedback loop is created, dictating iterative experimental design based on the data generated from the current and previous experiments. Collectively, such automated self-optimization platforms offer access to more rapid, cost-effective, and sustainable reaction development by minimizing the number of experiments and materials required during the optimization campaign. This continuous self-optimization approach has found successful application to an array of chemical transformations, including ultra-fast organolithium, photochemical and electrochemical transformations [32–34].

Complex, multi-step synthetic sequences are typically facilitated by continuous flow through telescoping each step into a singular, uninterrupted reaction network. Flow offers potential to minimize process downtime by avoiding laborious workup, purification, and cleaning procedures typically encountered in batch-type chemistry and minimizes waste generation, thereby

maximizing the associated E-factor [35]. As target molecules become more complex, development and optimization of telescoped pathways become challenging with key process input variables affecting the inherent chemistry, and limitations imposed by the physical and chemical interdependency between unit steps. The use of self-optimization can be employed to study the effects of multiple reaction parameters at once, with current developments enabling up to five independent reaction variables to be studied simultaneously [36].

Self-optimization of telescopic multistep sequences initially saw PAT positioned at the end of the entire sequence, with no discrimination between the influence of each individual unit step [37]. More rigorous understanding of each chemical step has since been achieved by the incorporation of multiple PAT tools along the telescoped flow path to facilitate multi-dimensional, data-rich experimentation [33, 38]. In 2022, a report from Kappe and co-workers screening a total of seven variables between two steps to optimize the synthesis of Edaravane in flow achieved >95% yield with 5.42 kg L^{-1} h^{-1} space-time yield following 85 iterative optimizations, with both IR and NMR spectroscopies used as viable PATs (Scheme 2a) [39]. The use of multiple analytical techniques per optimization campaign is an expensive endeavor, with a large up-front cost typically associated with the purchase of high-end analytical instruments. In this regard, Bourne and co-workers developed a continuous flow multi-step self-optimization platform using a bespoke multi-point sampling method, using only one analytical HPLC device, allowing samples to be extracted at the end of each reactor (Scheme 2b) [40]. A Bayesian optimization algorithm was employed alongside an Adaptive Expected Improvement to provide a balance between the exploration of chemical spaces and exploitation of

Scheme 2



Self-optimization of a telescoped reaction through multipoint analysis using a) in-line spectroscopic analysis at the end of each reactor unit [36], b) a single HPLC unit for multipoint sampling [37].

information. The reaction's global optimum was realized after only 13 experiments and 14 h, delivering the desired aryl ketone in an 81% overall yield. The use of a multipoint sampling approach proved to be key in understanding the individual reaction steps and provided mechanistic insights into the most favorable competing pathway.

High-throughput experimentation in flow

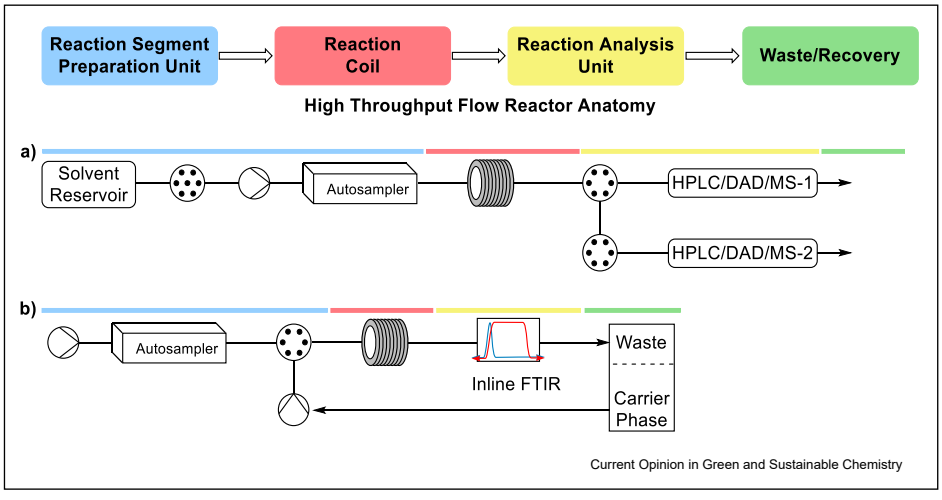
One methodology that has sustained interest within the pharmaceutical industry to accelerate reaction process development and optimization is high throughput experimentation (HTE) [41]. HTE traditionally uses multi-well plates to minimize material consumption at the screening stage while facilitating the parallelization of experiments, which allows multiple chemical input parameters to be screened simultaneously in a rapid and inexpensive way (Scheme 3a). HTE is typically performed in batch, but in 2018 Sach and co-workers at Pfizer reported an innovative, automated platform to conduct HTE inflow [42]. After validating their design, the authors applied their flow-based HTE platform to a palladium-catalyzed Suzuki–Miyaura cross-coupling, executing 5760 experiments on the nanomolar scale, with a throughput of ~1500 experiments per 24-h period. In 2022, the authors revised their platform for application in photoredox catalysis, with the optimization of a Minisci-type reaction providing access to complex bicyclic motifs [43]. Conducting 475 reactions in less than 12 h, the developed system was subsequently applied to over 50 unique substrates, with multiple heterocyclic and bicyclic ester motifs proving suitable. To further demonstrate the generality of this system, 31 substrate pairs were examined in a parallel medicinal chemistry format, achieving a 55% success rate of the library. Rapid reaction screening under continuous flow operation not only reduces chemical waste but also minimizes exposure to hazardous chemicals and enhances overall safety. Since the development of this continuous high throughput experimentation platform, there have been a limited number of contributions to the field [44]. Of note was a recent development detailing a flow-enabled approach to kinetic experimentation. The autonomous segmented flow platform could generate 216 unique kinetic profiles in just 90 h representing a 40-fold increase in experimental throughput and simultaneous reduction in material consumption when compared to the same chemistry in batch (Scheme 3b) [45].

The Covid-19 pandemic highlighted some of the major challenges within the pharmaceutical sector, not limited to those associated with lengthy drug development timelines but also with labor shortages. Consequently, automated manufacturing became a pivotal goal within the pharmaceutical industry to enable faster drug development with lowered operator demands.

Summary and outlook

Continuous flow plays a pivotal role in the development of green technologies and processes. The inherent benefits associated with continuous flow, namely the precise reaction control and small reactor dimensions, assist in minimizing waste generation, exposure of hazardous chemicals to operators, energy requirements, and overall process costs. Continuous flow is regularly employed to aid in the chemical synthesis of complex molecules and has recently found significant application in the field of automated reaction screening, development, and optimization. With strict regulatory

Scheme 3



Simplified depiction of a high throughput flow reactor anatomy. a) Use of a continuous flow reactor for high throughput reaction screening on the nanomole scale [38], b) the use of a segmented flow reactor for high throughput kinetic analysis [42].

requirements being constantly revised, the pharmaceutical industry must adapt and focus its attention on the implementation of new, innovative technologies such as continuous flow.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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In this study, the unity of flow chemistry and high throughput kinetic experimentation is detailed. The automated segmented flow platform provided a detailed kinetic analysis of an organocatalyzed aldol reaction, executing 216 experiments over a 90-h period, significantly shorter than the estimated timeframe for the equivalent batch analysis (3500 h) whilst simultaneously reducing the amount of material required.