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Self-optimising continuous-flow hydrothermal reactor for nanoparticle synthesis†

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An autonomous continuous-flow, hydrothermal synthesis reactor, capable of self-optimising nanoparticle size using an in-line characterisation technique and machine learning is presented. The developed system is used for synthesis of hematite (α -Fe₂O₃) nanoparticles across three process variables, optimising for a target particle size. Optimisation is achieved in under 7 h with only 500 ml of 0.1 M Fe(NO₃)₃·9H₂O aqueous stock solution used, and without human intervention.

Nanomaterials have numerous applications including catalysis,^{1–3} optics,⁴ drug delivery^{5–7} and energy storage,^{8,9} whilst low-cost iron oxide nanomaterials have potential utilization in pigments,¹⁰ wastewater treatments¹¹ and photovoltaic devices.¹² Hematite (α -Fe₂O₃) has previously been proven to be highly controllable in terms of size and shape of nanoparticles using hydrothermal synthesis.^{13–15}

Hydrothermal synthesis has traditionally been a batch process, which has served to limit production at large scale.¹⁶ Continuous-flow synthesis demonstrates many distinct advantages over traditional batch methods, such as enhanced control of heat and mass transfer, reduced batch variability and the ability to quickly modify and screen synthesis conditions.^{17,18} Flow systems can be further enhanced with the incorporation of online process analytical technologies (PATs)¹⁹ to provide real-time information on particle size, morphology or composition; these parameters are key attributes in the synthesis of nanoparticles and can significantly alter the physicochemical properties of the final product.²⁰

First reported in 1992 by Adschiri *et al.*,²¹ continuous-flow hydrothermal synthesis (CFHS) of nanomaterials has been demonstrated as a green and scalable alternative to traditional nanoparticle synthesis techniques.²² Hydrothermal synthesis involves the heating of precursor solutions above their standard boiling point in a pressurised reactor. As water is heated to near, or above, its critical point (647.15 K and 22.4 MPa), it exhibits vastly different properties, such as reduced density and polarity,²³ which can be actively exploited for the controlled synthesis of nanoparticles.^{24–26} The increased dissociation of water at near-critical conditions leads to high concentrations of H⁺ and OH[−] ions, which can then be used for the immediate hydrolysis and dehydration of metal salt precursors, resulting in the precipitation of metal oxide nanoparticles.²⁷ Historically, ferrihydrite was the first stable product synthesised using CFHS through hydrolysis of iron precursors.^{28,29} The transition of ferrihydrite to more stable forms such as goethite, akaganeite or hematite was found to be dependent on temperature, pH and synthesis time.³⁰

Automation of continuous flow synthesis can often reduce the time and cost required to optimise materials.³¹ One of the earliest examples of self-optimisation in a continuous flow reactor is the synthesis of CdSe quantum dot nanoparticles, using inline spectroscopy.³² Recent advances in both process equipment and supervised machine learning (SML) methods provide exciting potential in creation of “autonomous reactors”.³³ Such cyber-physical reactors have demonstrated the ability to finely tune particle size in continuous flow systems by integrating more complex reactor designs, reaction chemistries or machine learning and optimisation strategies into nanoparticle flow synthesis.^{34–38}

Here we present self-optimisation of hematite particles targeting a maximum particle size (with an acceptably low size distribution) in a benchtop autonomous millifluidic supercritical hydrothermal reactor, combined with inline dynamic light scattering (DLS). The system is integrated with supervised machine learning methods (SNOBFIT and a

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	Downflow temperature [°C]	Flowrate [ml min ⁻¹]	Flow ratio	DLS [nm]	PXRD [nm]	TEM [nm]
A	360	30.0	0.365	45.4	10.0	5.4 ± 3.0
B	367	28.1	0.356	54.1	10.3	7.1 ± 4.1
C	370	30.0	0.330	67.0	15.0	9.1 ± 2.7
D	380	27.4	0.369	76.2	18.2	10.7 ± 3.2
E	380	26.0	0.330	84.1	22.6	27.1 ± 8.2
F	380	25.0	0.330	91.7	23.7	27.0 ± 7.8

We used a Bayesian optimiser which explores areas of uncertainty against available data points.^{46–48} This approach can remain relatively robust, in the presence of experimental

a. Hematite Self-Optimisation using Custom SML

3D scatter plot showing Flowrate [$\text{mL} \cdot \text{min}^{-1}$] (vertical axis, 25 to 35) versus Flow Ratio (horizontal axis, 0.34 to 0.38) and Temperature [$^{\circ}\text{C}$] (depth axis, 360 to 380). The color of the data points represents Particle Size [nm], ranging from 40 (blue) to 90 (red). The plot shows a distribution of data points with vertical error bars, indicating the relationship between the three variables.

b. Hematite Self-Optimisation using SNOBFIT

3D scatter plot showing Flowrate [$\text{mL} \cdot \text{min}^{-1}$] (vertical axis, 25 to 35) versus Flow Ratio (horizontal axis, 0.34 to 0.38) and Temperature [$^{\circ}\text{C}$] (depth axis, 360 to 380). The color of the data points represents Particle Size [nm], ranging from 40 (blue) to 90 (red). The plot shows a distribution of data points with vertical error bars, indicating the relationship between the three variables.

Fig. 1 Schematic of the CFHS reactor highlighting supervised machine learning (SML) loop. BPR: back-pressure regulator.

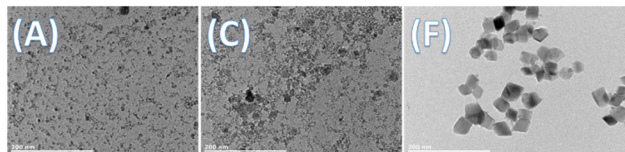


Fig. 3 TEM images of hematite samples A, C and F (left to right). Scale bar at 200 nm.

noise, making it an excellent way to optimise processes in the fewest possible experiments. This approach is discussed in more detail by Clayton and co-workers.⁴⁹

The outcomes of self-optimised experiments are presented in Fig. 2a and b. Both optimisation methods demonstrated similar behaviour of the response with respect to changes in process variables, showing an increased particle size at elevated temperature, reduced flow ratio and higher residence times. This result agrees well with literature where hematite nanoparticles were produced using batch process with the nucleation, phase transition and growth of hematite particles during synthesis.⁵⁰ PXRD analysis confirms the presence of hematite in all samples selected for offline analysis but shows contamination from NaNO_3 in samples E and F (Fig. S16, ESI†). This is presumed to be contamination due to NO_3^{2-} ions and Na^+ ions present in the DI water.

TEM images (Fig. 3) for all studied samples demonstrated various stages in the generation and growth of hematite nanoparticles (section 5, ESI†). Samples A and B (lowest temperature and fastest flowrate) primarily revealed spherical-cubic particles in the range 5–12 nm. This corresponds to the peak broadening shown in the PXRD patterns for these samples. Samples E and F (highest temperature and lowest flowrate) have distinct cubic $\alpha\text{-Fe}_2\text{O}_3$ particles, suggesting the particles have undergone Ostwald ripening, according to the LaMer model of nanomaterial synthesis.⁵¹ Application of the Scherrer equation to the PXRD patterns yields comparable particle sizes but the inline DLS measurements are shown to significantly overestimate particle size (Table 1 & sections 1, 2 and 4, ESI†), although the trend is comparable. This suggests that inline DLS may not be feasible for obtaining absolute values but is still appropriate for trend targeting, which is the main aim of this study.

This paper outlines the first use of a DLS technique for a self-optimised, continuous-flow hydrothermal synthesis reactor. Automated analysis and reactor control are combined with self-optimisation algorithms to achieve maximum particle size of hematite nanoparticles in under 7 h per optimisation experiment with only 500 ml reagent use. The use of the applied algorithm approach (based on ESI† Tables S2 and S3) shows that the maximum particle size was identified after only 9 of the 30 experiments in the factorial design. TEM images show the formation of small particles prior to aggregation and subsequent growth of hematite particles. DLS, XRD and TEM are all used to provide particle size analysis, with DLS hydrodynamic diameters showing

significantly larger measurements. Calibration of DLS method using TEM data as a reference could enable optimisation and tuning of the particle size in real time. The system presented is designed to be suitable to a range of nanomaterials already demonstrated for CFHS and can be used to efficiently determine the effects of different parameters such as temperature, precursor concentration or reaction time on the particle size and distribution.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Cameron Jackson: Conceptualization, methodology, formal analysis, investigation, validation, visualization, writing, editing. Vitaliy Sechenyh: Formal analysis, validation, visualization, writing, editing. Karen Robertson: Conceptualization, supervision, formal analysis, writing, editing. Thomas Chamberlain: Conceptualization, project administration, funding acquisition, editing. Richard Bourne: Conceptualization, project administration, funding acquisition, editing. Edward Lester: Conceptualization, methodology, formal analysis, supervision, project administration, funding acquisition, editing.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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