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Process analytical technologies and self-optimization algorithms in automated pharmaceutical continuous manufacturing

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ABSTRACT

The pharmaceutical industry is now paying increased attention to continuous manufacturing. While the revolution to continuous and automated manufacturing is deepening in most of the top pharma companies in the world, the advancement of automated pharmaceutical continuous manufacturing in China is relatively slow due to some key challenges including the lack of knowledge on the related technologies and shortage of qualified personnels. In this review, emphasis is given to two of the crucial technologies in automated pharmaceutical continuous manufacturing, *i.e.*, process analytical technology (PAT) and self-optimizing algorithm. Research work published in recent 5 years employing advanced PAT tools and self-optimization algorithms is introduced, which represents the great progress that has been made in automated pharmaceutical continuous manufacturing.

1. Introduction

In the 21st century, the chemical industry is undergoing significant transformation, looking forward to greener, safer, and more efficient and sustainable technology. Especially in the field of pharmaceutical manufacturing, the need for technological innovation and production mode transformation is quite urgent, due to the big challenges in quality control, production efficiency, safety and cost faced by the traditional batch production. Especially, the global outbreak of COVID-19 for the past few years has brought more attention to the pharmaceutical industry and, at the same time, made us acutely conscious of the limitations of traditional drug development and manufacturing. The rise of continuous flow has opened up a new way for drug manufacturing, and the importance of pharmaceutical continuous manufacturing (PCM) has been emphasized in recent years. In 2019, the Food and Drug Administration (FDA) published the long-awaited draft guidelines for implementing continuous and flow chemistry manufacturing, *i.e.*, "Quality Consideration for Continuous Manufacturing" [1]. Later in 2021, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) released the draft version of "Continuous Manufacturing of Drug Substances and Drug Production" for public consultation, and the final version was adopted in November 2022 [2]. PCM has been demonstrated to exhibit advantages including process intensification, improved safety, ease of integration, and, most importantly, reliable production of drugs of high and consistent quality [3–12].

However, the transition from batch to continuous mode is not the end of the ongoing evolution of pharmaceutical manufacturing. Drugs are special commodities for curing diseases and saving lives, therefore, the effectiveness, safety, stability and consistency of drug quality are quite important. Drug production is a key link to ensuring drug quality, and the strategies of quality by design (QbD) and quality by control (QbC) were put forward to emphasize the necessity of monitoring, evaluating and controlling the entire process of drug development and manufacturing [13–16]. In this context, a considerable number of continuous flow platforms, integrated with computer control of equipment, process analytical technology (PAT), computational algorithms, or a combination of them, have been developed to fully understand, monitor, control and optimize the drug manufacturing process and to provide safe and effective products of consistent quality [17–19]. Computer

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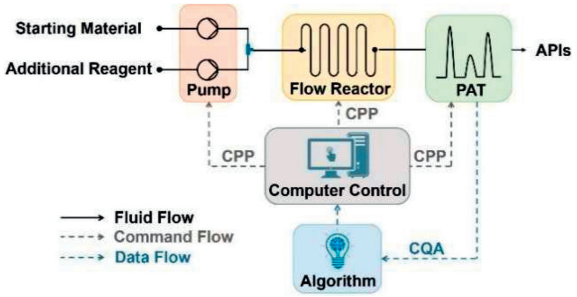

Fig. 1. The schematic diagram of continuous flow platform integrated with computer control, PAT and algorithms. Sometimes a simpler platform incorporating only one or two of the three elements is used depending on the practical needs. Abbreviations used are: CPP, critical process parameters; CQA, critical quality attributes; and API, active pharmaceutical ingredient.

control, PAT and algorithms are all powerful technical supports for developing highly automated and integrated pharmaceutical manufacturing platforms (Fig. 1), which can accelerate drug discovery and manufacturing process, improve the understanding of reaction mechanisms, and save manpower, materials and costs.

Despite a number of reviews related to PCM, reviews regarding the essential technical foundation used in the autonomous continuous flow platforms for drug development, synthesis and formulation are relatively rare. Since computer control of equipment is to communicate with the equipment with the computer commands which vary from one to another, it is not discussed in this review. Herein, we are going to briefly introduce some commonly used PAT tools and optimization algorithms in the PCM reported in the past five years.

2. Application of PAT in pharmaceutical continuous manufacturing

2.1. PAT concept and equipment

As stated in "Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance" published by FDA in 2004, PAT was defined as "a system for designing, analyzing, and controlling manufacturing processes through timely measurement of critical process parameters (CPP) which affect critical quality attributes (CQA)" [20]. PAT can serve as an effective tool to implement QbD or QbC in the pharmaceutical industry, helping to develop manufacturing processes, improve product quality and production efficiency, and shorten production cycles. What is exciting is that PCM provides a capable platform to readily integrate PAT and makes full use of the advantages of PAT in drug development, synthesis and preparation [18,21–25]. Reversely, the use of PAT helps to develop PCM platforms for autonomous multi-step synthesis, construction of compound libraries, process optimization and scale-up, *etc.*, therefore creating a synergistic effect.

A wide range of inline and online analytical tools has been developed for process monitoring over the past decades (Table 1). Spectroscopic techniques including UV-vis [26,27], infrared (IR) [28–31] and Raman [32,33] spectroscopy are currently the most used and preferred PAT tools because of their fast analysis speed and non-invasive and easy integration. Among them, inline UV-vis is one of the earliest tools used to implement PAT with mature development, but having low resolution and sensitivity and providing limited information. In contrast, inline IR and Raman spectroscopy is able to offer more reaction-related information, the former of which is relatively mature. The main difficulty for the development of inline Raman is to customize the flow cell and analysis probe to improve the detection sensitivity, and great progress has been made, for example, in the development of surface-enhanced Raman scattering (SERS) [34]. Mass spectrometry (MS) [35] and nuclear magnetic resonance (NMR) [36,37], two of the more powerful analytical techniques, have also been integrated as PAT tools into continuous flow platforms, which have higher resolution and are more sensitive. However, MS equipment is large and expensive, and the analysis process would be affected by the matrix effect, which often requires additional processing steps before analysis, so the integration is more difficult and the analysis is also slower. Beyond those mentioned above, chromatographic tools like high performance liquid chromatography (HPLC) [38] and gas chromatography (GC) [39], particle size analyzer [40] which can be used in crystallization and nanoparticle preparation processes, as well as various temperature and pressure sensors, can also serve as PAT tools to make efforts for drug quality assurance.

Table 1
Summary of the commonly-used PAT tools reported in the reference.

PAT tool	Equipment	Application	Ref.
UV-vis	Jasco UV-2075	Halogenation purification	[47]
	Avantes	Synthesis of edaravone	[48]
	AvaSpec-ULS2048	Synthesis of 5-acetylsalicylic acid	[49]
IR	Bruker Alpha FTIR spectrometer	Synthesis of 5-acetylsalicylic acid	[50]
	Mettler Toledo ReactIR 15	Synthesis of blocked polyisocyanate	[51]
		Asymmetric hydrogenation	[52]
Raman	Kaiser RamanRxn2® Hybrid analyzer	Formulation of 5-acetylsalicylic acid	[50]
NMR	Magritek Spinsolve Ultra	Addition–fragmentation chain transfer polymerization	[53]
		Synthesis of 1,5-disubstituted tetrazoles	[54]
		Grignard reaction	[55]
MS	Microsaic 4000 MiD	Aerobic oxidation reaction	[56]
HPLC	Shimadzu Nexera X2	Synthesis of edaravone	[48]
		Synthesis of 5-acetylsalicylic acid	[49]
SEC[a]	Custom-designed PSS system	Addition–fragmentation chain transfer polymerization	[57]
FBRM[b]	Mettler Toledo FBRM S400	Crystallization	[40]

[a] SEC is size exclusion chromatography.
[b] FBRM is focused beam reflectance measurement.

2.2. Flow platforms integrated with PAT tools

Over the past five years, a series of new flow platforms integrated with PAT tools have been reported. The applications for the various stages of drug development and manufacturing, including high-throughput drug synthesis, optimization process, formulation process, end-to-end pharmaceutical manufacturing, and even the synthesis of polymers and nanoparticles related to the medical domain, will be introduced in this section.

2.2.1. Library generation and high-throughput drug synthesis

The modularity of continuous flow platforms enables easy integration of automation and high-throughput technique, so as to rapidly build compound libraries or synthesize a large number of compounds, which can speed up the subsequent drug screening and discovery process, and free up the human operators from repetitive work [41–46]. And assisted by PAT like LC-MS, IR, NMR, *etc.*, real-time analysis of the synthesized product and feedback on the robustness of the process can be achieved.

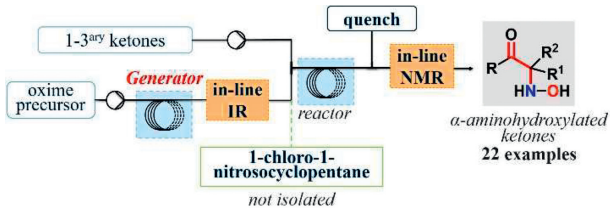

Fig. 2. Flow system for electrophilic α-aminohydroxylation of various primary, secondary and tertiary enolizable ketones.

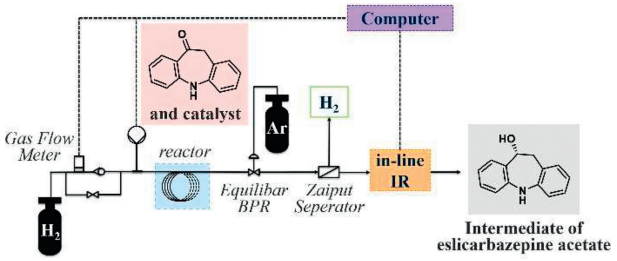

Fig. 3. The flow diagram of the key asymmetric hydrogenation step in the synthesis of eslicarbazepine acetate.

Gilmore and colleagues [41] reported a continuous flow automated radial synthetic platform, which could speed up and simplify the preparation of organic molecules. The platform had a special central switching station (CSS) configured with several radially-arranged thermochemical and photochemical reactors and inline analytical equipment, as well as a reagent delivery system (RDS) providing stocks for a variety of solvents and reagents. In this way, the platform could realize multi-step reactions and multi-condition experiments without reconfiguring the modules. Meanwhile, thanks to the integration of flow IR and NMR as the PAT tools, several synthetic routes of the anticonvulsant drug rufinamide were screened and optimized efficiently. Furthermore, a derivative library of rufinamide containing 12 compounds was constructed in an efficient manner.

Using the modular nature of flow platforms, Monbaliu's group [42] developed a system for electrophilic α-aminohydroxylation of various enolizable ketones (Fig. 2). The system was integrated with online purification equipment and multi-layer inline analytical procedures including NMR and IR, to safely and efficiently deal with toxic and unstable substances involved in the reaction, and to monitor the process in real time, greatly improving process safety. Based on this system, 22 α-aminohydroxylated ketones were prepared from primary, secondary and tertiary ketones, thus demonstrating the potential of the continuous flow system in constructing libraries and providing upstream supply for drug discovery.

Richardson, Sach and coworkers [43] exploited continuous flow technology integrated with equipment from biological analysis and screening, to construct a high-throughput synthetic platform for homogeneous reaction systems. The platform was capable of preparing and analyzing up to 1500 nanoscale reactions within 24 h, and simultaneously screening multiple discrete and continuous variables, enabling a wide range of conditional parameters to be explored with minimal material consumption. To maximize time efficiency, the reaction segment preparation unit was connected to two Agilent 1200 UPLC-MS equipment to enable online monitoring and rapid analysis of the reactor effluents. While one UPLC-MS was analyzing a reaction segment, the other was preparing to be triggered to analyze the next emerging reaction segment. The Agilent Chemstation software was used to pick up the key peaks in the UPLC-MS trace, and the off-line refinement of the data was carried out through iChemExplorer software successively followed by the visualization with Spotfire. The data analysis process for 1500 reactions only took 1 h. The Suzuki-Miyaura coupling reaction was selected as a model to test the utility of the platform, and a reaction matrix containing 7 electrophiles, 4 nucleophiles, 11 ligands, 7 bases, and 4 solvents was constructed. Benefitting from the integration of high-resolution UPLC-MS tools, useful information for 5760 reactions was successfully obtained by screening the whole set of variables.

2.2.2. Process study and development

The potential of applying continuous flow platforms to study the reaction mechanism and kinetics of organic synthesis has been demonstrated and emphasized in many publications [58–65], which provides a solid foundation for the process study and development in PCM. And integration of PAT in PCM platforms enables real-time assessment of CQAs, which assists the implementation of QbD and QbC principles. In 2017, Cooks, Thompson, Nagy and coworkers [35] from Purdue University, reported a highly-integrated continuous flow method for developing a synthetic process of the antihistamine diphenhydramine, using chlorodiphenylmethane and dimethylaminoethanol as starting materials. To solve the problems of the slow offline analysis, the system employed online MS equipped with an inductive ionization source to rapidly detect reactions and assist in optimizing process conditions. Additionally, an inline video microscope along with an optical sensor was also set up for real-time monitoring of droplets before entering the online MS, to ensure the stable operation of the system. Later, Wen and coworkers [52] developed a high-pressure slug flow reactor system integrated with an inline IR probe for the optimization of the asymmetric hydrogenation (AH) in the synthesis of the anticonvulsant eslicarbazepine acetate (Fig. 3). The *in-situ* Fourier transform infrared spectrometer (FTIR) used Lambert-Beer law and calibration to provide the concentration data of components in the reaction mixture and aided in efficiently attaining the optimal AH conditions that were eventually applied to the three-step continuous flow synthesis of eslicarbazepine acetate. Similarly, Pabbaraja, Singh and colleagues [66] also applied inline IR to a continuous flow platform for the manufacturing of active pharmaceutical ingredients (APIs) which was an integrated system that encompassed reaction, quenching, extraction and phase separation processes. And the IR analysis was used to monitor the effluent products in real time to assess the stability of the synthesis in long-time operation.

Besides real-time monitoring of single-step reactions in drug synthesis, research work has also been reported on multi-site monitoring of more complex drug manufacturing processes using several process analysis devices. In 2021, Kappe, Williams and coworkers [67] published their work on the development of a three-step continuous flow manufacturing process which used 2-chlorobenzoic acid as a starting material to synthesize mesalazine, a commonly-used drug for treating Crohn's disease and colitis, through nitrification, high-temperature hydrolysis, and hydrogenation (Fig. 4). Three inline liquid-liquid/gas-liquid separation tools were introduced to enable the tandem integration of multi-step reactions. At the same time, four complementary PAT tools were assembled to monitor the entire process at multiple sites, including inline NMR, UV-vis and IR and online UHPLC. Inline NMR was selected to monitor the nitrification reaction after quenching and extraction, which used an indirect hard model (IHM) for data quantification. Inline UV-vis was chosen to monitor the conversion of the high-temperature hydrolysis reaction, which implemented a neural network (NN) written by Python to quantify the concentration of analytes. After the hydrogenation, the effluent was processed by the gas-liquid separator and then analyzed by inline IR which used a partial least squares (PLS) regression model to pro-

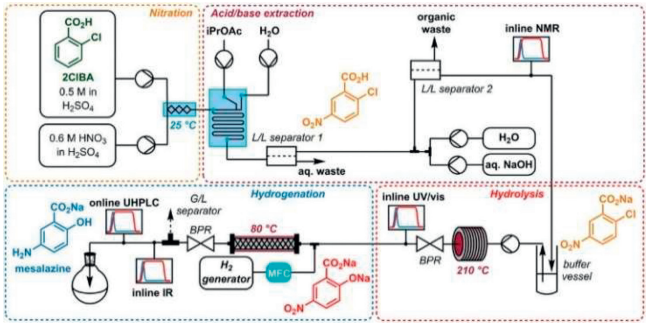

Fig. 4. The customized platform for three-step continuous flow manufacturing of mesalazine, where inline/online NMR, UV-vis, IR and UHPLC were assembled to monitor the entire process in real time at multiple sites. Copied with permission [67]. Copyright 2021, Wiley-VCH.

cess data, and the final product was quantitatively analyzed by online UHPLC. The different analytical techniques used in this system could ensure fast analysis speed and good process resolution, and its practicality had been verified by long-term stable operation and dynamic experiments of the system. Based on this work, Kappe and colleagues [49] recently took a closer look at the process. With the aid of flow platforms integrated with PAT tools, they developed process models based on reaction dynamics, process data and residence time distribution for controller design and automated fault detection, facilitating the automation of the platform.

2.2.3. Purification process monitoring

Purification is the important link between different reaction steps as well as the key interface for the transition from synthesis to formulation in drug manufacturing. Nevertheless, purification procedures are often tedious and become bottlenecks in process development. As a result, a considerable amount of work, integrating PAT techniques into the continuous drug purification processes, has been published.

Kappe, Cantillo and coworkers [61] developed a continuous multistage phase separation platform for the continuous flow synthesis of methyl oxime acetoacetate, where a smooth and stable extraction process was guaranteed and solvent consumption was greatly reduced by setting up inline pH monitoring and adjustment. Ley *et al.* [47] reported the integration of commercial automated flash chromatography into a continuous flow platform for inline purification. The chromatograph was equipped with an inline UV detector and an evaporative light scattering detector (ELSD) to monitor the output solution for product identification and ensure the stable operation of chromatographic separation. Another related work is the continuous crystallization technique reported by Nagy's group [40], in which Lasentec focused beam reflectance measurement (FBRM) was applied to the online monitoring of the crystal size distribution. With the help of the real-time size monitoring, the characteristics of several different crystallizers were compared, which provided a new concept and method for crystallization process intensification. The research on the merger of PAT and inline purification technology is contributing to the advancement of PCM platforms, promoting the transformation from batch to flow.

2.2.4. End-to-end pharmaceutical manufacturing

In the past few decades, researchers have made great efforts in the development of PCM, which are not limited to the study of the synthetic process but also include the investigation on the whole process from synthesis to formulation to commercially available products. This section is about to summarize some of the recently reported end-to-end continuous pharmaceutical manufacturing platforms [68–71] that integrated PAT tools for real-time monitoring of both the synthetic and formulation processes.

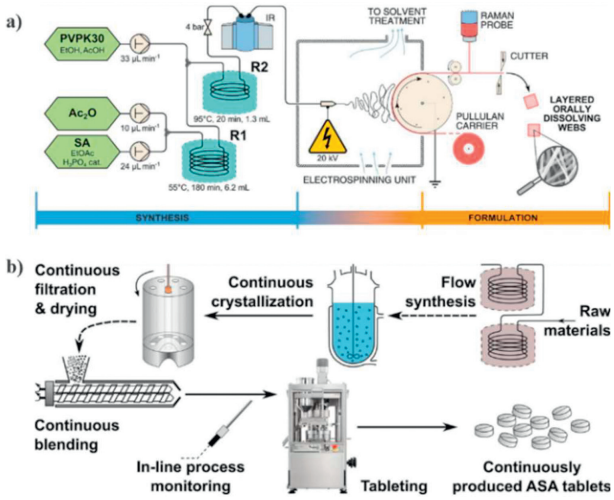

Fig. 5. (a) End-to-end platform for the production of the ODWs of ASA. Copied with permission [50]. Copyright 2018, Elsevier. (b) End-to-end platform for the manufacturing of ASA tablets. Copied with permission [68]. Copyright 2020, Elsevier.

Marosi, Balogh and coworkers [50] connected continuous flow synthesis and electrostatic spinning (ES) to develop an end-to-end platform for the production of solid pharmaceutical formulations and prepared the orally dissolving webs (ODWs) of acetylsalicylic acid (ASA) (Fig. 5a). Polyvinylpyrrolidone K30 (PVPK30) was used as a water-soluble polymeric excipient and mixed with the APIs, and the nanofibers were prepared by electrospinning with a needle spinel. Then the nanofibers were uniformly deposited on the pullulan carrier for further formulation. It deserves mentioning that an FTIR spectrometer was set up before ES to quantitatively analyze ASA purity in real time, and a Raman probe was also used as a PAT tool to monitor the fiber quantity and uniformity deposited on the carrier after the formulation was completed, so as to ensure that the final ODWs met the quality requirements. Later, Nagy and coworkers [68] reported another continuous flow platform for the end-to-end manufacturing of ASA, which focused more on API purification and formulation processes (Fig. 5b). The full continuous system consisted of a mixed suspension mixed product removal (MSMPR) crystallizer, a filter unit and an automatic tablet press for the production of ASA tablets. In this system, an inline near-infrared (NIR) probe was used to collect spectral data of the powder mixture which was then quantified by a calibration model based on PLS regression to determine the content of ASA, providing a guarantee for product quality.

In 2019, Mascia, Hu and coworkers [69] reported a fully automated, end-to-end platform for small molecule drug manufacturing, with a box of 30.7 m^2 modular footprint and capability of producing 40.3×10^6 tablets per year. Compared with traditional production systems, the platform offered significant improvements in solvent usage reduction, total waste reduction and energy saving, and, additionally, exploited multiple PAT tools rendering improved product quality control. ReactIR and FBRM were assembled to monitor the crystallization and resuspension processes, while NIR spectroscopy, Raman spectroscopy and particle size analyzer were utilized for the drying process to ensure that the APIs met the required specifications in respect of particle size and residual solvent in particles. The final extrusion-molding coating used NIR and Raman spectroscopy to assist in the analysis of the extrudate, thus assuring that qualified tablets were finally produced.

Not only for solid formulation production, the end-to-end continuous flow platforms for oral liquid dose production have also

been reported. Jensen, Jamison and coworkers [70] developed an advanced continuous flow platform that integrated upstream API synthesis with downstream formulation, and successfully produced three kinds of liquid doses that all met US Pharmacopeia standards, *i.e.*, the antibiotic ciprofloxacin hydrochloride, the muscle strengthener neostigmine methylsulfate and the anticonvulsant rufinamide. The system was equipped with 20 pieces of auxiliary equipment, like pressure sensors in upstream synthesis, and temperature and level sensors in downstream formulation, as well as single frequency ultrasound (SFU) probes to measure the API concentration of the liquid doses in real time.

To sum up, the end-to-end continuous pharmaceutical manufacturing platforms exhibit good prospects in the face of the challenges in drug production requirements and quality control, as well as the complexity of API manufacturing. PAT is an indispensable key component that can be used as a measure to activate precontrol or feedback control, and meanwhile provide essential information to assist in judging material transfer, preventing nonconforming products from entering downstream production and ensuring the quality of the final drug product.

2.2.5. Others

The development of nanotherapeutic systems for drug delivery that can afford better pharmacokinetics and controllable drug delivery and targeting, has been a critical topic in the pharmaceutical field. Since the traditional batch preparation of drug-related nanomaterials and polymers has many shortcomings, including poor reproducibility, uneven size distribution, and imprecise reaction control, the application of PCM integrated with PAT tools is largely studied [53,57,72,73]. For example, Besseling's group [72] developed a new non-invasive PAT tool, the NanoFlowSizer, to characterize the size and size distribution of pharmaceutical nanoparticles continuously and in real time. Junkers' group [57] incorporated size exclusion chromatography (SEC) into the continuous platform for polymer synthesis to measure polymer molecular weight distribution in real time, achieving enhanced control over the polymerization process. The continuous polymer synthesis system enabled autonomous high-throughput screening and self-optimization, showing great potential in developing systematic polymer libraries for drug delivery systems.

3. Continuous flow self-optimization algorithms

3.1. Algorithm in chemistry

An algorithm refers to a defined finite number of steps that a computer uses to conduct specified actions, and is commonly used in computation, data processing, and automatic reasoning. It accepts a value or a collection of values as input and produces an output that solves the problem. Cronin divided the algorithms used in chemistry into three categories: menial, assistive, and enabling [74]. The main use of the menial algorithm is to replace manual operations, such as algorithms that control the feeding of a syringe pump. The assistive algorithm is mainly used for data evaluation and processing [75], for example, processing and extracting spectral data using wavelet transforms [76], helping to build complex continuous flow platforms that perform chemical reactions without human intervention [77,78]. The enabling algorithm is a powerful and intelligent algorithm, which can perform deep learning based on chemical databases (*e.g.*, Reaxys and SciFinder), and the generated models can be used to predict new data, such as the biological activity of new drugs [79,80], new synthetic routes [81] and the corresponding reaction results [82]. At present, the most extensively studied algorithm in PCM is the self-optimization algorithm for automated continuous flow optimization platforms, which will be mainly discussed in this section.

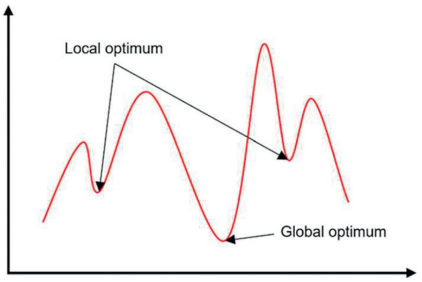

Fig. 6. Local optimum and global optimum for the minimization problem.

The self-optimization of chemical reactions is the optimization process using the flow reactor, PAT technique and optimization algorithm [83]. The PAT instruments analyze the reaction mixture from the flow reactor and transmit the results to the optimization algorithm, which then creates the next set of reaction conditions to be studied, forming a feedback loop. The above process is iterated repeatedly until the optimal solution is output. The closed-loop system improves the efficiency of reaction condition screening and reduces human error in the optimization process. Through the optimization algorithm, the optimal result is achieved with the least number of experiments [84,85]. Here, we will mainly introduce the algorithms used in the past five years for the self-optimization in PCM systems.

3.2. Local optimization and global optimization

Over recent years, various algorithms have been developed and used for the synthesis of drug molecules in continuous flow systems. Chemists choose different algorithms to optimize reaction conditions, including local optimization and global optimization. Local optimization is to find the optimal value in a limited region of the function, while global optimization is to find the optimal value in the whole region of the function (Fig. 6). Although the global optimal solution is the best in all the sets, the solving process is time-consuming and expensive. On the contrary, the local optimization algorithm usually converges quickly to the best result, and thereby is often more acceptable when the factors and information to be considered are too large.

3.3. Model-based DoE algorithm

Design of experiments (DoE) is an algorithm that allows different factors to vary simultaneously in order to screen out the best reaction condition value [86]. During chemical development, DoE has become a standard method to accelerate reaction optimization as it can evaluate a large number of reaction parameters using a small number of experiments. In the pharmaceutical industry, understanding the products and processes is essential for ensuring product quality. And DoE, which can simultaneously evaluate the impact of multiple factors (temperature, concentration, and pressure) on the reaction outcomes (yield, selectivity, and E-factor) [87–89], has been widely used to implement QbD in research and development over the past few years [90]. In 2020, Hone, Kappe and coworkers [91] reported a continuous flow platform for the preparation of β2-adrenergic receptor antagonists by Ru-catalyzed ester hydrogenation. The authors used a DoE approach to study the reaction and determined the effect of reaction parameters (temperature, pressure, and catalyst loading).

Lapkin and coworkers [92] reported a continuous flow device for C–H activated synthesis of aziridines, and a methodology for developing a process model based on model-based design of experiments (MBDoE) and a self-optimization approach in

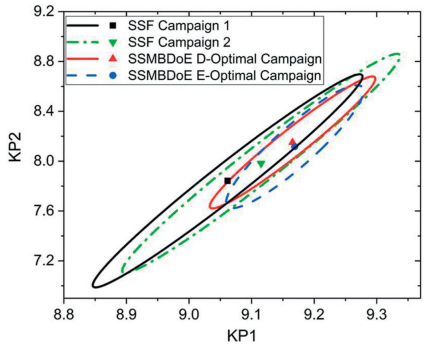

Fig. 7. Statistical certainty of the parameters KP1 and KP2 for the steady-state factorial (SSF) and steady-state MBDoE (SSMBDoE) D- and E-optimal campaigns, as illustrated by the 95% confidence ellipsoids. KP1 and KP2 are reparametrized forms of the Arrhenius parameters. Copied with permission [93]. Copyright 2019, the Royal Society of Chemistry.

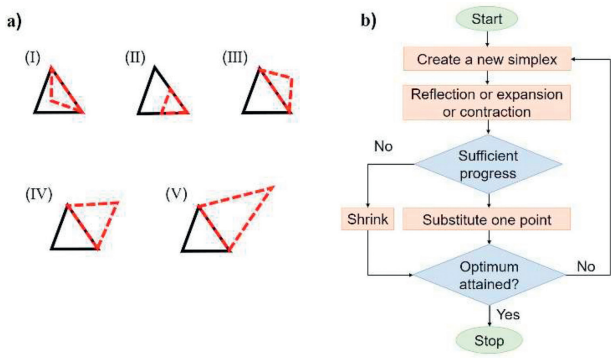

Fig. 8. (a) Five geometric transformations of the Nelder-Mead algorithms. (I) inside contraction; (II) shrinking; (III) outside contraction; (IV) reflection; (V) expansion. The black line represents the original simplex. The red line represents the new simplex. (b) Flowchart for the Nelder-Mead algorithm.

flow. Based on the initial model parameters from density functional theory (DFT) calculations and automated continuous flow experiments, the authors used MBDoE to rapidly generate a process model, which was then employed to train a surrogate model for self-optimization.

In 2019, Galvanin, Gavriilidis and coworkers [93] developed a flow microreactor platform for the automatic identification of kinetic models and accurately obtained the kinetic model parameters of sulfuric acid-catalyzed esterification of benzoic acid and ethanol. The platform performed steady-state experiments, where the conditions were optimized by MBDoE algorithms, with the aim of improving parameter precision. The steady-state experiments designed using the online MBDoE algorithm had more accurate parameter estimates than those designed with traditional factorial design. And the steady-state MBDoE campaigns produced much smaller confidence ellipsoids than the steady-state factorial campaigns (Fig. 7), demonstrating the advantage of online MBDoE in identifying kinetic models.

3.4. Nelder-Mead algorithm

The Nelder-Mead algorithm is an algorithm for finding the local minimum of multivariate functions, which has the advantage of not requiring the derivative information of the function and can converge to the local minimum faster [94]. A chemical reaction is regarded as a black box, converting input variables (*e.g.*, concentration, temperature, and residence time) into output variables (*e.g.*, yield and conversion). For an *N*-dimensional optimization problem, an (*N*+1)-dimensional simplex is constructed (*N* is the number of variables). The algorithm conducts random experiments in a given chemical space, and each vertex of the simplex represents the function value of the experiment, which is then analyzed and compared. New vertices and simplexes are constantly constructed until convergence conditions are reached (Fig. 8a). The method locates regions with better response, so successive simplex iterations converge to a locally optimal solution. Even if there are outliers in the data, the algorithm is able to self-correct the path to achieve the local optimum [95]. A flowchart showing the basic steps of the Nelder-Mead algorithm is given in Fig. 8b.

Felpin and coworkers [96] developed an autonomous flow platform that combined PAT tools and the Nelder-Mead algorithm for the synthesis of the natural product carpanone (Fig. 9). The flow reactor integrated various units (pumps, valves, pressure regulators) and online detection systems, which were controlled in real time by optimization algorithms. First, the algorithm created the initial experimental parameters, and then transmited the specific

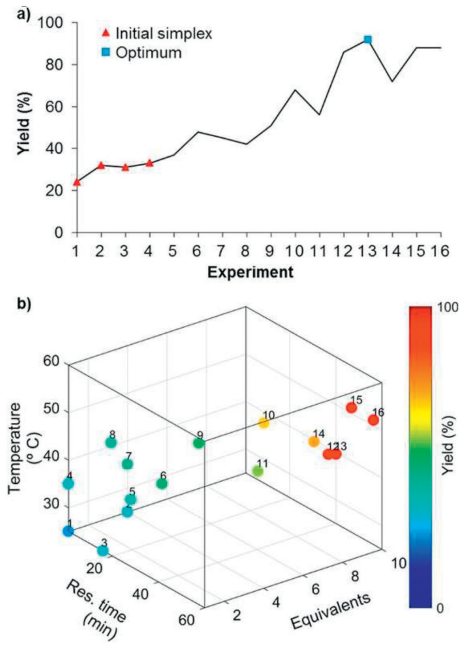

Fig. 9. Reaction optimization for the synthesis of carpanone using the Nelder-Mead algorithm. (a) Maximization of the yield of carpanone. (b) 3D representation of variables optimized to maximize yield for carpanone. Copied with permission [96]. Copyright 2018, the American Chemical Society.

experimental parameters to each unit of the flow reactor. After the reaction was completed, the real-time monitoring system (online HPLC or inline NMR) recorded the reaction results and fed the results back to the algorithm. Finally, new experimental parameters were proposed and evaluated in the flow reactor until the algorithm converged to the optimal value. This optimization algorithm was flexible, allowing the modification of experimental conditions based on different input variables (*e.g.*, temperature, residence time, and stoichiometry). The platform optimized the four-step synthesis of carpanone through 66 groups of experiments, with a total yield of 67%. The algorithm used by Felpin and coworkers had several breakthrough mechanisms, including (i) dimensionality reduction to explore bounds, (ii) diverse search beyond the already explored domain, (iii) continued reinforcement of unsatisfactory convergence results, and (iv) multiple termination criteria to reduce the number of expensive experiments.

3.5. Stable noisy optimization by branch and fit

Stable Noisy Optimization by Branch and Fit (SNOBFIT) is a global algorithm for noise optimization with bounded constraints on objective functions, specially designed to solve problems with noisy and computationally expensive objective functions [97]. SNOBFIT uses a combination of branching strategy and a quadratic surrogate model to determine the optimal point of the system. The user provides an initial point and its corresponding function value, and the SNOBFIT algorithm constructs a local quadratic model around the current optimal point as a new set of points which is then used as the next input. The algorithm produces widely distributed points in the objective space to increase the probability of finding the global optimal solution [98].

Jamison, Jensen and coworkers [99] developed an automated optimization platform based on the algorithm, flow chemistry and inline analytical techniques, with diverse modules such as the heated reactor, cooled reactor, photo reactor and liquid-liquid separator. The platform was compatible with different types of chemical reactions including C-C/C-N coupling, Horner-Wadsworth-Emmons olefination, Paal-Knorr reaction, reductive amination, aromatic nucleophilic substitution, cycloaddition, and photocatalytic reaction. In a typical procedure, the platform first performed a small number (35–45) of reactions under random conditions. After simultaneously evaluating the effects of multiple variables (temperature, time, and catalyst loading) on the yield or conversion in each reaction, a SNOBFIT-based algorithm designed the next set of reaction conditions until optimal reaction results were obtained. More than 50 different compounds were synthesized in high yields by applying optimized conditions from a certain range of substrates. Similarly, Bourne and coworkers [100] used the SNOBFIT algorithm to optimize the product yield of Claisen-Schmidt condensation, varying different variables (flow rate of benzaldehyde, molar equivalents of acetone, temperature, and molar equivalents of acetone) in 70 groups of experiments, and then fitting the data into the response surface model to obtain different reaction results (Fig. 10). The reaction was optimized at the mesoscale to yield 0.24 kg/day of the desired benzylideneacetone. George and coworkers [101] developed a continuous flow electrochemical synthesis platform using attenuated total reflection Fourier transform infrared spectroscopy (ATR FTIR) and GC as real-time monitoring techniques. The platform optimized the methoxylation of 1-formylpyrrolidine and the oxidation of 3-bromobenzyl alcohol using the SNOBFIT algorithm. The algorithm performed more tests in regions near the optimal conditions, while, at the same time,

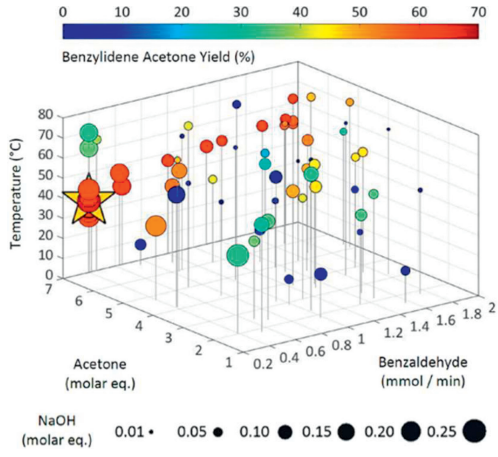

Fig. 10. Reaction optimization for Claisen-Schmidt condensation using the SNOBFIT algorithm. Copied with permission [100]. Copyright 2018, Elsevier.

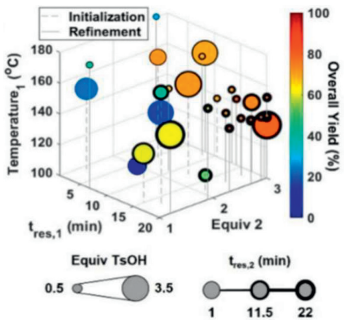

Fig. 11. Self-optimization results of the multi-step synthesis base on a Bayesian algorithm. Copied with permission [107]. Copyright 2022, Wiley-VCH.

randomly exploring the empty space to maximize the probability of finding the global optimum. The highest yield of methoxylation was obtained after 26 sets of experiments.

3.6. Bayesian optimization algorithm

Bayesian optimization (BO) algorithm is used for global optimization and based on an iterative response surface. By designing an appropriate surrogate model and acquisition function, BO can obtain the desired solution after only a few evaluations of the function, making it very suitable for complex optimization problems [102]. BO uses previously conducted experiments to infer experimental results and verifies its inference by evaluating a new set of conditions. In addition, the BO algorithm can be applied to different search spaces and multiple experiments can be selected in parallel [103–106].

Clayton, Bourne and coworkers [107] reported on an automated continuous flow platform for the development of multi-step synthesis based on a BO algorithm with an adaptive expected improvement acquisition function (BOAEI). The algorithm was initialized with nine Latin Hypercube (LHC) experiments, followed by 23 sequential iterations to determine the best overall yield of 81% in a total of 13 experiments (Fig. 11). Zhang, Yuan and coworkers [108] developed a continuous reaction optimization framework for optimizing complex gas-liquid-solid reactions based on BO and the Nelder-Mead simplex method. Researchers optimized four reaction parameters (temperature, hydrogen pressure, liquid flow rate and gas flow rate) for the hydrogenation of nitrobenzene, 3,4-dichloronitrobenzene and 5-nitroisoquinoline, respectively. The proposed Bayesian-based optimization algorithm achieves higher yield compared to the traditional one-variable-at-a-time (OVAT) method. Kim and coworkers [109] reported a microreactor platform driven by the BO algorithm that autonomously explored the optimal conditions for the ultrafast synthesis of bioactive thioquinazolinone. The highest yield of 88% was achieved within only 10 experiments, and 9 types of S-benzylic thioquinazolinone derivatives were synthesized in only 20 min under the autonomously optimized conditions.

3.7. Thompson sampling efficient multi-objective optimization algorithm

Usually, in the optimization of chemical processes, many objectives need to be considered, such as yield, conversion and selectivity [110]. Although single-objective optimization can be performed to determine the optimal solution of each objective, the optimal solutions for different objectives often conflict with each other, which means that the optimal solutions of the different objectives are located in different regions of the experimental space. For multi-objective optimization, using a single-objective optimization algorithm is often not a satisfactory result [111]. For example,

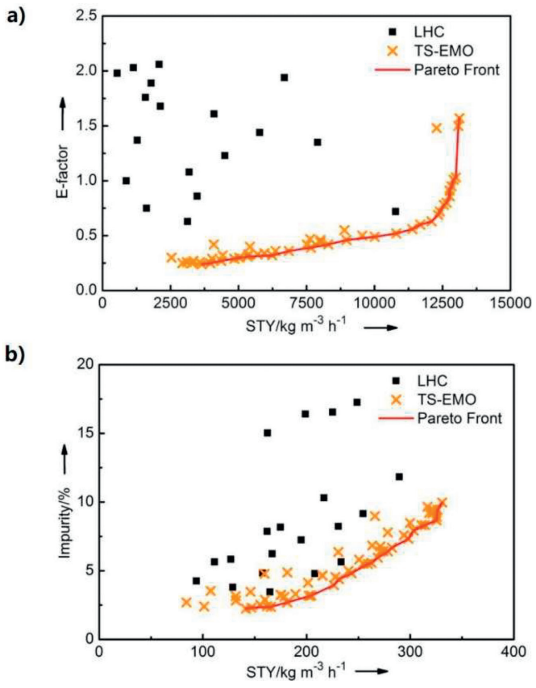

Fig. 12. Results of the four parameter multi-objective self-optimization of (a) the S_NAr reaction. (b) the *N*-benzylation. Copied with permission [114]. Copyright 2018, Elsevier.

Jensen used a single-objective optimization algorithm to optimize the Paal-Knorr reaction, resulting in a poor conversion (40%) under optimal yield conditions [112]. The Thompson sampling efficient multi-objective optimization (TSEMO) algorithm can be used for global multi-objective optimization of expensive-to-evaluate black-box functions with high computational costs [113].

Bourne, Lapkin and coworkers [114] reported a multi-objective machine learning self-optimization algorithm and evaluated S_NAr reaction and *N*-benzylation in continuous flow. The TSEMO algorithm successfully obtained the optimal conditions with good yield and E-factor (Fig. 12). In 2020, Bourne and coworkers [115] combined the TSEMO algorithm with a self-optimizing platform to optimize the Sonogashira reaction and the Claisen-Schmidt condensation reaction respectively. Specially, the researchers optimized the multi-step condensation reaction and separation process within 65 h for three objectives (purity, spacetime yield, and reaction mass efficiency), simultaneously explored the trade-off between conversion and spacetime yield without user interaction. In 2022, Bourne, Warren and coworkers [116] developed a continuous flow platform for polymer synthesis and analysis, where reversible addition-fragmentation chain transfer (RAFT) polymerization was carried out and optimum parameter space was identified in fewer experiments in an autonomous manner. The platform optimized the RAFT polymerization of *tert*-butyl acrylate, *n*-butyl acrylate, and methyl methacrylate using the TSEMO algorithm which allowed simultaneous evaluation of the molar mass dispersion and monomer conversion.

4. Summary and outlook

With the advent of Industry 4.0, the pharmaceutical industry is confronted with great challenges, and revolution in pharmaceutical manufacturing is inevitable. Pharmaceutical continuous manufacturing has been demonstrated and even encouraged as a powerful solution to turn the challenges into opportunities. In the process of the digitalization and intelligentization of PCM, PAT and algorithms are two essential elements and have both played an important role to make drug discovery, synthesis, purification and formulation more efficient, flexible, reliable and precise. When implementing PAT and algorithms in PCM, researchers need to be more cautious due to the complexity of drug molecules and formulations and the requirement in drug quality control. Collaboration of researchers from the pharmaceutical filed and other fields is needed to bring pharmaceutical manufacturing into a new era.

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.

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References

[1] Quality Consideration for Continuous Manufacturing Guidance for Industry, U.S. Food and Drug Amministration, 2019 February.
[2] Continuous Manufacturing of Drug Substances and Drug Products Q13, International Council for Harmonisation of Technical Requirments for Pharmaceuticals for Human Use, 2022 November.
[3] T. Tsubogo, H. Oyamada, S. Kobayashi, Nature 520 (2015) 329–332.
[4] D.R. Snead, T.F. Jamison, Angew. Chem. Int. Ed. 54 (2015) 983–987.
[5] C. Liu, J. Xie, W. Wu, et al., Nat. Chem. 13 (2021) 451–457.
[6] R. Jiang, X. Xue, F. Zhao, et al., Chem. Eng. J. 429 (2022) 132207.
[7] D.E. Fitzpatrick, T. Maujean, A.C. Evans, S.V. Ley, Angew. Chem. Int. Ed. 57 (2018) 15128–15132.
[8] F. Ferlin, D. Lanari, L. Vaccaro, Green Chem. 22 (2020) 5937–5955.
[9] J. Britton, C.L. Raston, Chem. Soc. Rev. 46 (2017) 1250–1271.
[10] A. Adamo, R.L. Beingessner, M. Behnam, et al., Science 352 (2016) 61–67.
[11] K.P. Cole, J.M. Groh, M.D. Johnson, et al., Science 356 (2017) 1144–1150.
[12] A. Domokos, B. Nagy, B. Szilágyi, G. Marosi, Z.K. Nagy, Org. Process. Res. Dev. 25 (2021) 721–739.
[13] Q8 (R2) Pharmaceutical Development, U.S. Food and Drug Amministration, 2009 November.
[14] V. Mishra, S. Thakur, A. Patil, A. Shukla, Expert. Opin. Drug. Deliv. 15 (2018) 737–758.
[15] Q. Su, S. Ganesh, M. Moreno, et al., Comput. Chem. Eng. 125 (2019) 216–231.
[16] F. Destro, M. Barolo, Int. J. Pharm. 620 (2022) 121715.
[17] I.R. Baxendale, R.D. Braatz, B.K. Hodnett, et al., J. Pharm. Sci. 104 (2015) 781–791.
[18] A. Gioiello, A. Piccinno, A.M. Lozza, B. Cerra, J. Med. Chem. 63 (2020) 6624–6647.
[19] C.P. Breen, A.M.K. Nambiar, T.F. Jamison, K.F. Jensen, Trends Chem. 3 (2021) 373–386.
[20] M.A. Bezerra, V.A. Lemos, D.M. de Oliveira, Microchem. J. 155 (2020) 104731.
[21] D.C. Fabry, E. Sugiono, M. Rueping, React. Chem. Eng. 1 (2016) 129–133.
[22] V. Sans, L. Cronin, Chem. Soc. Rev. 45 (2016) 2032–2043.
[23] M. Baumann, Org. Biomol. Chem. 16 (2018) 5946–5954.
[24] M. Rodriguez-Zubiri, F.X. Felpin, Org. Process Res. Dev. 26 (2022) 1766–1793.
[25] C.N. Talicska, E.C. O'Connell, H.W. Ward, et al., React. Chem. Eng. 7 (2022) 1419–1428.
[26] H. Lu, M.A. Schmidt, K.F. Jensen, Lab Chip 1 (2001) 22–28.
[27] N. Wang, F. Tan, Y. Zhao, et al., Sci. Rep. 6 (2016) 28928.
[28] T. Brodmann, P. Koos, A. Metzger, P. Knochel, S.V. Ley, Org. Process. Res. Dev. 16 (2011) 1102–1113.
[29] G. Zhou, K. Emerson, E. Majusiak, C. Anderson, O. Sudah, Org. Process Res. Dev. 16 (2012) 204–213.
[30] P. Sagmeister, J.D. Williams, C.A. Hone, C.O. Kappe, React. Chem. Eng. 4 (2019) 1571–1578.
[31] K.S. Rao, F. St-Jean, A. Kumar, Org. Process. Res. Dev. 23 (2019) 945–951.
[32] J. Harting, P. Kleinebudde, Eur. J. Pharm. Biopharm. 125 (2018) 169–181.
[33] Y. Miyai, A. Formosa, C. Armstrong, et al., Org. Process. Res. Dev. 25 (2021) 2707–2717.
[34] J. Liu, H. Sun, L. Yin, et al., Acta. Chim. Sinica 77 (2019) 257–262.
[35] B.P. Loren, M. Wleklinski, A. Koswara, et al., Chem. Sci. 8 (2017) 4363–4370.
[36] S. Kern, K. Meyer, S. Guhl, et al., Anal. Bioanal. Chem. 410 (2018) 3349–3360.
[37] J. Bemetz, A. Wegemann, K. Saatchi, et al., Anal. Chem. 90 (2018) 9975–9982.
[38] J.J. Heiland, R. Warias, C. Lotter, et al., Lab. Chip 17 (2016) 76–81.
[39] A.I. McNab, A.J. McCue, D. Dionisi, J.A. Anderson, J. Catal. 362 (2018) 10–17.
[40] R. Peña, J.A. Oliva, C.L. Burcham, D.J. Jarmer, Z.K. Nagy, Cryst. Growth Des. 17 (2017) 4776–4784.

[41] S. Chatterjee, M. Guidi, P.H. Seeberger, K. Gilmore, Nature 579 (2020) 379–384.
[42] V.E.H. Kassin, R. Morodo, T. Toupy, et al., Green Chem. 23 (2021) 2336–2351.
[43] D. Perera, J.W. Tucker, S. Brahmbhatt, et al., Science 359 (2018) 429–434.
[44] C. Schotten, L.G.T. Leist, A.L. Semrau, D.L. Browne, React. Chem. Eng. 3 (2018) 210–215.
[45] R. Grainger, T.D. Heightman, S.V. Ley, F. Lima, C.N. Johnson, Chem. Sci. 10 (2019) 2264–2271.
[46] S.A. Biyani, Q. Qi, J. Wu, et al., Org. Process. Res. Dev. 24 (2020) 2240–2251.
[47] D.E. Fitzpatrick, R.J. Mutton, S.V. Ley, React. Chem. Eng. 3 (2018) 799–806.
[48] P. Sagmeister, F.F. Ort, C.E. Jusner, et al., Adv. Sci. 9 (2022) 2105547.
[49] S. Sacher, I. Castillo, J. Rehrl, et al., Chem. Eng. Res. Des. 177 (2022) 493–501.
[50] A. Balogh, A. Domokos, B. Farkas, Chem. Eng. J. 350 (2018) 290–299.
[51] G. Glotz, K. Waniek, J.P. Schöggl, et al., Org. Process. Res. Dev. 25 (2021) 2367–2379.
[52] F. Guan, A.J. Blacker, B. Hall, et al., J. Flow. Chem. 11 (2021) 763–772.
[53] M. Rubens, J. Van Herck, T. Junkers, ACS Macro. Lett. 8 (2019) 1437–1441.
[54] P. Sagmeister, D. Kaldre, J. Sedelmeier, et al., Org. Process. Res. Dev. 25 (2021) 1206–1214.
[55] M. Bornemann-Pfeiffer, J. Wolf, K. Meyer, et al., Angew. Chem. Int. Ed. 60 (2021) 23202–23206.
[56] H. Sheng, E.B. Corcoran, Z.E.X. Dance, et al., Org. Process. Res. Dev. 24 (2020) 2611–2618.
[57] M. Rubens, J.H. Vrijsen, J. Laun, T. Junkers, Angew. Chem. Int. Ed. 58 (2019) 3183–3187.
[58] R. Galaverna, M.C. Breitkreitz, J.C. Pastre, ACS. Sustain. Chem. Eng. 6 (2018) 4220–4230.
[59] B. Li, S.M. Guinness, S. Hoagland, et al., Org. Process. Res. Dev. 22 (2018) 707–720.
[60] V. Mancino, B. Cerra, A. Piccinno, A. Gioiello, Org. Process. Res. Dev. 22 (2018) 600–607.
[61] R. Lebl, T. Murray, A. Adamo, D. Cantillo, C.O. Kappe, ACS. Sustain. Chem. Eng. 7 (2019) 20088–20096.
[62] A. Pomberger, Y. Mo, K.Y. Nandiwale, et al., Org. Process. Res. Dev. 23 (2019) 2699–2706.
[63] E. Içten, A.J. Maloney, M.G. Beaver, et al., Org. Process. Res. Dev. 24 (2020) 1861–1875.
[64] O.C. Dennehy, D. Lynch, S.G. Collins, A.R. Maguire, H.A. Moynihan, Org. Process. Res. Dev. 24 (2020) 1978–1987.
[65] C.G. Thomson, C. Banks, M. Allen, et al., J. Org. Chem. 86 (2021) 14079–14094.
[66] V.K. Sthalam, A.K. Singh, S. Pabbaraja, Org. Process. Res. Dev. 23 (2019) 1892–1899.
[67] P. Sagmeister, R. Lebl, I. Castillo, et al., Angew. Chem. Int. Ed. 60 (2021) 8139–8148.
[68] A. Domokos, B. Nagy, M. Gyurkes, et al., Int. J. Pharm. 581 (2020) 119297.
[69] C. Hu, C.J. Testa, W. Wu, et al., Chem. Commun. (Camb) 56 (2020) 1026–1029.
[70] P. Zhang, N. Weeranoppanant, D.A. Thomas, et al., Chemistry 24 (2018) 2776–2784.
[71] S. Steiner, J. Wolf, S. Glatzel, et al., Science 363 (2019) eaav2211.
[72] R. Besseling, M. Damen, J. Wijgergangs, et al., Eur. J. Pharm. Sci. 133 (2019) 205–213.
[73] S.A. Damiati, S. Damiati, Front. Mol. Biosci. 8 (2021) 677547.
[74] A.B. Henson, P.S. Gromski, L. Cronin, ACS. Cent. Sci. 4 (2018) 793–804.
[75] G.M. Escandar, A.C. Olivieri, N.M. Faber, et al., Trac. Trends. Anal. Chem. 26 (2007) 752–765.
[76] Y. Sulub, R. LoBrutto, R. Vivilecchia, B.W. Wabuyele, Anal. Chim. Acta. 611 (2008) 143–150.
[77] A.J. Parrott, R.A. Bourne, G.R. Akien, D.J. Irvine, M. Poliakoff, Angew. Chem. Int. Ed. 123 (2011) 3872–3876.
[78] R.A. Skilton, A.J. Parrott, M.W. George, M. Poliakoff, R.A. Bourne, Appl. Spectrosc. 67 (2013) 1127–1131.
[79] D.C. Elton, Z. Boukouvalas, M.D. Fuge, P.W. Chung, Mol. Syst. Des. Eng. 4 (2019) 828–849.
[80] F. Strieth-Kalthoff, F. Sandfort, M.H.S. Segler, F. Glorius, Chem. Soc. Rev. 49 (2020) 6154–6168.
[81] T.J. Struble, J.C. Alvarez, S.P. Brown, et al., J. Med. Chem. 63 (2020) 8667–8682.
[82] J.M. Granda, L. Donina, V. Dragone, D.L. Long, L. Cronin, Nature 559 (2018) 377–381.
[83] A.D. Clayton, J.A. Manson, C.J. Taylor, et al., React. Chem. Eng. 4 (2019) 1545–1554.
[84] C. Mateos, M.J. Nieves-Remacha, J.A. Rincón, React. Chem. Eng. 4 (2019) 1536–1544.
[85] B.J. Reizman, K.F. Jensen, Accounts. Chem. Res. 49 (2016) 1786–1796.
[86] R.A. Fisher, The Design of Experiments, 6th. ed., Oliver and Boyd, Edinburgh and London, 1935.
[87] S.A. Weissman, N.G. Anderson, Org. Process. Res. Dev. 19 (2015) 1605–1633.
[88] P.M. Murray, F. Bellany, L. Benhamou, et al., Org. Biomol. Chem. 14 (2016) 2373–2384.
[89] B.J. Reizman, K.F. Jensen, Chem. Commun. 51 (2015) 13290–13293.
[90] S.N. Politis, P. Colombo, G. Colombo, D.M. Rekkas, Drug. Dev. Ind. Pharm. 43 (2017) 889–901.
[91] M. Prieschl, J. García-Lacuna, R. Munday, et al., Green. Chem. 22 (2020) 5762–5770.
[92] A. Echtermeyer, Y. Amar, J. Zakrzewski, A. Lapkin, Beilstein. J. Org. Chem. 13 (2017) 150–163.
[93] C. Waldron, A. Pankajakshan, M. Quaglio, et al., React. Chem. Eng. 4 (2019) 1623–1636.
[94] J.A. Nelder, R. Mead, Comput. J. 7 (1965) 308–313.
[95] P. Milavec, A. Podgornik, R. Štravs, T. Koloini, Bioproc. Biosyst. Eng. 25 (2002) 69–78.
[96] D. Cortés-Borda, E. Wimmer, B. Gouilleux, et al., J. Org. Chem. 83 (2018) 14286–14299.
[97] W. Huyer, A. Neumaier, ACM Trans. Math. Software 35 (2008) 1–25.
[98] N.V. Queipo, R.T. Haftka, W. Shyy, et al., Prog. Aerosp. Sci. 41 (2005) 1–28.
[99] A.C. Bedard, A. Adamo, K.C. Aroh, et al., Science 361 (2018) 1220.
[100] M.I. Jeraal, N. Holmes, G.R. Akien, R.A. Bourne, Tetrahedron 74 (2018) 3158–3164.
[101] J. Ke, C. Gao, A.A. Folgueiras-Amador, et al., Appl. Spectrosc. 76 (2022) 38–50.
[102] B. Shahriari, K. Swersky, Z. Wang, R.P. Adams, N.D. Freitas, P. IEEE 104 (2016) 148–175.
[103] F. Häse, L.M. Roch, C. Kreisbeck, A. Aspuru-Guzik, ACS Cent. Sci. 4 (2018) 1134–1145.
[104] R.R. Griffiths, J.M. Hernández-Lobato, Chem. Sci. 11 (2020) 577–586.
[105] P. Jorayev, D. Russo, J.D. Tibbetts, et al., Chem. Eng. Sci. 247 (2022) 116938.
[106] B.J. Shields, J. Stevens, J. Li, et al., Nature 590 (2021) 89–96.
[107] A.D. Clayton, E.O. Pyzer-Knapp, M. Purdie, et al., Angew. Chem. Int. Ed. 62 (2023) e202214511.
[108] R. Liang, X. Duan, J. Zhang, Z. Yuan, React. Chem. Eng. 7 (2022) 590–598.
[109] G.N. Ahn, J.H. Kang, H.J. Lee, et al., Chem. Eng. J. 453 (2023) 139707.
[110] D.N. Jumbam, R.A. Skilton, A.J. Parrott, R.A. Bourne, M. Poliakoff, J. Flow Chem. 2 (2012) 24–27.
[111] D. Cortés-Borda, K.V. Kutonova, C. Jamet, et al., Org. Process. Res. Dev. 20 (2016) 1979–1987.
[112] J.S. Moore, K.F. Jensen, Org. Process. Res. Dev. 16 (2012) 1409–1415.
[113] E. Bradford, A.M. Schweidtmann, A. Lapkin, J. Global Optim. 71 (2018) 407–438.
[114] A.M. Schweidtmann, A.D. Clayton, N. Holmes, et al., Chem. Eng. J. 352 (2018) 277–282.
[115] A.D. Clayton, A.M. Schweidtmann, G. Clemens, et al., Chem. Eng. J. 384 (2020) 123340.
[116] S.T. Knox, S.J. Parkinson, C.Y.P. Wilding, R.A. Bourne, N.J. Warren, Polym. Chem. 13 (2022) 1576–1585.