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Droplet microfluidic flow platforms for automated reaction screening and optimisation

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Abstract

The demand for efficient and sustainable chemical process development has driven significant advancements in automated droplet flow platforms, which, when coupled with high-throughput experimentation, offer powerful solutions for generating synthetic libraries and optimising reaction parameters. Droplet flow platforms allow for reactions to take place on a microfluidic scale, enabling rapid and sustainable process optimisations. The size of the droplet is varied, with the technique of generating the droplet differing from multiple pumps to advanced robotics. Approaches to integrate multiple analytical tools, phase sensors and parallel reactors have been developed, broadening the capabilities and increasing the throughput of these platforms. Herein, we review recent advancements made within this field, highlighting the type of chemical reactions investigated and the digital technologies which have enabled closed-loop optimisations.

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Automation, Continuous flow, Microfluidics, Optimisation, Robotics.

Introduction

Over the past two decades, flow chemistry has been increasingly exploited for the development of new processes within the fine chemical and pharmaceutical industries [1–3]. The increased safety, improved mass and heat transfer, ease of automation and precise control of experimental conditions are some of the reasons chemists in industry and academia are evaluating a continuous mode of operation. Optimising processes improves sustainability while simultaneously reducing costs, thus increasing the accessibility of products. State-of-the-art 'self-optimising' systems involve; the pumping of liquids, which are mixed and activated (via heat, light, electrochemical potential etc.) in a reactor for a defined time which are quantified using online analytical technologies and together with optimisation algorithms create an active learning feedback loop (Figure 1a) [4–9]. From this data, the algorithm produces the next set of experimental conditions to test for the desired objectives, for example, yield, selectivity, and space-time yield (STY), resulting in a closed-loop system [4,6,10,11].

During the optimisation of a continuous flow synthesis, an uninterrupted supply of reagents is required, which often results in the consumption of a significant amount of materials. The analysis is performed once steady state is achieved, i.e. transient flow conditions no longer exist in the system. This typically requires approximately 2–4 reactor volumes depending on the physical characteristics of the reactor. For example, in the optimisation of a Heck–Matsuda reaction, a 5 mL tubular reactor was used. The reaction was not sampled until at least 15 mL had passed through the reactor of which <1 % is used for analysis [12,13].

Batch high-throughput experimentation (HTE), which has been used extensively within the pharmaceutical sector, requires equipment capable of working on a micromole scale, reducing material consumption during screening [14]. Furthermore, such equipment allows for a multitude of categorical variables (e.g. catalysts, ligands, substrates) to be screened in parallel. This increases the speed at which potential drug compounds can be identified and optimised, reducing the time taken for development [15]. Batch HTE for optimisations however, has some drawbacks which include:

I. Limited to non-volatile solvents as the systems used are not usually pressurised.
II. Very limited operating window (e.g. low temperatures).

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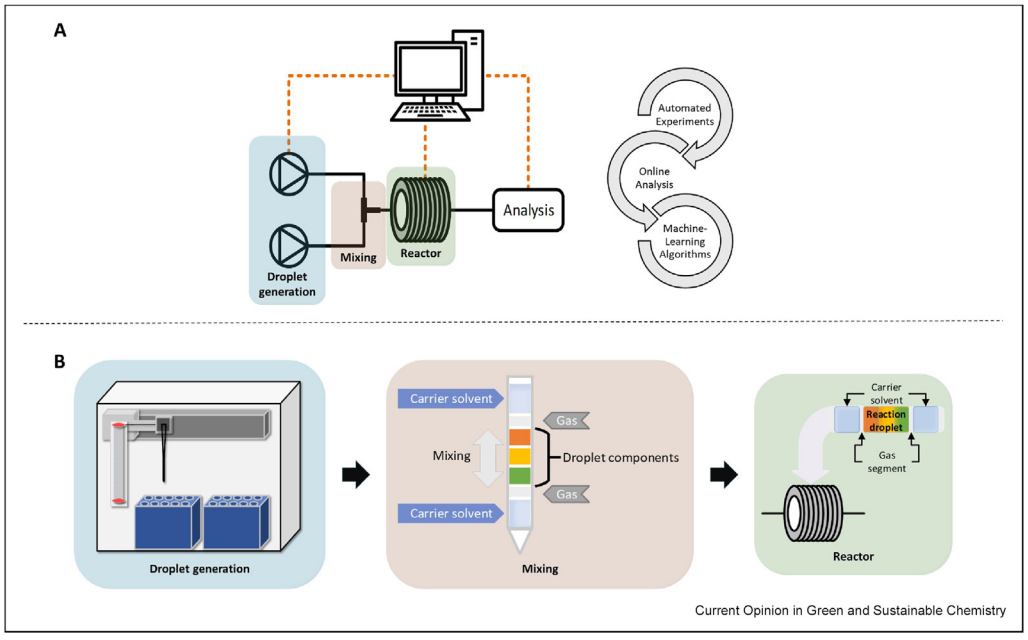
Figure 1



(a): Automated continuous flow platform equipped with analytics and optimisation algorithms creating a feedback loop. Reproduced and adapted from Ref. [11] under the terms of CC BY-NC 4.0 with permission from the Authors. **(b)**: Schematic of droplet flow generation, when using robotics and mixing via the liquid handler. The reaction droplet is shown separated from the carrier solvent using gas segments which are not always incorporated.

III. Difficult to adjust continuous variables in parallel, i.e. well plates are usually at one fixed temperature.

Notably, many of these limitations can be solved by the design and application of automated continuous flow platforms. There is therefore significant interest in developing microscale flow reactors which can explore process-relevant conditions. While other reviews have focused on the fundamental principles of droplet flow-based reactors [16], this review highlights recent applications of these approaches for autonomous reaction optimisation.

Automated droplet flow platforms

Miniaturised flow platforms typically use liquid-handling robotics to create reaction droplets from minimal material quantities, which are then transferred into the reactor using a carrier phase (Figure 1b). This carrier phase can be the same solvent as the liquid phase, an immiscible liquid to the reaction phase, or an inert gas. Utilising droplets in these platforms allows for reaction optimisations at the microfluidic scale with various reagents. Liquid-handling robots facilitate precise droplet generation, ensuring specific droplet sizes without excessive use of materials and at a small scale. Alternatively, multiple pumps can be employed to generate droplets, allowing for variations in concentration and equivalents, though this may require larger volumes of reagent stocks [16–19].

In recent years, the advantages provided by HTE and flow chemistry have been combined to produce platforms capable of screening a large range of substrates efficiently, whilst also testing a number of reaction conditions, catalysts and reagents. Such platforms allow for material and time-efficient screening, avoiding solvent evaporation and improved mixing, simultaneously developing a further understanding of the reaction space. Furthermore, access to a wider and more process-relevant region of parameter space is provided, compared to batch HTE, with the ability to test higher temperatures and pressures. In turn, the efficiency of drug discovery and development is improved as well as potential synthetic conditions discovered [14]. Advancements within the automated droplet flow platforms have included multiple analysis techniques, robotics to formulate reaction droplets and facilitate mixing as well as optimisation algorithms for mixed variables and multiple objectives (Table 1).

Sachs et al. (2018) cite the use of a liquid handler, combining HTE with the capabilities of flow to screen thousands of reaction conditions for a Suzuki–Miyaura cross-coupling reaction in a short time span [20]. By use of an autosampler, reaction segments between 5 and 80 µL were created. The combination of robotics with a flow setup enabled rapid screening of mixed variables, something that would not have been possible in a batch system. Combining the time required for the preparation and analysis of each reaction droplet, the platform developed

Table 1

Overview of droplet size, flow, reaction type and analytical techniques for all the research papers discussed within this review. PAT = process analytical technologies.

Group	Droplet Formation Method	Droplet Size (μL)	Flow	Reaction	PAT
Sachs *et al* (2018)	Liquid Handler	5	Continuous	Suzuki–Miyaura	LC-MS
Kappe *et al* (2024)	Pumps	300	Continuous	Buchwald-Hartwig amination	IR & HPLC
Noel *et al* (2024)	Liquid Handler	650	Continuous	Photocatalytic chemistry	Phase sensors & Flow NMR
Jensen *et al* (2015)	Liquid Handler	16.1	Oscillating flow	Mono-Alkylation	LC-MS
Jensen *et al* (2016)	Liquid Handler	17.5	Continuous	Suzuki–Miyaura cross-coupling	HPLC
Bourne *et al* (2022)	Liquid Handler	1000	Stopped flow	Amide library investigating coupling agents	IR & HPLC
Jensen *et al* (2023)	Liquid Handler	25–120	Stopped flow	Buchwald-Hartwig amination	HPLC

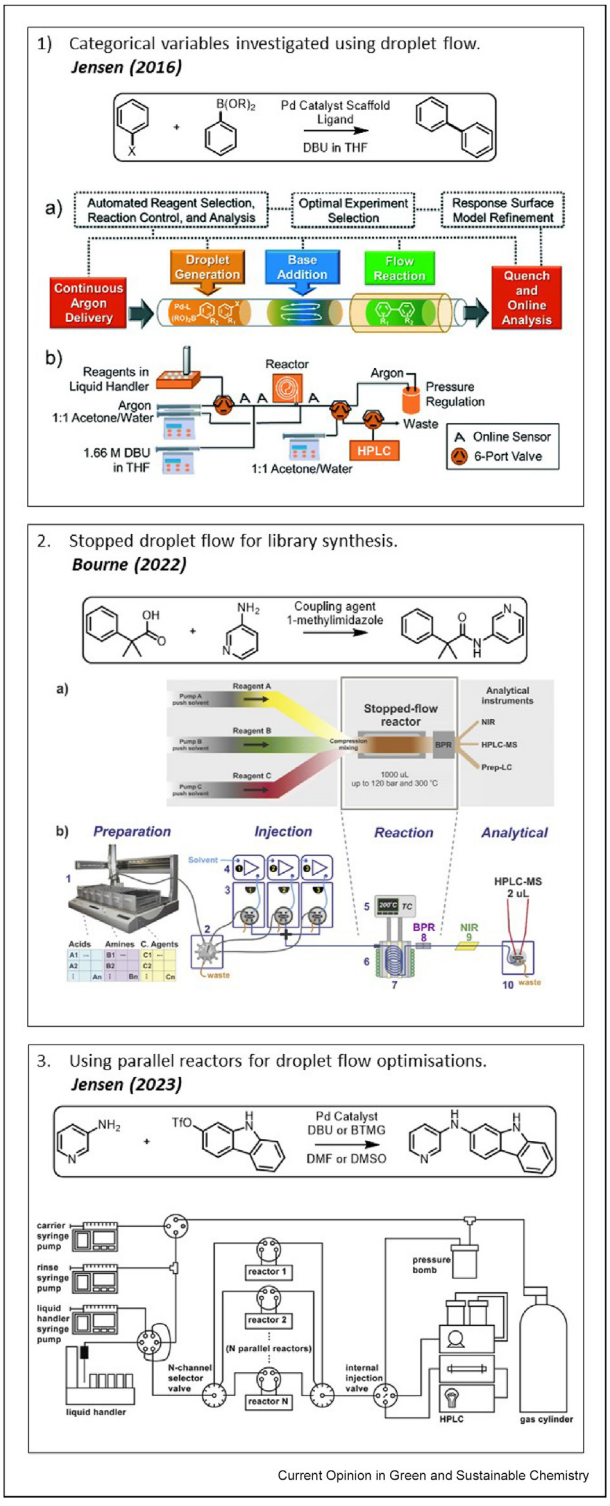
by this group was able to perform around 1500 reactions within 24 h. As the reaction components diffused into the carrier solvent upon injection, this allowed for solvents to be screened as a variable in this study with a suitable dilution. However, this diffusion can make accurate quantification using online analytics challenging for other applications such as optimisation studies.

Whilst Sachs et al. have shown rapid screening can be combined with flow, such setups can also be coupled with process analytics and optimisation algorithms, producing a fully autonomous workflow to find optimal reaction conditions in a shorter time frame. The Kappe group used a set of HPLC pumps to formulate the reaction droplet, with gas used to separate the droplet from the carrier solvent [21]. This was done to avoid dispersion of the reaction mixture into the carrier solvent thereby maintaining the reactant concentration. Variables such as the loading of base and the loading of catalyst were optimised for a Buchwald-Hartwig amination. The system allowed for many possible reaction variables to be studied, enabling six variable and multi-objective self-optimisations. A potential bottleneck when conducting HTE in flow is the wait time for the specified analysis; using two analysis tools allows for the potential for reactions to occur in parallel with different reaction conditions. A possible complication when using droplet flow can arise when using such small volumes, as without precise control there can be uncertainty as to the droplet location. This can be particularly problematic for online analysis which requires precise sample injection. Kappe et al. show how using a spectroscopic technique, Fourier transform infrared (FTIR), can be used to detect the droplet and in turn trigger the injection into the ultra-high performance liquid chromatography (UHPLC), combining two process analytical technologies (PAT). The reaction was successfully explored using three different optimisation techniques-kinetic experiments, self-optimisation using a Thompson sampling efficient multi-objective (TSEMO) Bayesian algorithm and design of experiments (DOE), demonstrating the multi-functional capabilities of the system. However, as liquid handling robotics were not integrated in this set-up, the optimisations were limited to only continuous variables.

The method of tracking the reaction segment through the reactor was used in a similar setup for the optimisation of a variety of photocatalytic transformations, a first-time application for droplet flow. Recent research conducted in the Noël group incorporates a liquid handler to formulate the reaction segment, with an inert gas segment injected to separate the reaction from the carrier [22]. Phase sensors were used to track the position of the reaction segment, identifying the gas segment, a technique which increases the control for the user. When investigating such transformations on this platform, 60 MHz benchtop NMR was utilised to enable automated optimisations. Using NMR as the analysis technique removed the need for calibrations which most other quantitative analytical tools require. Whilst the cited platform can be adapted for other analytical techniques, the use of NMR increased the volume of the reaction segment as more material, a 650 μL slug, is required when compared to HPLC etc. due to flow cell volumes. Both single and multi-objective optimisations were conducted, where the ideal conditions were identified in a small number of experiments (between 18 and 36). When compared to batch, the productivity improvement was 70−100 times greater, with space-time yields increasing by 500 times. Furthermore, the algorithm generated higher throughput and product yield which in some of the case studies was greater than 90 %.

Reizman and Jensen combined droplet flow platforms with robotics to conduct discrete variable optimisations [23]. Using droplets of 16 μL, the smallest volume quoted for this application, the yield for an alkylation reaction was optimised to above 60 %, in 93 experiments overall. Whilst varying the temperature and residence time, the solvent system was investigated, identifying interesting mechanistic properties connected to the choice of solvent for this particular chemistry. This led to further experimentation to understand the effect

Figure 2



(1) Droplet flow platform, coupled with robotics, multiple pumps and HPLC analysis for categorical variable optimisations for a Suzuki Miyaura reaction. Copied and adapted from Ref. [24] under the terms of CC BY-NC 3.0 with permission from the Authors and from the Royal Society of Chemistry. (2) The developed platform to enable stopped droplet flow for the library synthesis for amide coupling reactions, utilising multiple switching valves for droplet generation and NIR to track the droplet position before analysis. Copied and adapted from Ref. [26] under the terms of CC BY-NC 3.0 with permission from the Authors and from the Royal Society of Chemistry. (3) A platform fitted with parallel reactors capable of running a closed loop optimisation for a Buchwald Hartwig reaction. Copied and adapted from Ref. [27] under the terms of CC BY-NC 3.0 with permission from the Authors and from the Royal Society of Chemistry.

solvent polarity can have on the yield of a reaction. This highlights the capabilities of HTE coupled with flow chemistry, enabling rapid insight into potentially unexplored (side-) reactions whilst also fast-tracking reaction optimisations. The system was limited to a maximum residence time of 10 min however, resulting in a time-restricted reaction space exploration.

Following on from this work, Jensen et al. demonstrated how a similar platform can be used for a Suzuki–Miyaura cross-coupling reaction, with an 8 % increase in droplet size [24]. Precatalysts and other reagents were stored under argon in the liquid handler, demonstrating a further complexity of the chemical applications of the platforms (Figure 2). Whilst previously, an oscillation technique within the reactor was used by the group, in this study, the droplet was mixed three times in the headspace of the probe under argon.

Platforms discussed thus far have controlled residence time via continuous unidirectional movement of the droplet through the reactor. However, droplet-based flow has been used successfully in the screening of libraries for a variety of medicinal chemistries at small scales, choosing to oscillate the segments to induce mixing or slow the flow rate of the carrier solvent for the desired residence times. The back-and-forth movements of the liquids can provide some advantages over continuous flow such as allowing for more controlled mixing of the reagents within droplets and allows for residence time to be independent of flow rate, a limiting factor depending on the type of pumps used. This can also provide a solution to the challenge of controlling gas flow rates within flow, providing more uniform residence times and flexibility in flow rate adjustments. This can however lead to reagent residue on the walls of the reactor, requiring a potentially extensive cleaning procedure between reactions which can limit the experimental throughput.

A stopped-flow platform effectively demonstrated liquid–liquid droplet flow for high-throughput drug discovery [25]. The Bourne group have demonstrated how liquid–liquid droplet systems with stopped flow can be utilised for library synthesis and rapid optimisation using machine learning directed experimentation [26]. As the same solvent is used for the reaction and carrier phase, the reaction segment required further analytics to track the phase. This is due to an increased risk of dispersion into the carrier phase to ensure the

correct segment is sampled. Near infra-red (NIR) sensors were used to track the droplet and trigger the analytical instrument. A stopped flow approach can reduce solvent loss issues and loss on reactor walls compared with oscillation, which can occur at high temperatures and pressures; both of which are attractive features of flow chemistry [27]. This research shows the capability to increase the success rates when developing libraries for synthesis and doing so with a large reduction in material and waste. This allowed for ~5 reactions to be run per hour, which in continuous flow would require a large amount of material and solvent and in batch would require increased operator hours. The system was used to conduct 900 experiments in HTE mode, integrating a feed-forward neural network to predict reaction conditions for unseen substrates which resulted in an 80% correct predictions. This platform allowed for higher temperatures and pressures to be used, increasing the initial library synthesis success rate. The system however, was limited to one droplet at a time which significantly limits experimental throughput.

Jensen et al. detail a platform for thermal and photochemistry as well as investigating the kinetics of a reaction in a time and material efficient manner by conducting reactions in parallel [27]. Droplets were prepared in parallel to ongoing reactions and sequentially delivered to the coiled reactor, using stopped-flow. This in turn reduced the time between reactions, as the wait time between reactions then depended on the time to heat or cool the reactor and the analytical time, diminishing some potential bottlenecks. To make multiple reactor droplets *in situ*, a scheduling algorithm was used to ensure droplets are unable to collide by shifting the preparation time of the droplets. Not currently investigated is the effect of mixing at room temperature when parking the droplets and the consequent effect on the objectives as this wait time may not always be the same or accounted for. Within this setup, it was limited to two reactions in parallel which reduces time in-between but could be increased by use of multiple reactors or different heated zones allowing for multiple reactions to take place simultaneously.

Future outlook

Discussed above are some of the major advances made in this field, with efforts made to improve accuracy, efficiency, cost, time and waste of materials. Categorical variables (e.g. ligands, coupling agents) can now be optimised on such platforms, increasing the scope of the chemistries and the interactions between mixed variables. Robotics have been incorporated to improve accuracy and help autonomise the applications of these platforms. Notably, integration of liquid handling robotics with continuous flow systems have provided a method for preparing micro-volume reaction droplets. These can be delivered to the reactor using a single pump, where they can be oscillated or held stationary, thus overcoming limitations associated with the use of multiple pumps.

As demonstrated by Jensen et al., parking droplets improves the efficiency of automated droplet platforms and can reduce time between reactions. Employing multiple reactors in the system, with valves to direct the flow, could be of assistance in reducing wait time for reactors to reach within 1 °C of a desired temperature. Different fixed temperature zones within the same coiled reactor is another technique which could improve the throughput by deploying droplet to the appropriate zones. Although complications could arise due to the complexity with downstream analysis, potentially requiring additions such as phase sensors or by coupling multiple PAT tools.

Whilst running droplet reactions in parallel is desirable for enhanced experimental throughput, the performance of optimisation algorithms often decreases with increasing group size. As the set of experiments is typically constructed using iterative predictions from the current model rather than evaluated data points, it is possible that redundant experiments can be suggested, particularly early in the optimisation when model accuracy is lower. Therefore, development of robust optimisation methods for suggesting sets of parallel experiments will be required to fully realise the potential of self-optimising droplet flow reactors in the future.

Furthermore, a challenge which remains is the analysis time of many methods. Improvements have been made by employing UHPLC which can shorten a method used in HPLC by significant percentage [28]. Some chemistries however, are incompatible with such short columns and methods. The obstacle remains with the need for more advanced real-time analytics that can accurately quantify the products. Robotics can also require lengthy loading times. Generating multiple segments to save time is effective, however the time taken to formulate the droplet can be time-consuming. Multiple robotics can be employed to autonomise some of the manual work still required by scientists, thus improving the accuracy. However, this comes with added costs, complexity and potential volume limitations.

Increasing the throughput of droplet flow platforms via fully-automated, efficient analysis and advancements in chemical machine learning offer solutions to challenges presented within the current generation of HTE, providing an efficient approach for the future of process optimisations.

Editorial disclosure statement

Given the role as Guest Editor, Adam Clayton had no involvement in the peer review of the article and has no

access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Sebastian Cosgrove.

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

No data was used for the research described in the article.

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