



Self-driving laboratory for emulsion polymerization

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ABSTRACT

Modern approaches to chemical product discovery are exploiting the benefits of flow-chemistry, online characterization, and smart automation to rapidly screen and optimize chemical transformations. The present work describes the development and application of an automated continuous-flow reactor platform for the rapid prototyping of latexes prepared via seeded free-radical emulsion polymerization. Using a multi-reactor system comprising a cascade of miniature continuous stirred-tank reactors (CSTRs) followed by a sonicated tubular reactor (STR) with five pumps for reagent delivery, the capability to explore a four-dimensional parameter space of surfactant concentration, seed fraction, monomer ratio, and feed-rate is demonstrated. With user-defined boundary conditions, a one-factor-at-a-time (OFAAT) approach first illustrates the capability to prepare products with unique and tuneable properties. Subsequently, an experimental design is constructed to explore a three-dimensional parameter space, with 16 reactions completed in under three days of platform time. This rapid generation of product prototypes allowed features of the polymer system to be evaluated on a timescale much shorter than traditional methods with a significant reduction in manual effort and human-chemical interaction. The resulting response surface model was applied for *in silico* optimization using the Thompson-sampling efficient multi-objective (TSEMO) optimization algorithm. Finally, online dynamic light scattering (DLS) was applied with the physical platform which enabled self-optimization of the polymerization, identifying the attainable particle sizes whilst minimizing the amounts of seed and surfactant used. Closing the loop resulted in a fully operational self-driving laboratory.

1. Introduction

Polymeric products are ubiquitous in all areas of our daily live, including as important additives in a wide range of formulated products in the healthcare to automotive industries. However, there is now a critical demand for materials with superior performance which also address concerns surrounding life-cycle circularity and feedstock sustainability. The difficulty in delivering these products on useful time-scales requires acceleration in new product development [1,2]. To meet the pace required for developing these new materials, researchers in chemical science must be equipped with modern tools that accelerate their discovery. Several technologies have been deployed in labs around the world to this end that are increasingly being adopted for materials research [3,4]. These technologies represent a fundamental change in the way benchtop chemistry is carried out, exploiting advances in automation, computation, and manufacturing to increase experimental efficiency with respect to human and chemical resources. Such technologies include automated and high-throughput parallel synthesis

platforms [5,6] microfluidic reactors, [7–9] cyber-physical systems, [10] lab robots, [11] and continuous-flow platforms, [12,13] which each afford unique benefits to their user. Continuous-flow platforms are becoming increasingly popular for several reasons; for instance, flow reactors often bear large surface-area to volume ratios leading to enhanced heat and mass transfer and hence shorter reaction times. The rapid heat transfer coupled with typically small holdup volumes means flow platforms bear an inherent level of safety, whereby reaction exotherms are quickly dissipated. In addition, flow reactors are easily automated, and lend themselves well to integration of downstream processing and online analytical techniques, which subsequently afford the potential to incorporate machine learning algorithms for closed-loop and self-driving optimization [12,14–16]. Another benefit is the ease of cleaning between reactions by simply switching to an appropriate solvent to flush out the remaining contents, especially in situations where reactor fouling is a concern. Finally, flow platforms give access to exceptional repeatability, are regarded as highly scalable, and can make accessing more extreme reaction conditions facile given they usually

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<https://doi.org/10.1016/j.cej.2025.160700>

Received 6 December 2024; Received in revised form 5 February 2025; Accepted 14 February 2025

Available online 15 February 2025

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operate at elevated pressures [17]. These benefits make continuous-flow platforms an appealing tool for streamlining the new product development workflow. There is growing interest in the application of continuous-flow reactors to lab-scale polymer synthesis, [4,13] with many reports of products prepared efficiently in solution and dispersed-phases. For solution-based systems in particular, these platforms have been combined with online analysis and machine-learning algorithms to enable closed-loop self-optimization [12,18].

Emulsion polymerization represents a mechanistically complex but highly versatile process used in the preparation of aqueous nanoparticle dispersions from hydrophobic monomers [19–21]. Products of emulsion polymerization span all scales of chemical manufacture, from commoditized coatings and adhesives, to more designer particles used in biomedical applications. Conventional aqueous emulsion polymerization involves the free-radical polymerization of one or more hydrophobic monomers which are dispersed in a continuous phase of water by emulsification. A water-soluble initiator forms oligomeric radicals from small amounts of solubilised monomer, which eventually form primary particles stabilized within surfactant micelles. During the synthesis, monomer is transported from the dispersed droplets to the growing particles where further propagation proceeds. This continues until the droplets are depleted and the remaining monomer resides in the polymer particles, continuing to propagate on the growing chains until it is consumed. For a given application, developing an emulsion polymerization process requires not only selection of appropriate reagents but also tuning of monomer composition, surfactant concentration, initiator concentration, pH, temperature, reaction time, and mixing. To overcome challenges related to particle nucleation a seeded fed-batch routine is often used, wherein monomer feeding rate (including whether that monomer is pre-emulsified) and seed loading must also be considered [22–25]. Evidently, the parameter space for such polymerizations is vast owing to extraordinary opportunities for the discovery of important new materials, however these opportunities are characterized by time-consuming development and optimization procedures using traditional methods. To navigate the high dimensionality of emulsion polymerization, Lapkin and coworkers adopted a machine learning algorithm in the self-optimization of a styrene-butyl acrylate emulsion copolymerization [26]. In as many as 14 input variables, a campaign of seeded semi-batch reactions was used to optimize the polymerization for full conversion and a defined particle size in just 17 experiments. This represents an important step-change for product development and highlights the potential of machine learning algorithms in their application to the chemical sciences. However, the need to manually clean and prepare the reactor after each iteration remains cumbersome and could likely benefit from the use of continuous-flow chemistry to ‘close the loop’.

Emulsion polymerization presents unique challenges with respect to the use of continuous-flow reactors, which on the lab scale are conventionally comprised of simple heated tubular coils. However, given the multiphasic nature of this polymerization process and its propensity to coagulate on particle destabilization, it is essential to ensure the reactor contents remain well-mixed to produce the desired product and avoid issues of clogging. Despite this, many flow reactor concepts have been successfully applied to emulsion polymerization [27]. Examples include tubular reactors adapted with static mixing, [28,29] to Taylor-Couette vortex reactors which exploit the secondary flow phenomena in the annulus of two concentric cylinders to enhance mixing and narrow residence time distributions (RTD) [30–32]. In such designs, the mixing performance is closely coupled to the flow rate and physical characteristics of the reaction mixture, resulting in limited versatility. It is unsurprising therefore that the flexibility of stirred batch reactors is so often adopted for the benchtop exploration of new emulsion polymer recipes [26]. One possibility is to modify such a stirred batch reactor to include an inlet and outlet line and operate it as a continuous stirred tank reactor (CSTR) [33–35]. The use of a single CSTR is rarely recommended on account of the broad RTD, but,

importantly for emulsion polymerization, results in oscillations of conversion and multiple steady states due to the complexities of particle nucleation in mixed flow. Using a cascade of CSTRs can narrow the RTD and suppress these oscillations, though it is common to skip nucleation altogether by using a pre-prepared latex seed onto which further particle growth dominates [36,37]. CSTR cascades are flow-chemistry’s answer to the versatility of batch processing, decoupling mixing performance from conditions of the bulk flow, whilst offering multiple reaction stages in which distinct operations can be performed. In principle, there is no limit to the number of CSTRs in a cascade, being restricted only by the space and capital available whilst the improvement in reactor performance diminishes with each additional vessel – five CSTRs is a reasonable maximum. Traditionally, lab-scale CSTRs have operated on the scale of litres, meaning the material cost and environmental impact associated with bringing such a volume to steady state (conventionally five times the reactor volume for a single CSTR) quickly becomes an important bottleneck to efficient product development. Recently, miniaturised lab-scale CSTR cascades have emerged which offer the many benefits of traditional CSTRs but on a scale better-suited to meeting the needs of an economically and environmentally conscious workflow [38–40].

The work presented here describes the development and application of an autonomous continuous-flow platform based on a miniature CSTR cascade for the seeded emulsion polymerization of styrene-butyl acrylate-acrylic acid copolymers. We demonstrate the capability for accelerated screening of emulsion polymer recipes initially using one factor at a time (OFAAT) automation to prepare products with distinct properties. A three-dimensional parameter space is then explored in under three days of platform time using an automated design of experiment (DoE) approach. A response surface generated from the DoE is used to build an emulator for evaluating *in silico* the performance of two optimization strategies employing a freely available multi-objective optimization algorithm (Thompson-sampling efficient multi-objective, TSEMO). The first approach involves size *targeting*, which aims to prepare several particle sizes in separate simulated optimization campaigns. The second approach involves size *mapping*, which is facilitated by the algorithm alternately maximizing and minimizing the particle size objective. The exploratory nature of TSEMO results in an efficient determination of the range of attainable particle sizes. Each strategy simultaneously aims to minimize surfactant and seed concentrations. Finally, we ‘close the loop’ by introducing online dynamic light scattering (DLS) with TSEMO to perform the optimization autonomously on the physical platform. An overview of the work presented is given in Fig. 1.

2. Experimental

2.1. Materials

The reagents styrene (ST) (>99 %, stabilized with 4-*tert*-butylcatechol, Sigma-Aldrich), butyl acrylate (BA) (>98 %, stabilized with 50 ppm 4-methoxyphenol, Thermo Fisher Scientific), acrylic acid (AA) (stabilized with 200 ppm 4-methoxyphenol, Sigma-Aldrich), *tert*-dodecylmercaptan (t-DDM) (98.5 %, mixture of isomers, Sigma-Aldrich) sodium dodecylbenzenesulfonate (SDBS) (Sigma-Aldrich), ammonium persulfate (APS) (>98 %, Sigma-Aldrich), were all used as received without further purification. A constant amount of chelating agents were also used in each reaction. For cleaning between reactions, a 1:1 V/V mixture of tetrahydrofuran (THF) (>99.9 %, Sigma-Aldrich) and 1,4-dioxane (>99 %, stabilized with <25 ppm BHT, Sigma-Aldrich) was used. Deionized water was used throughout this work.

2.2. Batch Poly(styrene)-co-poly(butyl acrylate) latex seed synthesis

For all continuous-flow experiments, a latex seed was prepared in batch according to the following procedure: The chelating agents and SDBS (1.2074 g, 3.46 mmol) were added to a 500 mL two-necked round-

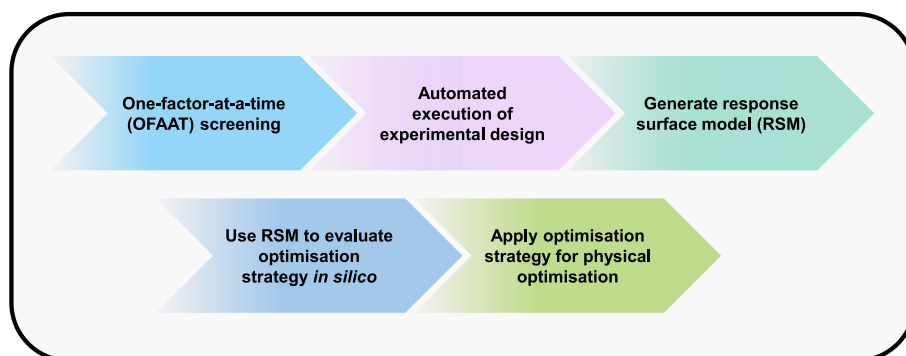


Fig. 1. Flowchart summarising the workflow presented in this paper.

bottom flask and dissolved in deionized water (257.9242 g). The monomer mixture containing ST (13.6372 g, 0.1309 mol), BA (13.9214 g, 0.1086 mol), AA (0.8524 g, 0.0118 mol), and t-DDM (0.0284 g, 0.14 mmol) was added to the same flask. This was sealed and stirred rapidly (1,000 rpm) to form an emulsion using an overhead stirrer fitted with a straight two-blade PTFE impeller (collapsible 70 mm diameter) and heated in a temperature-controlled oil bath set to 56 °C. APS initiator (0.1392 g, 0.61 mmol) was added to a separate vial and dissolved in deionized water (20.00 g). After allowing the emulsion at least 15 min to reach the reaction temperature, the stirring speed was reduced to 300 rpm and the APS solution injected using a syringe. After 1.5 h the oil bath temperature was increased to 76 °C and after another 1.5 h the temperature controller switched off. The flask was left to fully cool before the product was collected and characterized. Prior to all subsequent experiments, the latex seed was filtered through a standard

cellulose filter paper to remove any coagulum.

2.3. Automated flow reactor platform

An outline of the platform developed for the high-throughput and autonomous exploration of free-radical emulsion polymerizations is given in Fig. 2 (platform photograph and screenshot of user interface provided in Fig. S1). Reagents were delivered by a series of pumps, with inlets designated Aq2, solvent/surfactant solution, and water for the stopped flow DLS using a ReaXus 6010R reciprocating HPLC pump (Teledyne ISCO). The inlet for Aq1 used a MilliGAT high flow high pressure rotary positive displacement pump (Global FIA, 628 μL per revolution), and the inlets for monomer feeds 1 and 2 (M1 and M2) both used MilliGAT low flow high pressure rotary positive displacement pumps (Global FIA, 100 μL per revolution). The latex seed was delivered

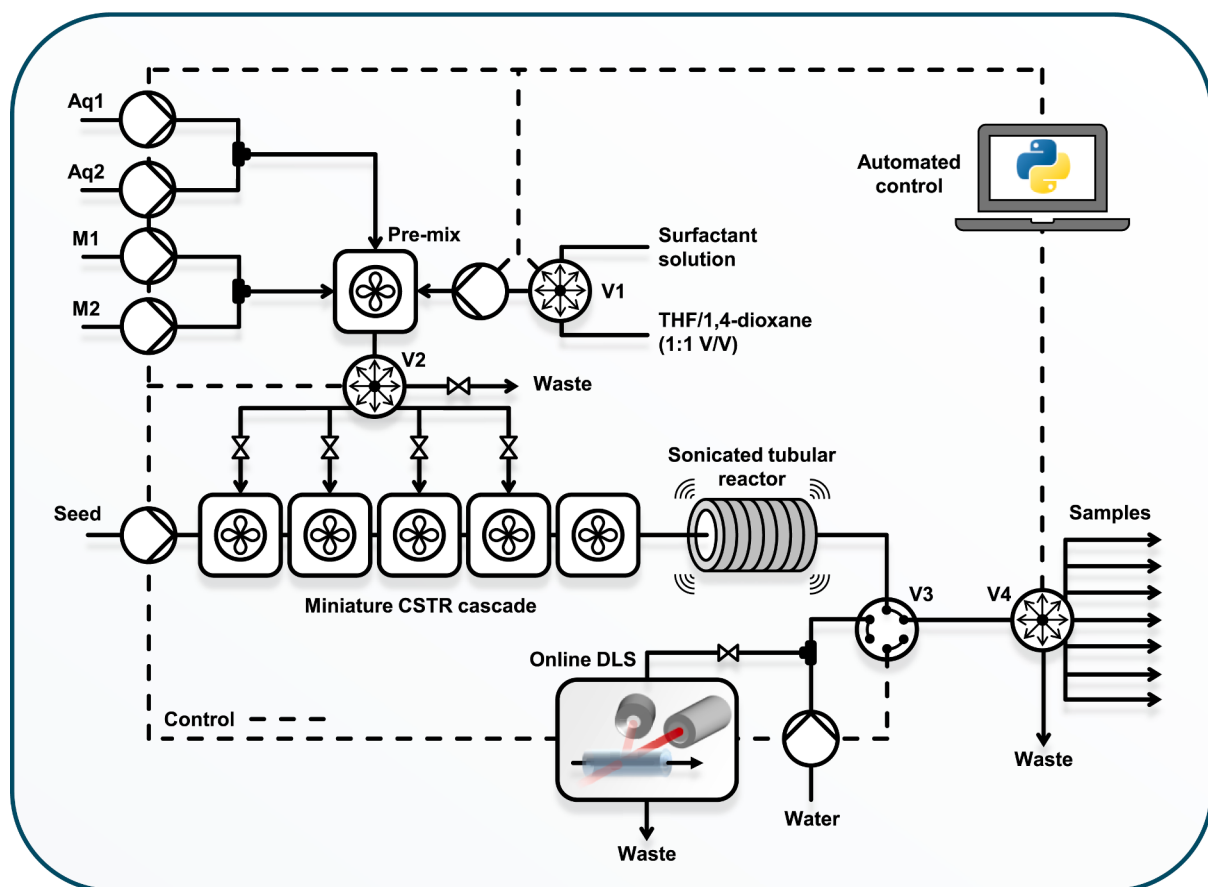


Fig. 2. Outline of the autonomous flow reactor platform for conventional free-radical emulsion polymerization.

by a Fusion 6000X high-pressure syringe pump (Chemyx) fitted with a 100 mL stainless steel syringe. A series of computer-controlled valves facilitated several functions necessary for fully autonomous operation. Valve V1 was an eight-port rotary selection valve (BioChem Fluidics) used to alternate between solvent (THF:1,4-dioxane = 1:1 V/V) and an aqueous solution of SDBS (0.66 % w/w). Details of the cleaning routine are given in the [supporting information](#) (Fig. S2). Valve V2 was a six-port medium-bore (1.3 mm diameter) rotary selection valve (BioChem Fluidics) and was used to continuously dose the pre-emulsion into the different CSTRs of the main cascade towards replicating a fed-batch procedure in continuous-flow. 100 psi back-pressure regulators (BPRs) on the emulsion feeding tubes were essential to allow consistent flow rates into each CSTR due to the pressure-drops involved (Fig. S3). Valve V3 was a six-port wide-bore (2.4 mm diameter) rotary switching valve (BioChem Fluidics) used to extract samples for online analysis of particle size. Valve V4 was an eight-port wide-bore (2.4 mm diameter) rotary selection valve (BioChem Fluidics) used to automatically collect product samples from each reaction. All valves were operated using stepper motors controlled by uStepperS32 PCBs programmed in Arduino.

2.4. Inline emulsification

For the emulsification step, a single miniature CSTR (1.5 mL, 15 mm diameter $\times$ 10 mm depth fReactor, Asynt) containing a cross-shaped PTFE magnetic stirrer bar (10 mm diameter, 5 mm thickness) was used with a high-speed magnetic stirrer (2500 rpm, IKA color squid). The emulsion was directed to valve V2 before being distributed into the main CSTR cascade. The effective emulsion dosing profile is illustrated in Fig. S4 relative to an equivalent semi-batch reaction.

2.5. Reactor environment

The main CSTR cascade comprised five more miniature 1.5 mL CSTRs each stirred by individual magnetic drivers as demonstrated previously [41,42]. Each CSTR was connected by 8 cm lengths of 1/16" OD perfluoroalkoxy (PFA) tubing (ID = 0.762 mm). For the emulsion inlets, tubes were protruded approximately 2 mm into the CSTRs to deliver emulsion close to the stirrer bar. The CSTR cascade was heated by an aluminium heating block containing a pair of heating cartridges controlled by a Eurotherm temperature controller. To enhance the magnetic coupling and improve mixing reliability, it was determined that rare-Earth ellipsoidal stirrer bars (10 mm length, 6 mm thickness) were more appropriate than the standard cross-shaped geometry. These stirrers rotated centrally in the miniature CSTRs at approximately 400 rpm.

To increase monomer conversion the overall residence time could be increased, however, to avoid going below the recommended range of the pumps a sonicated tubular reactor (STR) was added downstream of the CSTR cascade. This was a 2.53 m length (5 mL volume) of 1/8" OD PFA tubing (ID = 1.575 mm) submerged in a temperature controlled ultrasonic water bath (FB11002, Fisher), with the aim of exploiting the action of the ultrasonics to i) accelerate conversion ii) provide additional mixing, and iii) prevent, or break up any coagulum to avoid blockages.

2.6. Sampling system

Whilst it would be ideal to perform all product characterization in real time making use of online analysis, there is very often still a requirement to obtain physical samples whether for validation or additional testing, which is not amenable to online methods (measurement of glass transition temperatures for instance). Therefore, an auto-sampling system was implemented to serve this purpose but also perform the secondary function of back-pressurizing the reactors. This was achieved by attaching eight pressure-rated (1.5 bar) glass bottles (Duran) to the eight outlet ports of valve V4 using three-port solvent delivery caps. A second port on each of these caps was attached to a

regulated self-relieving compressed air line via an eight-way manifold, with the third port plugged by a blanking nut. Seven of the bottles were 100 mL for collecting samples, with the eighth bottle being 1000 mL used for collecting the waste between reaction steady states. Using this system, the reactors could be reliably pressurized to 1.5 bar without the need for narrow-channelled back-pressure regulators which frequently cause blockages in particle forming processes. Furthermore, the computer-controlled sampling valve V4 could simply switch between each position to dispense the reaction product into the sample bottles when steady state had been achieved for each reaction. To reach steady state it was determined that three reactor volumes of the target composition needed to be passed through the system (Fig. S5).

2.7. Control software

A custom interface was built using the *PyQt5* library in Python version 3.9.0, with all pumps and valves controlled through serial communication. For the selected methodology, the programme captured all user inputs to define the experimental parameters before building the experimental design and calculating the flow rates for each reaction. The *doePy* library was used to build the DoE experiment, whilst the *summit* library was used for its distribution of the TSEMO algorithm. Source code for the platform is available at https://github.com/PPittaway/S DL_for_EP. On starting the experiment, the programme iterated through each set of conditions to run reactions according to the running sequence defined in the [supporting information](#). For closed-loop self-optimization, after sampling for the DLS, a loop was used to detect the latest set of size data uploaded to a target folder which was then extracted, read, and appended to the current dataset before being passed to the algorithm.

2.8. Continuous emulsion polymerization

A general procedure for the continuous emulsion polymerization using the platform was as follows: First, the experimental procedure was defined using the platform interface, which calculated the flowrates for each experiment according to the material balance equations below.

Considering the average residence time of a seed particle, τ_{seed} , entering the reactor at the first CSTR, with emulsion added into n_{fed} CSTRs and the seed latex entering the first CSTR of a total n CSTRs, the average residence time of a seed particle is given by Eq. (1.1).

$$\tau_{seed} = V_{CSTR} \sum_{i=1}^n \frac{1}{V_i} = \begin{cases} v_s + \left(\frac{i}{n_{fed}}\right)v_e, & i \leq n_{fed} \\ v_s + v_e, & i > n_{fed} \end{cases} \quad (1.1)$$

where V_{CSTR} is the volume of a single CSTR, v_s is the flowrate of the latex seed, and v_e is the flowrate of the emulsion. Defining the seed fraction, R , as the contribution of the solids content in the seed to the total solids content (TSC) of the final product:

$$R = \frac{w_s \rho_s v_s}{w_f \rho_f v_f} \quad (1.2)$$

where w_s and w_f are the TSC of the latex seed and final product respectively, ρ_s and ρ_f are the densities of the latex seed and final product respectively, and v_f is the total flowrate. Considering that the total flowrate is the sum of the seed and emulsion flowrates, the emulsion flowrate is defined as:

$$v_e = \frac{v_s \rho_s}{\rho_e} \left(\frac{w_s}{R w_f} - 1 \right) \quad (1.3)$$

Substituting this into Eq. (1.1), the flowrate of the latex seed for a given target residence time can be calculated for any seed fraction and number of emulsion feeds:

$$v_s = \frac{V_{CSTR}}{\tau_{seed}} \sum_{i=1}^n \frac{1}{v_i} = \begin{cases} 1 + \frac{i\rho_s}{n_{fed}\rho_e} \left(\frac{w_s}{Rw_f} - 1 \right), & i \leq n_{fed} \\ 1 + \frac{\rho_s}{\rho_e} \left(\frac{w_s}{Rw_f} - 1 \right), & i > n_{fed} \end{cases} \quad (1.4)$$

For an emulsion feed with a solids loading w_e , and a target surfactant concentration, w_{Aq} , the total aqueous and monomer flowrates, v_{Aq} and v_m respectively are determined by:

$$v_{Aq} = \frac{\rho_e v_e (1 - w_e)}{\rho_{Aq} (1 - w_{Aq})} \quad (1.5)$$

$$v_m = \frac{\rho_e v_e (w_e - w_{Aq})}{\rho_m (1 - w_{Aq})} \quad (1.6)$$

where ρ_{Aq} and ρ_m are the densities of the total aqueous and monomer feeds respectively. These can be split into the four separate flowrates which comprise the two aqueous and two monomer feeds (v_{Aq1} , v_{Aq2} , v_{m1} , and v_{m2} respectively) depending on the concentrations of aqueous inlets 1 and 2 (w_{Aq1} and w_{Aq2} respectively) and the targeted mass fraction of monomer feed 1, x_{m1} .

$$v_{Aq1} = \frac{v_{Aq} (w_{Aq} - w_{Aq2})}{w_{Aq1} - w_{Aq2}} \quad (1.7)$$

$$v_{Aq2} = \frac{v_{Aq} (w_{Aq} - w_{Aq1})}{w_{Aq2} - w_{Aq1}} \quad (1.8)$$

$$v_{m1} = \frac{\rho_m v_m x_{m1}}{\rho_{m1}} \quad (1.9)$$

$$v_{m2} = \frac{\rho_m v_m (1 - x_{m1})}{\rho_{m2}} \quad (1.10)$$

ρ_{m1} and ρ_{m2} are the individual densities of the monomer mixtures.

After defining the experimental routine and calculating flowrates, the flasks were prepared for each pump. For pump Aq1 the flask typically contained chelating agents, SDBS (2.2627 g, 6.50 mmol), APS (0.9605 g, 4.21 mmol), and water (226.27 g). This represented a 0.01 g/mL solution of SDBS. For pump Aq2 the flask typically contained chelating agents, SDBS (11.3135 g, 32.47 mmol), APS (0.9605 g, 4.21 mmol), and water (226.27 g). This represented a 0.05 g/mL solution of SDBS. For pump M1 the flask typically contained t-DDM (0.1348 g, 0.67 mmol), AA (4.0426 g, 56.10 mmol), and ST (136.00 g, 1.3058 mol). For pump M2 the flask typically contained t-DDM (0.1377 g, 0.68 mmol), AA (4.1290 g, 57.30 mmol), and BA (136.00 g, 1.0611 mol). Multiples of these quantities were used depending on the number of planned reactions, with all reagents pumped from a refrigerator set to 4 °C. The seed syringe was filled by first filtering the seed through filter paper, filling 100 mL of the seed, and expelling any air before affixing to the syringe pump. The 0.66 % w/w SDBS solution used for reactor cleaning was pumped through the full system at 2 mL/min to assist in the removal of trapped air bubbles before the reactor was pressurized by opening the compressed air inlet and heated to the reaction temperature. For all reactions the temperature of the CSTRs heating block was set to 80 °C (to target a reaction temperature of 70 °C [41]) and the temperature of the sonicated water bath also to 80 °C. Once a reaction was started, three reactor volumes of the targeted composition were passed through the system to ensure steady state was obtained before sampling commenced. Between each reaction, the reactor was cleaned with both the solution of SDBS and mixture of THF and 1,4-dioxane.

2.9. Experimental design

2.9.1. One-factor-at-a-time experiments

Three levels of experimental design are used throughout this work.

The first level used a one-factor-at-a-time (OFAAT) approach to systematically explore the effect of changing one independent variable. This was used to conveniently demonstrate that unique products could be obtained within the proposed parameter space. Values for the manipulated variable were selected by dividing the space between the user-defined upper and lower bounds into seven equally spaced points. Seven experiments were chosen as this is the number of samples that could be collected without the need to clean and replace the bottles in the sampling system.

2.9.2. Design of experiments

The second level used a full factorial design of experiments (DoE) approach to vary multiple parameters simultaneously. DoE as an approach is regarded as an efficient means to characterize chemical systems, and as such its use is well-reported in the literature [43–45]. Therefore, the following is a brief explanation of the approach used for this work. User-defined upper and lower bounds of these parameters were used to build a central composite inscribed (CCI) experimental design, with the centre point of the design repeated in the middle and at the end of the experimental run to evaluate repeatability of the data. For an experimental design with three input variables, Fig. 3 illustrates the approach with the star points representing the extremes of the selected conditions.

A summary of reaction parameters and reagent flow rates is given in Table 1 for the three-dimensional CCI of surfactant concentration, w_{Aq} , seed fraction, R , and styrene fraction, x_{m1} .

Following completion of the experiment, the results were used to generate a response surface, which served as a model to predict the performance of the chemical system over the entire parameter space. The surface $f(x_1, x_2, x_3)$ was generated by fitting the experimental data to the response surface function in Eq. (1.11) to find the coefficients β_0 , β_i , β_{ii} , and β_{ij} .

$$f(x_1, x_2, x_3) = \beta_0 + \sum_{i=1}^3 \beta_i x_i + \sum_{i=1}^3 \beta_{ii} x_i^2 + \sum_{i < j} \beta_{ij} x_i x_j \quad (1.11)$$

Fitting of these coefficients was achieved using the *curve_fit* function from the *scipy.optimize* module in Python. The generated surface was subsequently used to find results for *in silico* evaluation of the performance of the self-optimization algorithm for the present problem, as described below.

2.10. Closed-loop self-optimization

2.10.1. TSEMO algorithm

The TSEMO algorithm is suited to efficiently solving optimization

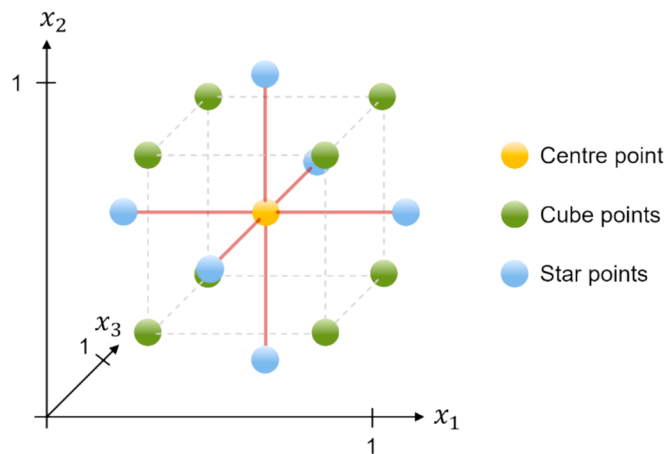


Fig. 3. Central composite inscribed design of experiment methodology for three input variables x_1 , x_2 , x_3 . Star points intersect the faces of the unit cube for input variables normalized between 0 and 1.

Table 1Summary of conditions and flow rates used in the automated CCI DoE varying surfactant concentration (w_{Aq}), seed fraction (R), and styrene fraction (x_{m1}).

Reaction ID	w_{Aq} [g/mL]	R [g/g]	x_{m1} [g/g]	v_{seed} [m L/min]	v_{Aq1} [m L/min]	v_{Aq2} [m L/min]	v_{m1} [m L/min]	v_{m2} [m L/min]
R1	0.019	0.061	0.330	0.042	0.092	0.025	0.022	0.045
R2	0.041	0.061	0.330	0.042	0.026	0.094	0.021	0.042
R3	0.019	0.061	0.670	0.042	0.092	0.025	0.044	0.022
R4	0.041	0.061	0.670	0.042	0.026	0.094	0.042	0.021
R5	0.019	0.168	0.330	0.094	0.031	0.009	0.016	0.032
R6	0.041	0.168	0.330	0.094	0.009	0.032	0.015	0.032
R7	0.019	0.168	0.670	0.094	0.031	0.009	0.032	0.016
R8	0.041	0.168	0.670	0.094	0.009	0.032	0.031	0.016
R9	0.030	0.114	0.500	0.070	0.037	0.037	0.027	0.028
R10	0.010	0.114	0.500	0.070	0.073	0.000	0.028	0.028
R11	0.050	0.114	0.500	0.070	0.000	0.076	0.026	0.027
R12	0.030	0.114	0.200	0.070	0.037	0.037	0.011	0.044
R13	0.030	0.114	0.800	0.070	0.037	0.037	0.043	0.011
R14	0.030	0.020	0.500	0.016	0.083	0.083	0.038	0.038
R15	0.030	0.209	0.500	0.110	0.009	0.009	0.021	0.022
R16	0.030	0.114	0.500	0.070	0.037	0.037	0.027	0.028

problems with multiple competing objectives [15,46]. This is achieved through the training of Gaussian Process (GP) surrogate models for each objective. In this work, the default configuration of the TSEMO algorithm distributed in the *summit* library was used. GPs are initially trained using the Exponential kernel of GPy. Spectral sampling of the GPs identifies possible evaluation conditions, with 1500 sample points. Samples are optimized using a non-dominated genetic sorting algorithm (NSGA-II) with 100 generations and a population size of 100 to generate an optimized set of candidate experiments. A hypervolume improvement criterion then selects a single set of conditions expected to offer the biggest hypervolume improvement to be executed as the next reaction on the platform.

2.10.2. Simulated (in silico) optimization campaigns

Before commencing with the third experimental approach involving closed-loop experimental self-optimization (and to also allow retrospective evaluation of the importance of running the physical experiment), the response surface generated from the physical DoE was used as an emulator for simulated optimization (i.e. running "in silico" experiments). For all optimization campaigns, the TSEMO algorithm was applied with the objectives of minimizing seed fraction and surfactant concentration. Two approaches were used to handle particle size as an objective, i) particle size targeting, and ii) particle size mapping. For particle size targeting, Eq. (1.12) was defined as a function to be minimized for obtaining a series of targeted particle size, D_{target} , with the value of D_{meas} obtained from the response surface based on the conditions selected by the algorithm.

$$f = \left(\frac{D_{meas} - D_{targ}}{D_{targ}} \right)^2 \quad (1.12)$$

The particle size mapping approach was chosen as a convenient way to find the optimum conditions for synthesizing any feasible particle size. To do this, the algorithm was set to alternate between maximizing and minimizing the raw particle size, relying on the intrinsic randomness of the TSEMO algorithm to explore the parameter space across the full range of possible sizes.

The general process for performing simulated optimizations is as follows: An initial dataset was generated from 10 Latin hypercube (LHC) sampling points. For each point, the conditions were passed to the emulator which returned a corresponding particle size based on the DoE-generated response surface. The TSEMO algorithm then selected a new set of conditions which were passed to the emulator to again return a particle size. This was repeated for a total of 30 experiments (10 LHC + 20 TSEMO). The performance of the algorithm for each of the two strategies was evaluated using the hypervolume metric [47].

2.10.3. Experimental self-optimization campaigns

Having evaluated the performance of the algorithm *in silico*, a closed-loop self-optimization was conducted using the physical platform. Rather than generating a new set of training data (using LHC sampling for instance), we elected to train the algorithm with the data from the previous DoE, which reduced experimental time and reagent consumption. These results were passed to the TSEMO algorithm, which was set to follow the particle size mapping strategy whereby the particle size objective was alternated between minimization and maximization on each experimental iteration. TSEMO would then pass a suggested set of conditions to the platform and the reaction would proceed before the particle size was measured using the online stopped-flow DLS. The results from the DLS were processed and the new dataset passed back to TSEMO in a closed loop. TSEMO suggested the next set of conditions and the process was repeated for a total of 21 iterations, whilst samples were taken every three reactions for offline validation.

2.10.4. Seeded semi-batch synthesis of poly(styrene)-co-poly(butyl acrylate) polymers

For comparison of the products prepared in the continuous-flow platform to those prepared by a conventional semi-batch method, a cross-section of products was synthesized in an equivalent semi-batch process. A single batch of latex seed was prepared as described above, with four stock solutions representing the four reagent feeds of the flow platform prepared and used for all five semi-batch reactions. The stock solutions were two aqueous and two monomer mixtures, prepared according to the amounts in Tables S1 to S4. A general procedure for the semi-batch synthesis involved adding 17.6145 g of the pre-prepared latex seed suspension to a 100 mL three-necked round-bottom flask containing an ellipsoidal magnetic stirrer bar. The flask was sealed and heated to 70 °C in a temperature-controlled oil bath. In a separate glass bottle containing a cross-shaped magnetic stirrer, 11.2028 g of the Aq1 solution, 11.2028 g of the Aq2 solution, 7.4111 g of the M1 mixture, and 7.4238 g of the M2 mixture were added and stirred at 1500 rpm for five minutes to make the emulsion. A ReaXus 6010R reciprocating HPLC pump (Teledyne ISCO) was primed with this emulsion before feeding to the reactor was started at 0.76 mL/min for a feeding time which matched the effective feeding time of the equivalent flow reaction (42.4 min in this case). 50 min after feeding started, the temperature was increased to 80 °C and the reaction was left to react until the total reaction time reached that of the equivalent flow reaction (75.2 min in this case) at which point a sample was extracted and the hot plate switched off. The reactor was left stirring in the oil bath until it had cooled, and a final sample was taken. The reaction parameters of the seeded semi-batch reactions are summarized in Table 2.

Table 2

Parameters used in seeded semi-batch reactions used to replicate a selection of reactions from the automated CCI DoE on the continuous-flow platform.

Reaction ID	w_{Aq} [g/mL]	R [g/g]	x_{m1} [g/g]	m_{seed} [g]	$v_{emulsion}$ [mL/min]	$t_{feeding}$ [min]	t_{total} [min]
R3B	0.019	0.061	0.670	9.361	0.938	43.33	72.22
R6B	0.041	0.168	0.330	25.872	0.579	41.70	77.68
R9B	0.030	0.114	0.500	17.615	0.763	42.44	75.16
R12B	0.030	0.114	0.200	17.590	0.764	42.44	75.18
R15B	0.030	0.209	0.500	32.218	0.432	41.19	79.36

2.11. Material characterization

2.11.1. Dynamic light scattering

Particle size and particle size distributions were measured by dynamic light scattering (DLS) using a Malvern Zetasizer Nano series instrument at 25 °C with a scattering angle of 173°. Slightly different measurement protocols were used for the online and offline measurements but were separately validated to ensure agreement between the two values.

2.11.2. Online analysis

For online analysis, the instrument was set to continuously measure particle size for the duration of the experiment and the size data stored as a.csv file in a dedicated folder where each subsequent measurement replaced the previous. When a particle size value was required, a search loop was initiated in the programme to extract the last scan uploaded to this folder and saved separately. Samples were diluted inline using an automated sampling system (Fig. 2) comprising a switching valve (V3) and dedicated water pump. Each sample was extracted by first starting the water pump at 1 mL/min to pressurize the 1/16", 0.5 mm ID PFA tubing to the flow cell (ZEN0023 quartz cell, Hellma) before the switching valve diverted product via 1/8" PFA tubing to a T-piece for dilution with the water. The product was diverted for at least three volumes of this tubing to replace product from the previous measurement and then the required water flow rate was calculated and set based on the particular conditions (total reactor flow rate and product concentration) to dilute the product to 1 % w/w. 1 % w/w was used as this could be achieved within the maximum flow rate of the water pump for all the reaction conditions, and was determined to provide sufficiently accurate size measurements when validated against offline measurements at 0.1 %w/w (Fig. S6). The dilution continued until at least three volumes of the flow cell had been replaced before the pumps were paused and the search loop started. One measurement (5 runs, 10 s run duration) was recorded for each sample, and once saved the reactor outlet was diverted back to the sampling system and either sampling or reactor cleaning commenced.

2.11.3. Offline analysis

Offline DLS was performed with the same instrument as the online DLS using standard disposable cuvettes. Samples were diluted to 0.1 % w/w and the average of three measurements was taken for each.

2.11.4. Gravimetric analysis

Total solids content (TSC) was used to determine monomer conversion by measuring the loss on drying of the product samples. To do this, samples of the aqueous dispersions were weighed into aluminium dishes in triplicate and left to dry for three days in a vented oven at 105 °C. TSC was calculated according to Eq. (1.13).

$$TSC = \frac{m_{dry} - m_{dish}}{m_{sample} - m_{dish}} \quad (1.13)$$

m_{dry} is the mass of the aluminium dish containing the sample after drying, m_{dish} is the mass of the aluminium dish, and m_{sample} is the mass of the aluminium dish containing the latex before drying. The total monomer conversion, accounting for the amount of seed contributing to the measured TSC, is then calculated according to Eq. (1.14).

$$X_m = \frac{TSC - TSC_{target}R}{TSC_{target}(1 - R)} \quad (1.14)$$

2.11.5. Gel permeation chromatography

Offline GPC measurements were conducted with an Agilent 1260 Infinity system, fitted with two 5 µm Mixed-C columns (with guard column), an RI detector and a UV-Vis detector operating at 254 nm. THF containing 1 %v/v triethylamine and 0.05 %w/v butylated hydroxytoluene was used as the eluent system at 1 mL/min, with the column oven and RI detector at 35 °C. A series of near-monodisperse polystyrene standards were used (M_p : 580–3,152,000 g/mol) for calibration. Samples were dried and redissolved in the THF eluent before being filtered through a 0.22 µm syringe filter and characterized in triplicate.

2.11.6. Laser light scattering

The inline emulsification was evaluated against two separate batch approaches with laser light scattering (LLS; Mastersizer 3000 + Ultra, Malvern) used to measure droplet size distributions. For evaluating continuous-flow emulsification, an aqueous solution of SDBS (0.75 %w/w) and ST were pumped from separate pumps (ReaXus 6010R, Teledyne ISCO) at 0.70 and 0.33 mL/min respectively into a single miniature CSTR to yield a 30 %w/w emulsion. After five reactor volumes the outlet was diverted into the dispersion cell (Hydro MV) of the laser light scattering instrument before the analysis commenced. 1 mL/min was used as the total flow rate so that enough sample could be collected without aging the emulsion before characterization. The two batch approaches involved adding 56 g of a 0.75 %w/w SDBS solution and 24 g of ST to a 100 mL beaker firstly with a cross-shaped magnetic stirrer at 2000 rpm and secondly with a high-shear homogenizer (UltraTurrax) at 5000 rpm. After two minutes, samples were extracted for analysis using the automated measurement routine.

2.11.7. Analytical centrifugation

In addition to LLS, analytical centrifugation (LUMiSizer) was used to assess space- and time-resolved light extinction profiles under centrifuge to support the LLS data and assess stability. Samples were centrifuged at 1000 rpm with scans taken every 5 s for a total of 400 scans.

2.11.8. Differential scanning calorimetry

Glass transition temperatures were measured by differential scanning calorimetry using a DSC 8000 instrument (Perkin Elmer). Samples containing at least 5 mg of polymer sample were dried for three days at 105 °C in standard aluminium pans before being sealed and analyzed. Each sample was initially cooled to −50 °C and heated to 80 °C at 20 °C/min to erase the thermal history before being cooled down to −70 °C and then up to 150 °C (or to the temperature at which the sample melted at which point the analysis was aborted) also at 20 °C/min.

3. Results and discussion

3.1. Batch poly(styrene)-co-poly(butyl acrylate) latex seed synthesis

Characterization of the latex seed indicated high monomer conversion and a monomodal particle size distribution (Fig. S7). A new batch of the latex seed was prepared for each set of experiments, which was characterized to ensure consistency. Typically, the TSC was around 9.4

% and did not vary by more than 0.2 % between each seed latex used, with the particle size typically measured to be 53 nm and monomodal (PDI = 0.04), varying by no more than 3 nm for each batch. The exact TSC for each new seed was measured and used as an input to the continuous-flow platform to ensure accurate flow rate calculations.

3.2. Emulsion characterization

To evaluate the performance of the inline emulsification, samples were compared to two separate batch emulsification processes using either rapid stirring with a magnetic stirrer (2000 rpm) or stirring with a high-shear mixer (UltraTurrax, 5000 rpm). The smallest droplets were achieved using the high-shear mixer ($\sim 0.33 \mu\text{m}$) followed by the batch stirring ($\sim 0.40 \mu\text{m}$), and then the continuous-flow emulsification ($\sim 0.51 \mu\text{m}$) (Fig. S8). This trend was verified using space- and time-resolved light transmission which demonstrated that the droplets prepared in continuous-flow separated quicker under centrifuge and were less monodisperse likely because of the inherent RTD (Fig. S9). Overall, the emulsion prepared in the in-line CSTR had droplet sizes on the same order of magnitude as those prepared in batch, with separation rates slow enough to be considered appropriate for the subsequent downstream emulsion polymerization process.

3.3. One-factor-at-a-time screening

To demonstrate the capability of the platform to synthesize products with unique characteristics a series of OFAAT screening experiments were performed to represent each of the parameters that could be manipulated. Each of these were defined by inputting minimum and maximum bounds for the parameter of interest along with the number of experiments. The OFAAT function on the user interface then calculated

the flow rates required to perform a systematic sequence of experiments with equal spacing of the target variable. The first experiment explored the influence of surfactant concentration between an aqueous phase concentration of 0.01 and 0.05 g/mL. This was first done without the downstream STR however monomer conversion was low for most of the samples (Fig. S10). Therefore, the STR was added to the platform and used for all remaining experiments as a simple means of increasing monomer conversion. The other OFAAT experiments varied the seed fraction, R , from 0.01 g/g to 0.15 g/g, ST fraction from 0.2 to 0.8 g/g, and the number of emulsion feeds from 1 to 4.

When each of the parameters were varied independently, products with unique properties were obtained. For surfactant concentration (Fig. 4a), a greater amount of surfactant in the aqueous feed was shown to result in a smaller measured particle size. When more surfactant is used, it is likely that particles remain more stable, reducing the likelihood of coagulation leading to an overall smaller size. In addition, increasing amounts of surfactant can increase the potential for secondary particle nucleation, as propagating radicals formed in the aqueous phase – or radicals which may exit the particles already formed – are able to find themselves in an increasing number of surfactant micelles [24,25]. This secondary nucleation would be characterized by an overall reduction in particle size and a slight increase in the polydispersity index (PDI) of the sample, which was observed at higher surfactant concentrations (Fig. S10b). When the fraction of ST was increased (Fig. 4b) there was no change in particle size observed, instead a greater fraction of ST resulted in a higher glass transition temperature enabling multiple product characteristics to be targeted with the platform (Fig. S11). As the seed fraction was increased (Fig. 4c) there was also a reduction in particle size of the final product, except for the very low seed quantities where it is likely the small number of seed particles relative to the amount of surfactant may not be enough to prevent secondary

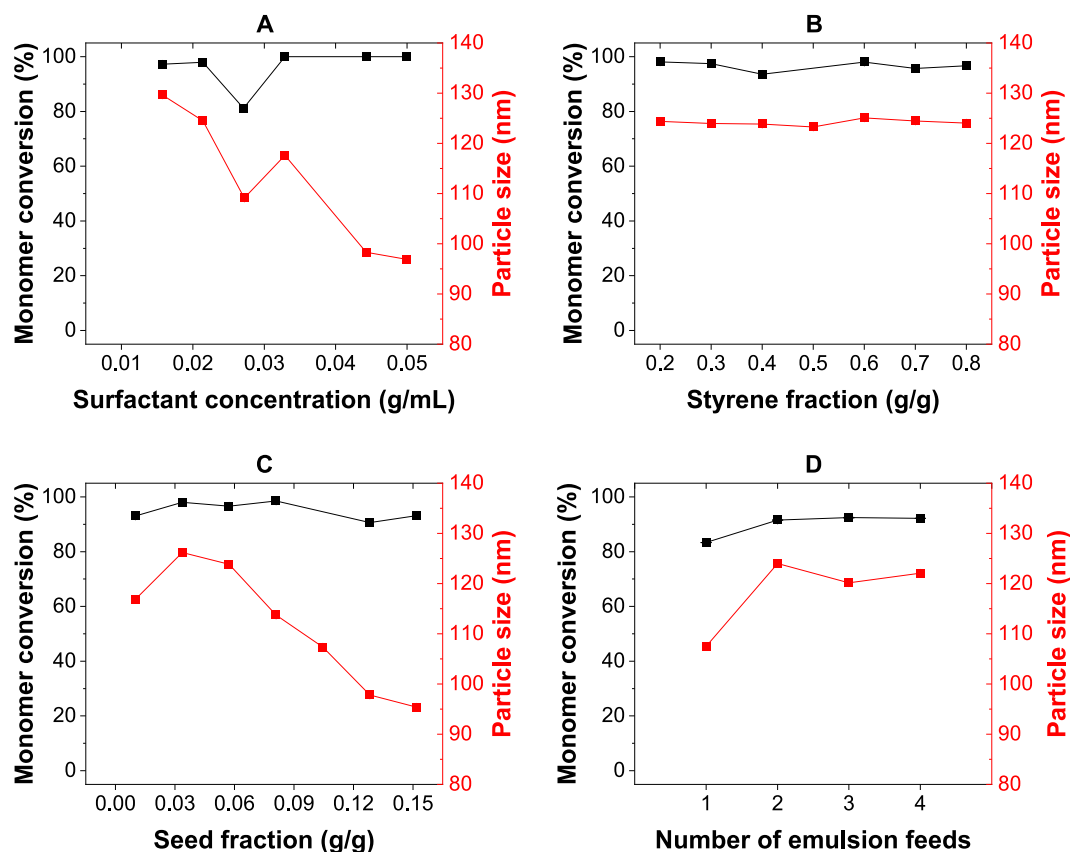


Fig. 4. Monomer conversion and offline particle size measurements for automated one-factor-at-a-time screening experiments varying A) surfactant concentration, B) styrene fraction, C) seed fraction, and D) number of emulsion feeds. All experiments at 30 %w/w, reactions at 70 °C, for a 50-minute residence time in the CSTR cascade.

nucleation, with propagating radicals finding their way into surfactant micelles instead. Finally, varying the number of emulsion feeds (and in effect the emulsion feed rate) also appeared to have little effect on the product characteristics (Fig. 4d). However, it was observed qualitatively that the reaction with only one emulsion feed appeared to generate more fouling than the others. To minimize the monomer concentration and best represent a semi-batch reaction, all other experiments using the platform were conducted with four emulsion feeds.

3.4. Design of experiment screening and response surface modelling

Whilst the OFAT method is useful for probing a single variable in detail, there are more efficient approaches to quickly evaluating the parameter space. Following a similar protocol, a series of reactions (Table 1) were programmed according to a central composite inscribed (CCI) DoE by inputting the upper and lower limits of surfactant concentration, seed fraction, and ST fraction. In this way, three parameters were varied simultaneously covering a full range of conditions in a single experiment. The central point was repeated both in the middle of the sequence and at the end to give insights into the repeatability of the experiment.

For each reaction, a 5 mL sample was collected once steady state was reached with the platform pausing after every seventh reaction to allow the sample bottles to be cleaned and replaced. Particle size, monomer conversion, and molecular weight distributions were measured offline for each of the samples collected (Table S5). Within the parameter space

explored, a range of particle sizes were obtained whilst the total monomer conversion was high (>90 %) for all reactions (Fig. 5). The duplicated reaction (R9 and R16) exhibited the excellent repeatability of the platform, owing to the precision afforded by continuous-flow synthesis (Fig. 5b). Analysis of the molecular weight distributions (Fig. S12) revealed slight variation amongst the resulting polymer characteristics for the samples generated. This is typical of free-radical polymerisation where there is limited control over the evolution of molecular weight. In this case, no particular molar mass characteristics were desired, though such properties could readily be explored through the application of additional online monitoring techniques as has been demonstrated in recent literature [12,18].

Including the initial setup (filling reagent flasks and preparing the reactor), all 16 reactions were completed within three days of experiment time. For each reaction this included the time taken to reach steady state, collect the sample, and perform reactor cleaning (approximately 225, 20, and 15 min respectively). Volumes collected in the waste bottle and consumed from the seed syringe were tracked so that the experiments were automatically paused to allow these to be emptied or filled during normal working hours. After starting, the only user input required was to replace the sample and waste bottles on two occasions and refill the seed syringe. This represents a large increase in throughput for the exploration of emulsion polymer systems, offering the opportunity to accelerate development timelines whilst reducing labour requirements and minimizing risks associated with chemical contact.

Whilst the platform can rapidly explore the parameter space and

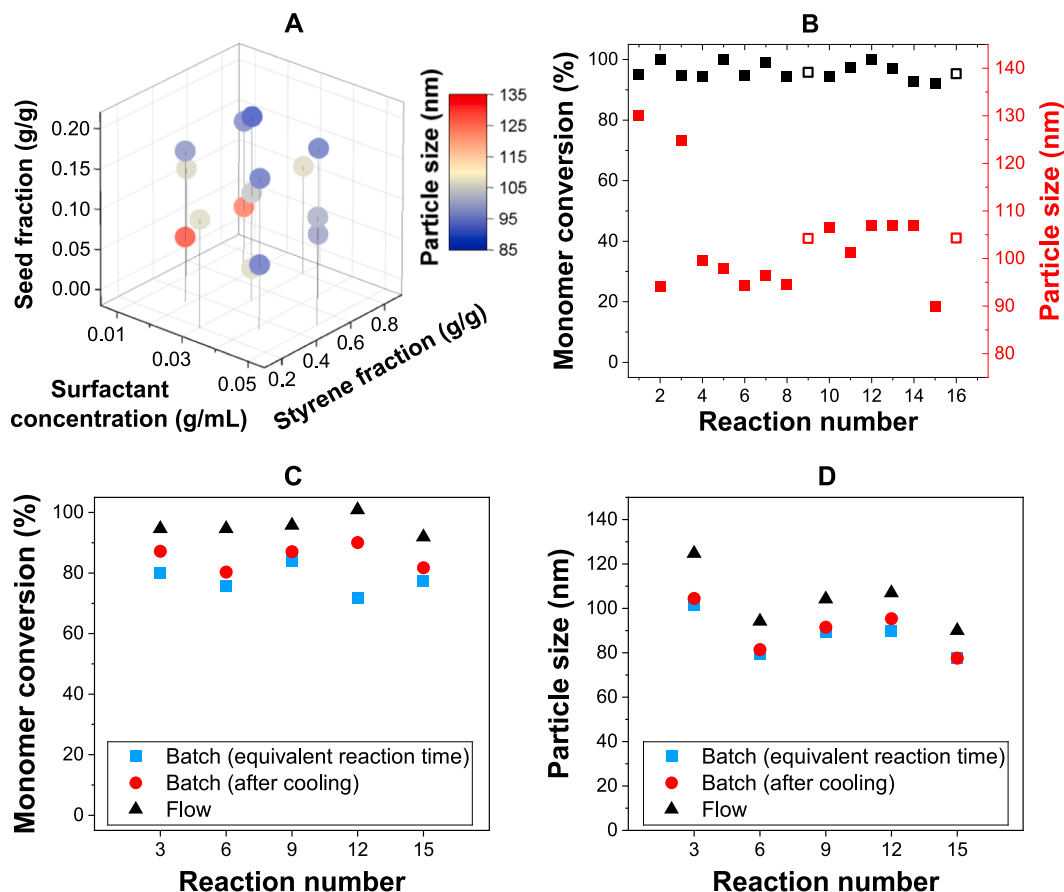


Fig. 5. Summary data for the 16 automated continuous-flow emulsion polymerizations. A) CCI experimental design and particle size colour-mapping. B) Measured conversion and particle sizes for the 16 reactions. Hollow squares represent the centre point of the CCI repeated at the beginning and end of the experiment. C) Conversion measured for five semi-batch reactions compared to their corresponding flow reactions (black triangles), measured with a sample taken at the equivalent reaction time (blue squares) and after the product had cooled (red circles). D) Particle size measured for five semi-batch reactions compared to their corresponding flow reactions measured at the equivalent reaction time and after the product had cooled. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

generate product samples useful for evaluating the system in continuous flow, the final manufacturing process may still adopt a semi-batch routine. Therefore, to assess the similarity between the two methods, five of the reactions (R3, R6, R9, R12, and R15) were replicated in semi-batch (Fig. 5c and d) according to the conditions in Table 2. The semi-batch reactions were sampled and characterized both at a reaction time equivalent to that of the flow reaction, and after the batch had cooled as the final product. Between these two samples there was a noticeable increase in both particle size and conversion, though conversion was still below that achieved in flow likely because of the improved mass and heat transfer achieved in the flow reactor. Despite this disparity, the results revealed similar trends in particle size and conversion across the five samples, and it is hence likely that very similar products could be obtained by using longer batch reaction times to reach higher conversion. Further similarity could be achieved by using even more emulsion feeds for the flow reactor. Having more feeds would enable the semi-batch emulsion feeding profile to be more precisely represented by the flow platform, since using just four does result in a large degree of deviation (Fig. S4). This would, however, also require additional CSTRs, valves, and associated equipment which would be impractical. Furthermore, since the total flow rate accelerates with each emulsion feed, the dosing profile in this system is non-linear, though it would be possible to overcome this by manipulating the switching time for different stages to account for this.

Data from the CCI was used to build a response surface (Fig. 6) of the parameter space according to Eq. (1.11) where x_1 , x_2 , and x_3 are the seed fraction, surfactant concentration, and ST fraction respectively. The

inset table (Fig. 6) summarizes the fitting parameters obtained. The resulting 3D surface revealed a very limited influence of ST fraction on the final particle size, which is expected since, for a constant number of particles, the same total mass of monomer is available to grow the particle irrespective of the monomer used.

The response surface indicates the possible combinations of conditions required to prepare products with specific particle sizes, but also offers insights into the mechanisms of emulsion polymerization. At the low values of both surfactant concentration and seed fraction, the amount of monomer used is spread between a reduced number of particles, hence the particle size of the product increases. At higher values of seed fraction, the total number of particles increases to provide the opposite effect. Increasing surfactant concentration can also contribute to an increased particle number, particularly if the surfactant amount is large enough to cause secondary particle nucleation, wherein propagating radicals are transported into surfactant micelles instead of the particles which have grown from the seed. This would also have the effect of reducing the overall particle size, as is observed in the response surface. At low concentrations of surfactant and seed the system is likely to be unstable, which would result in an increase in the measured particle size as particles coagulate. This behaviour is also suggested by the model under these conditions.

3.5. Closed-loop multi-objective self-optimization

Before continuing with a self-optimization on the physical platform, the response surface generated from the automated CCI was used as a

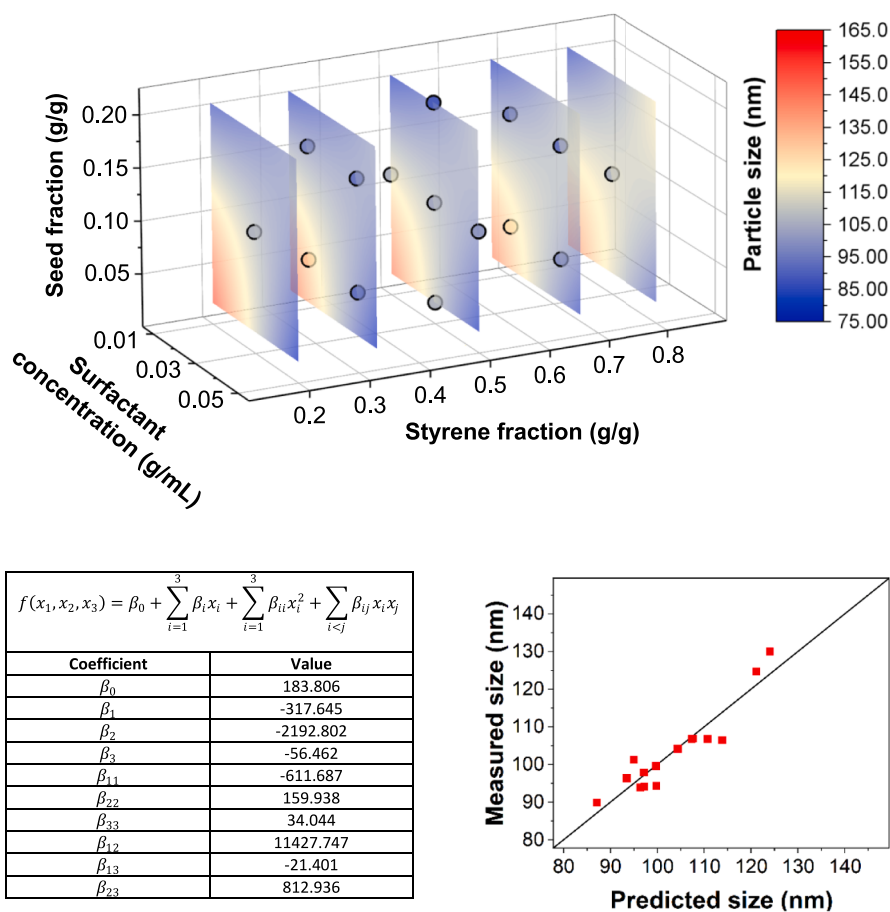


Fig. 6. Response surface plots of the automated CCI DoE experiment. (Top) Slices of the 3D response surface at the five unique monomer compositions with experimental points mapped onto each slice. Experimental points coloured independently from the response surface using the same colour scale. (Bottom) Fitting parameters and predicted versus measured values of particle size for the 3D CCI ($R^2 = 0.8737$).

digital version of the chemical system to evaluate the performance of the TSEMO algorithm. Two optimization methods were evaluated *in silico* with the first – size *targeting* – targeting distinct particle sizes to evaluate the capability to exploit specific areas of interest by minimizing the objective function (Eq. (1.12)). The second method – size *mapping* – employed a strategy of alternating between minimizing and maximizing an objective of raw particle size, utilising the exploratory behaviour of the TSEMO algorithm to map the attainable particle sizes within the parameter space. In both cases, the objectives of minimizing surfactant concentration and seed fraction were also applied.

3.6. Simulated optimization

A Python script was written to provide reaction conditions (surfactant concentration and seed fraction) to the digital system which returned the corresponding particle size. An initial dataset was generated from 10 pseudo-random experiments using Latin hypercube (LHC) sampling before the TSEMO algorithm took over to complete 20 further simulated reactions. On each iteration, the new conditions and resulting particle size were appended to the existing dataset which was in turn used by the algorithm to select the next conditions. Two examples of the simulated optimizations are shown in Fig. 7, where separate size *targeting* experiments were used to target particle sizes of 80 and 130 nm (simulations for other size targets given in Fig. S13). For the 80 nm target there is a clear trade-off between reaching the minimum in the objective function and minimizing both surfactant concentration and seed fraction, where more surfactant and seed are required to access the smaller sizes. As a result, the possible solutions are further from the utopian point and a three-dimensional pareto front can be visualised. In contrast, there is a much closer approach to the utopian solution for the 130 nm target since this particle size is accessed by reducing the amounts of seed and surfactant. To evaluate the performance of the size *mapping* strategy for identifying the optima which correspond to these same particle size targets, the results of a single optimization using this approach are plotted (Fig. 7, red points) alongside both sets of size *targeting* data (Fig. 7, blue points). Since no single size was targeted using the mapping approach, the data is distributed more evenly over the objective space, particularly for the 130 nm size target where the targeting approach prefers to exploit the conditions which achieve this size. The broad range of particle sizes identified by this strategy is shown in Fig. 8a which summarizes the results of a single size *mapping* optimization. Six further size targeting optimizations were simulated for sizes of 90, 100, 110, 120, 140, and 150 nm and the hypervolume metric used to quantify the approach to the utopian solution (Fig. 8b). This first

confirmed that 30 reactions were sufficient to characterize the system well, with the hypervolume values being almost fully converged for each size target. Secondly, this again shows that the utopian solution is more difficult to obtain at smaller size targets, reaching a value of only 0.79 for the 80 nm target versus >0.99 for the target of 130 nm. The size mapping data was also normalized to each of the size targets using the particle size objective function (Eq. (1.12)) to assess its capability to provide insights relating to specific size targets.

Overall, the hypervolume achieved from the single size mapping optimization was comparable to the eight separate size targeting optimizations providing an efficient and easy to access approach to exploring the system. Furthermore, the size mapping approach did not require any prior information relating to the achievable particle sizes, since the algorithm was simply asked to maximize or minimize the objective, rather than meet a specific size. Given these practical benefits, this strategy was taken forward for use on the physical platform to minimize the number of experiments required.

3.7. Experimental optimization

The size-mapping optimization strategy was employed on the physical platform (Fig. 2) for the seeded free-radical copolymerization of ST and BA. Z-average particle size measured by online stopped-flow DLS was passed to the TSEMO algorithm to select the next experiment, which alternated between maximizing and minimizing the particle size. Instead of starting with LHC sampling to generate a training dataset, the algorithm was initially trained using CCI data from the DoE (the same data which used to generate the response surface). Once the platform was prepared (reagents weighed and reactors heated), the 21 reactions were undertaken, with automatic size analysis for each reaction and automatic sample collection for every third reaction. After starting, the only manual input required was to empty the waste bottle and refill the seed syringe, with the Python programme tracking the available volumes in each and pausing the experiment to allow for these tasks to be done when necessary. The 21 closed-loop optimization reactions were completed within four days of experiment time with only a morning of preparation beforehand. Conditions which were autonomously generated for each iteration are shown in Table S6 and all particle size distributions are given in Fig. S14.

The physical optimization campaign successfully mapped out the possible sizes achieved using the defined parameter space (Fig. 9a). In particular, the algorithm quickly identifies the region where particle size is maximized coinciding with minima in both surfactant concentration and seed fraction. Since this region meets all three objectives the

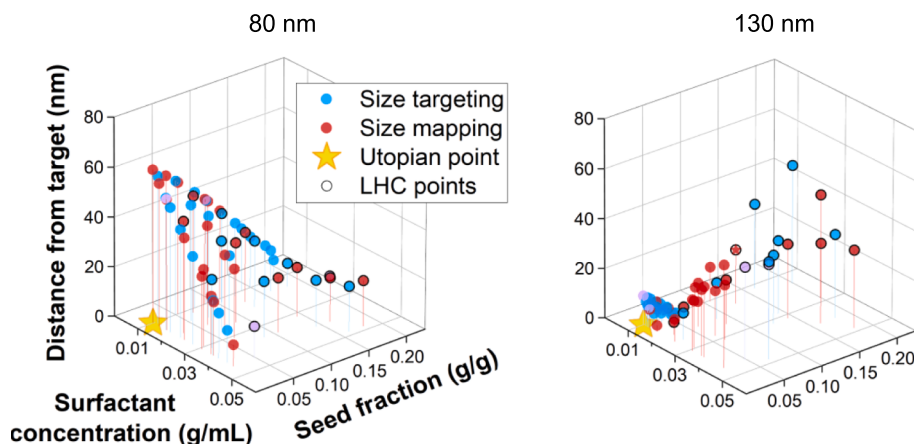


Fig. 7. Simulated closed-loop self-optimizations with objectives to minimize surfactant concentration and seed fraction. Each simulated optimization started with 10 LHC reactions. Two optimization strategies aim to either minimize the particle size objective function for target sizes of 80 nm (Left) and 130 nm (Right) (blue spheres, five size targeting simulations), or alternate between maximizing and minimizing raw particle size (red spheres, one size mapping simulation). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

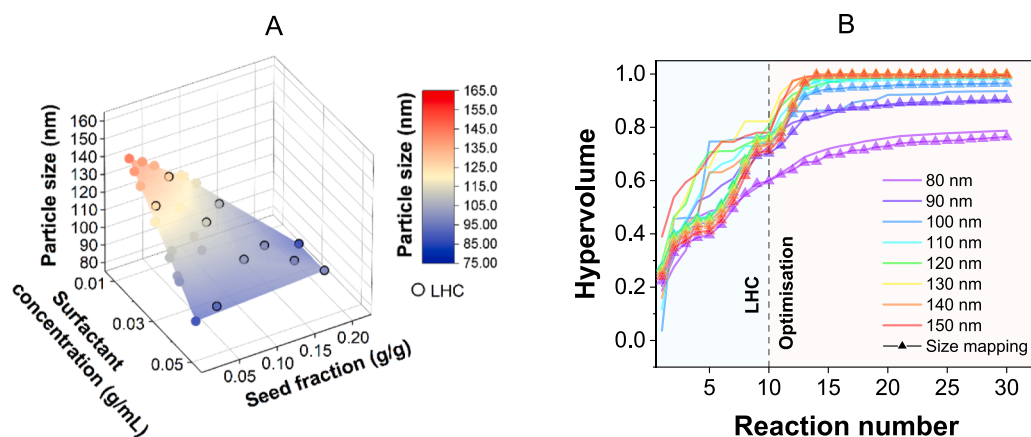


Fig. 8. (A) Simulated particle size mapping optimization based on the response surface model generated from the automated CCI. Circled points are the 10 initial Latin hypercube (LHC) reactions. (B) Hypervolumes achieved during simulated optimizations relative to six different particle sizes, with optimizations performed using a particle size targeting versus a particle size mapping strategy.

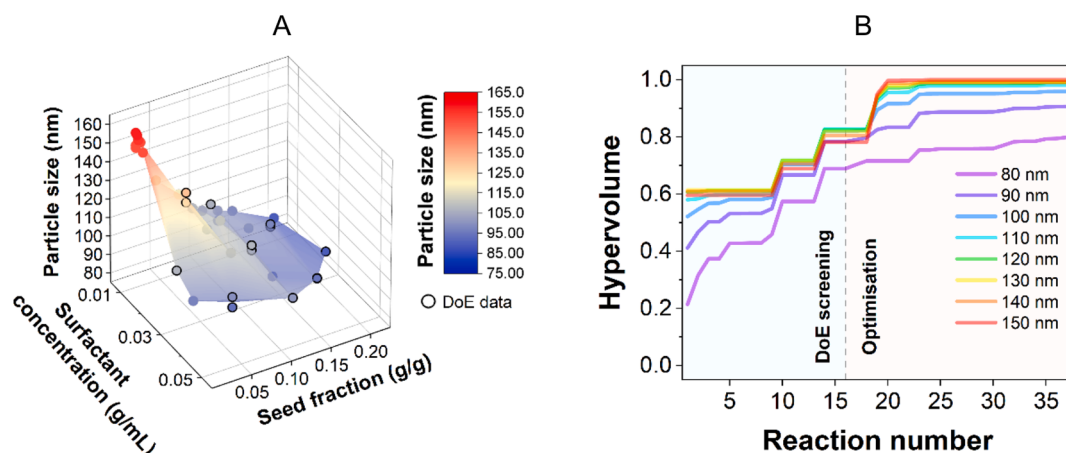


Fig. 9. Particle size mapping optimizations to minimize surfactant concentration and seed fraction whilst alternating between maximizing and minimizing particle size in (A) the physical optimization and (B) Hypervolume evolution for each particle size target using all experimental data from both the automated CCI and closed-loop optimization.

algorithm tended to exploit this on iterations where the particle size objective is being maximized and exploration is limited until later in the experiment (Table S6). More exploration was observed on iterations where the particle size objective was minimized due to the competing objectives of minimizing surfactant concentration and seed fraction. Whilst the automated CCI contributed to most of the gain in hypervolume, the application of the algorithm in fewer than 10 subsequent experiments provided a significant amount of additional information with respect to areas of interest within the objective space, characterized by large increases in hypervolume (Fig. 9b).

To evaluate the utility of the simulated optimization, the conditions of the physical optimization were inputted to the response surface model and the predicted values of particle size compared to those that were measured (Fig. 10). The response surface model derived from the automated CCI provided a reasonably accurate description of the system, however, the measured sizes from the experimental optimization campaign deviate more significantly from the prediction (particularly where particle size is maximized). This is likely inherent to the subtle changes in platform (including online vs offline analysis), and the subtle variation in the stock solutions and seed batches used during the different experiments. It should be noted the fact that these variations are in-part due to human error during the manual preparation processes.

4. Conclusions

An autonomous continuous-flow reactor platform capable of seeded emulsion polymerization has been developed based on a cascade of miniature CSTRs and an inline sonicated tubular reactor. High conversion was achieved with residence times that are relatively short in the context of emulsion polymerization (~75 mins), whilst automated sampling allowed for the collection of product prototypes for offline characterization. OFAAT automation varying surfactant concentration, seed fraction, monomer composition, and the number of emulsion feeds demonstrated the ability to generate products with unique performance. Applying DoE methodology enabled efficient high-throughput screening of the parameter space in three dimensions for the generation of a response surface model. The combination of DoE experimentation and response surface modelling represented a straight-forward route to understanding the parameter space. Simulated optimizations were conducted using the generated model in combination with a Bayesian multi-objective optimization algorithm (TSEMO) to minimize amounts of surfactant and seed whilst targeting various particle sizes. An optimization strategy of alternating between maximization and minimization of particle size was found to further accelerate exploration of the parameter space as quantified by the hypervolume achieved with respect to the possible particle sizes obtained. This was applied to the

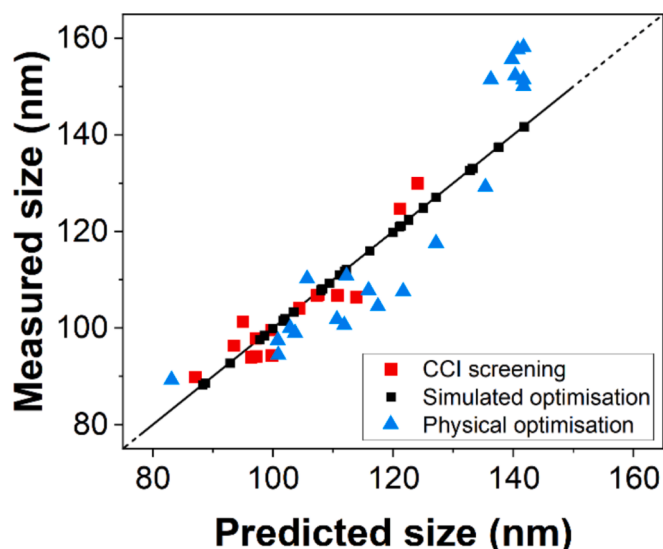


Fig. 10. Predicted versus measured particle sizes for the conditions used in the simulated and physical optimizations. Predicted sizes are based on the response surface model generated from the 3D CCI experiment. Dashed lines indicate sizes outside the limits predicted by the response surface model.

physical platform with particle size characterized using online stopped-flow DLS to ‘close the loop’. Though the model was accurate for the DoE data, the existence of optima at more extremes of the parameter space meant it was less successful in predicting product properties when compared to data obtained in the physical optimization. In this case, supplementing the DoE with just a few optimization experiments enabled a more comprehensive characterization of the chemical system with respect to identification of the optimized conditions. Whilst particle size was the only product property to be optimized, minimization of seed and surfactant quantities were also included as objectives of the optimization. Such aspects can be just as important to optimize (say for economic, safety, or environmental reasons) as the product performance characteristics themselves. Additional online monitoring techniques would however be easily incorporated given the modularity of the system to explore other characteristics. The increasing availability of such techniques is critical to advancing the capability of these autonomous reactor platforms, particularly for emulsion polymerization where relationships between product performance are so multi-dimensional. Overall, this work represents the first instance of a reactor platform capable of closed-loop self-optimization of emulsion polymers, unlocking the ability to accelerate the development of new polymeric materials.

5. Associated content

Additional experimental details including detailed description of reactor platforms, cleaning and operation workflows, flow rate calculations, emulsion stability and additional DLS and DSC data obtained for several samples.

CRedit authorship contribution statement

Peter M. Pittaway: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Stephen T. Knox:** Writing – review & editing, Methodology, Data curation. **Olivier J. Cayre:** Writing – review & editing, Supervision, Methodology. **Nikil Kapur:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Lisa Golden:** Supervision, Methodology. **Sophie Drillier:** Supervision, Methodology. **Nicholas J. Warren:** Writing – review & editing, Supervision, Project administration,

Methodology, Investigation, Funding acquisition, Conceptualization.

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.

Acknowledgments

EPSRC are thanked for PhD funding via a Doctoral Training Partnership (for P. M.P.), and for grants EP/V055089/1 (for N.J.W. and S.T.K.), EP/X024237/1 (for N.K.) and EP/V027646/1 (for O.C.). Synthomer are thanked for industrial support for P. M.P.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cej.2025.160700>.

Data availability

The data that support the findings of this study are openly available in the University of Sheffield data repository DOI: 10.15131/shef.data.28350506

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