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SUPPLEMENTARY INFORMATION

Process Intensification of Dendritic Fibrous Nanospheres of Silica (DFNS) via Continuous Flow: A Scalable and Sustainable Route to a Conventional Hydrothermal Synthesis

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KEYWORDS

Process Intensification, Continuous Flow Chemistry, Heterogeneous catalyst, DFNS, Dendritic Fibrous Nanospheres of Silica

MATERIALS AND METHODS

A. Reagents

Tetraethyl orthosilicate *(TEOS), ≥99.0% (GC)* was purchased from *Sigma Aldrich Co., St. Louis, MO, USA.* Cyclohexane was obtained from *Emplura®, Merck Life Science Private Limited, Mumbai.* Decalin and p-Xylene were obtained from *Spectrochem Pvt. Ltd. Mumbai*. CTAB *(puriss AR)* was purchased from *Spectrochem Pvt. Ltd. Mumbai.* Urea was obtained from *Emparta®, ACS, Merck Specialities Private Limited, Mumbai.* Pentan-1-ol *LR* was purchased from *Loba Chemie, Mumbai*. Methanol (> 99 %, HPLC grade), Ethanol (> 99 %, HPLC grade), purchased from *Emplura®, Merck Life Science Private Limited, Mumbai,* and distilled water were used in purification and characterization purposes.

B. Tools and Instruments

a) Laboratory-scale continuous flow synthesis:

The DFNS Precursor Emulsion was prepared using a High-Speed overhead magnetic stirrer *(IKEA Rotor-stator)*. For the batch experiments, the emulsion was subjected to hydrothermal treatment using a microwave *(Anton Parr)*, autoclave, and round bottom flasks (250 ml) in different experiments *(mentioned in the further parts of the same section)*. For the continuous flow experiments, the feed inclusive of the emulsion and the individual emulsifying reagents were pumped in using different pumps; including the Vapourtec *(R-series, double-piston)*, Fuji, HPLC *(Jasco)* and Knauer *(Azure 2.1S)* pumps. Reactor coils of ¼ ” (Outer Diameter of 6.3 mm) of varying volumes; in a range from 70 ml to 150 ml were used. The desired process temperature was maintained using varied means; inclusive of the Oil-bath and High-temperature Alumina Furnace *(Ants Ceramics).*

b) Process intensified continuous flow synthesis:

Vapourtec *(R-series, double-piston)* and HPLC *(Jasco)* pumps were used for the dosing of the reagents into the reactors. Spinning Disk Reactor R-10® (FlowFlex SpinPro R10, Three-stage volume 19.3 mL, Pressure limit of 10 bar, Operating temperature range of –20 °C to +140 °C, Working range of rotational speed 1000–8000 rpm, with an MoC of Silicon Carbide)[1] was used for the *in situ* DFNS precursor emulsification process. The Coflore Agitated Tube Reactor (ATR)® (Single tube with a volume capacity of 0.35 L, Agitation speed of 2–9 Hz, Pressure limit of 50 bar, Operating temperature range of –40 °C to +140 °C, with an MoC of Hastelloy C276)[2] was used for the scalable continuous flow synthesis of DFNS. The Julabo Presto A-45 was used as the temperature controller (chiller) for the process. Swagelok SS Back Pressure

Regulator (1L)[3] was used to maintain the liquid reagents/solvents below their boiling points and accommodate the suspended precipitous product.

C. Experimental section

a) Synthesis of the DFNS precursor emulsion through batch

CTAB (10 g, 55 mmol) and Urea (12 g, 400 mmol) were dissolved with the aid of ultrasound waves (sonicator) in 500 ml distilled water (aqueous solvent) until a homogeneous minute dispersion was formed (Solution A). This solution was equipped with an overhead magnetic stirrer and allowed to stir at a speed of 1400 rpm. Meanwhile, TEOS (46 g, 450 mmol) was mixed with 500 ml of an organic solvent; viz. Cyclohexane (B.P. 81 °C), p-Xylene (B.P. 138.4 °C), Decalin (B.P. 190 °C) until homogeneous (Solution B). Once both the solutions were ready, Solution B was added dropwise into the stirring Solution A over a duration of around 20 minutes (an approximate droplet addition speed of 0.5 ml/sec) [this step was tried both manually and using a syringe pump – there was no marked difference in the efficiencies of both additions]. Once the addition was complete, the mixture was allowed to further stir for a period of 10 minutes to ensure homogeneous incorporation of the phases with one another. Following this, 1-Pentanol (30 mL, 545 mmol) was added to the above mixture under stirring; over a duration of around 5 minutes (an approximate droplet addition speed of 0.1 ml/sec). This was subsequently allowed to stir further for a period of 10 minutes to ensure the attainment of emulsion stability. This DFNS precursor emulsion was employed in various synthesis methods.

b) Synthesis of the individual emulsifying-solutions of DFNS for use in step (c)

The two individual (organic and aqueous) solutions for the preparation of DFNS emulsion were prepared as follows: ***Solution A, Organic:*** TEOS (46 g, 450 mmol) was taken into a 1 L measuring cylinder. 500 ml organic solvent; viz. either Cyclohexane (B.P. 81 °C), p-Xylene (B.P. 138.4 °C), or Decalin (B.P. 190 °C) was added into it. After leaving undisturbed for around 10 minutes, 1-Pentanol (30 mL, 545 mmol) was added into this mixture. Once the solution was homogeneous, it was vacuum-filtered and stored in a clean, dry Schott-Duran bottle. ***Solution B, Aqueous:*** CTAB (10 g, 55 mmol) and Urea (12 g, 400 mmol) were weighed into a 500 ml Schott-Duran bottle. Into this, 500 ml distilled water (aqueous solvent) was added slowly with mild mechanical stirring. Once the addition was complete, the contents of the bottle were sonicated for around 15 minutes till a homogeneous, whitish, hazy solution was produced. This was vacuum-filtered and stored in a clean Schott-Duran bottle.

c) Continuous flow emulsification of precursor DFNS emulsion

The individual emulsification solutions were as synthesized by the above protocol. After a preliminary pump calibration with respective solvents and system equilbration, the aforesaid organic and aqueous emulsification solutions were let in through the top and side-top inlets respectively of the SDR viz. R-10© at a rotational speed of 6000 rpm for 5 seconds at a temperature of 30 °C under a total flow rate of 5.83 mL/min. The emulsion thus formed was collected momentarily into a collection vessel before passing into the continuous flow reactor for thermal treatment.

d) Emulsion-mediated continuous flow synthesis of DFNS

Preliminarily, a 1 L quantity of the DFNS Precursor Emulsion was prepared and filtered under high vacuum. Meanwhile, the continuous flow setup was assembled with the required accessories, viz. pumps, reactor coils, temperature controller and SS Swagelok metal Back Pressure Regulator-cum-collector. Initially, the system was allowed to attain equilibrium by flowing solvent (water) at the desired temperature and pressure (see Table for the various reaction parameters chosen for optimization). Once equilibrium was attained and a few millilitres of solvent as equilibration volume was allowed to be discarded, the pump was switched to the emulsion. At this point, based on the desired residence time (as mentioned in the **Table 2** of the manuscript), the flowrate was set. After carrying out a discard of two reactor volumes for attainment of steady state, the reaction was allowed to proceed for the required amount of time (sufficient to generate around 50 ml of reacted mixture or product); and collected into the SS Swagelok metal BPR. Finally, the outlet knob of the BPR was momentarily released slowly without allowing significant pressure drop and the product was collected carefully into an external collection vessel.

e) Telescoped Process Intensified Continuous Flow synthesis of DFNS

For performing a telescoped flow process intensification of DFNS, the outlet of the SDR was connected to the inlet of a single tube of the ATR. Once preliminary calibrations and temperature equilibration with solvents were complete, the individual emulsifying solutions were passed into the R-10© at individual flowrates of 2.91 mL/min through Vapourtec pumps, under an ambient temperature of 30 °C at 6000 rpm for a residence time of 5 seconds. Meanwhile, the ATR (single-tube) was maintained at a temperature of 150 °C into which the emulsion formed in the SDR posed as a direct inlet, thus giving a residence time of 1 hour. After discarding two volumes of the reaction mass, the steady-state sample was collected up to a total volume of 1 L and isolated to yield DFNS.

f) Protocol for product purification (Workup)

The purification of obtained reaction streams was performed with minor modifications as reported in literature. All the collected product mixtures were allowed to naturally cool down to room temperature. Following this, the organic supernatant was decanted carefully; and the residual aqueous part containing the DFNS product was washed multiple times with equal-volume mixtures of water and ethanol through centrifugation at speeds of 10,000 rpm for around 30 minutes. In-between washes, the product was sonicated for a few minutes; and the washings were so continued till the smell of unreacted TEOS and white-haziness of CTAB almost disappeared from the product. The white, solid and fluffy DFNS powder thus obtained was allowed to air-dry overnight at room temperature. Following this step, it was transferred into quartz crucibles and calcined at a temperature of 550 °C for a period of 6 hours; till all the organic matter was burnt off. The final product DFNS obtained was an off-white, amorphous, fine, solid powder.

D. Characterization

The morphology and size of the synthesized DFNS were studied by microscopic imaging techniques like Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). For the preparation of SEM samples, the dried solid DFNS powder was weighed and dispersed homogeneously by sonication in Ethanol such that the final concentration was around 1 mg/ml. Around 10-15 µL of this uniform dispersion was then drop-cast onto aluminium foil and left to air-dry before imaging. Energy Dispersive X-ray Spectroscopy (EDX) was also performed on the same samples to determine the elemental purity of the material formed. TEM samples were prepared similarly by drop-casting the abovementioned dispersion on copper grids and allowing to dry overnight before imaging. Surface area of the material was studied by the Branneur-Emmet-Teller (BET) Surface area measurements. Samples were prepared by degassing the vacuum-dried powder for 2 days at 100°C before analysis using Nitrogen as the adsorbate gas. Thermogravimetric analysis (TGA) was performed in order to estimate the purity of the sample. 5 mg of the dried powder was degassed overnight at 70 °C before subjecting to analysis. Dynamic Light Scattering (DLS) was performed to obtain an estimate of the particle size and polydispersity of DFNS obtained. Around 1 mg of the dried, powder sample was dispersed in Methanol under the aid of sonication, and measured at room temperature in a Quartz couvette for particle size and polydispersity.

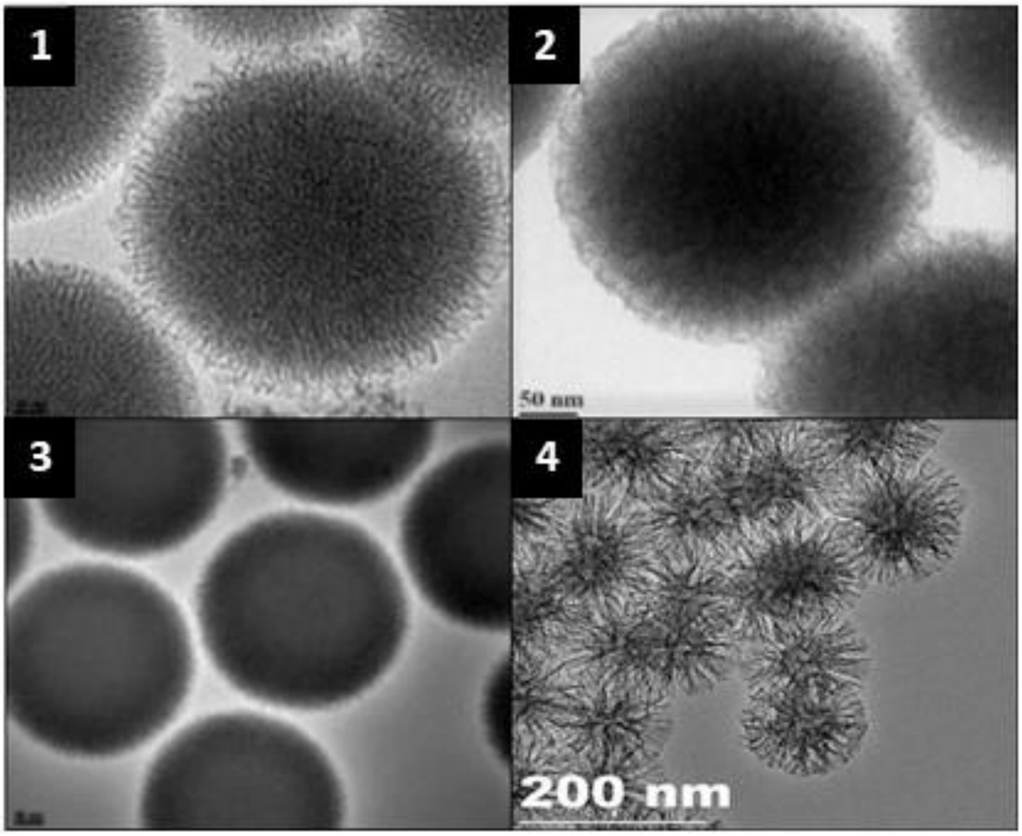


Figure S1*:* The Transmission Electron Microscopy (TEM) images of reproduced experiments where DFNS was synthesized through various batch reported techniques; viz. (1) Microwave irradiation at 120 °C for 1 hour; Hydrothermal (autoclave) heating for 1 hour at (2) 125 °C and (3) 150 °C; (4) Conventional open-vessel reflux at 138 °C for 2 hours

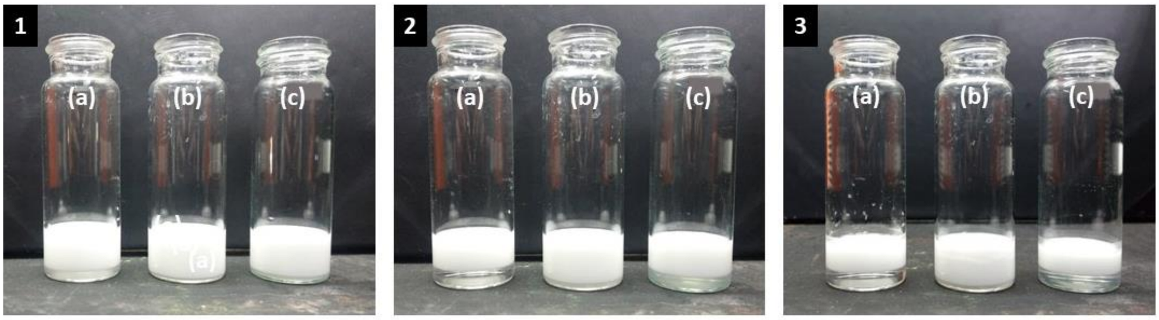


Figure S2*:* A comparison between the phase separation capabilities of the various emulsion-preparation media used in this work at different times; viz. (1) Soon after preparation; (2) After 6 hours; and (3) After 24 hours; where the emulsions were synthesized by (a) A normal Round-Bottom-Flask (RBF)-based stirring of the emulsion constituents; (b) A rotor-stator; (c) The Synthetron (a form of Spinning Disk Reactor). This image shows that the emulsion formed using the Rotor-stator (employed in this work in all emulsion-based reactions) yielded the best emulsion, followed by that formed through the Spinning Disk Reactor, finally succeeded by that formed by the conventional stirrer-based system

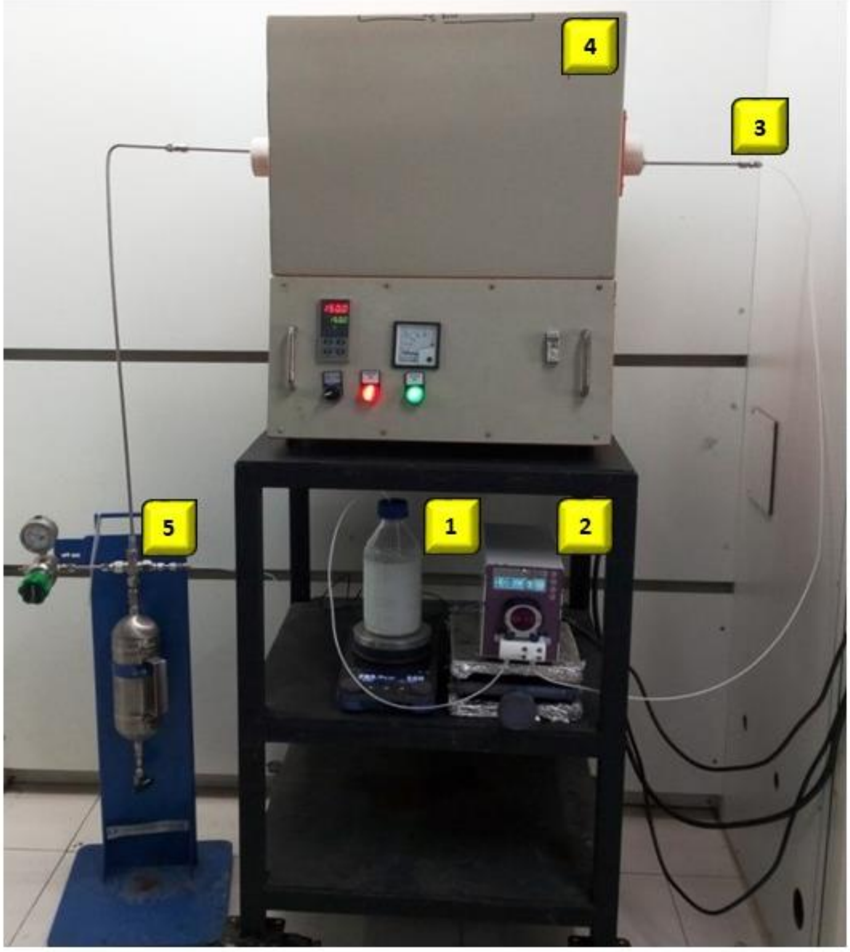


Figure S3*:* The continuous flow setup used for synthesis of DFNS through simple coil flow reactor; (1) Emulsion under stirring, (2) Pump for pumping emulsion; (3) Reactor coil; (4) High-Temperature Alumina furnace; (5) Back Pressure Regulator-cum-collector

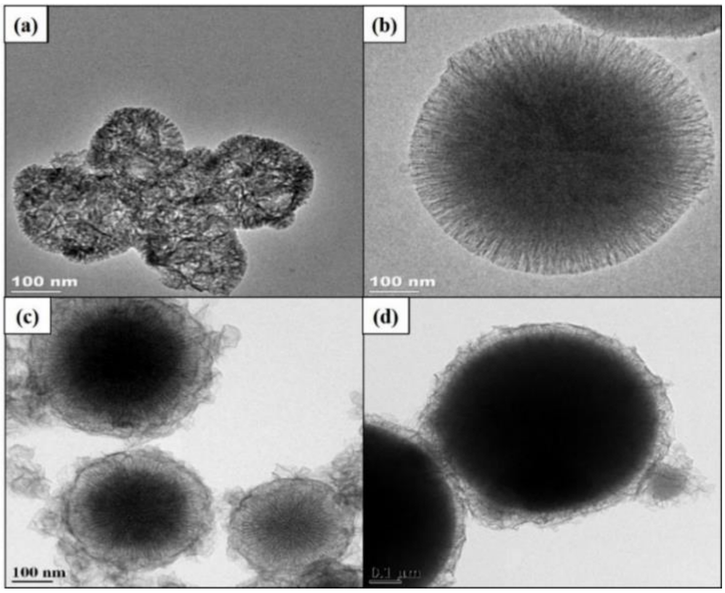


Figure S4: Transmission Electron Micrographs (TEM) of optimizations carried out in emulsion-mediated continuous flow synthesis of DFNS using Cyclohexane as solvent at 175 °C for (a) 10 min; (b) 20 min; (c) 30 min; (d) 40 min

Figure S5*:* The continuous flow setup used for process intensified continuous flow synthesis of DFNS; (1) and (2) Pumps for organic and aqueous solutions; (3) Spinning Disk Reactor for *in situ* emulsification; (4) Agitated Cell Reactor for scalable performance; (5) Chiller for maintaining reaction temperature; (6) Back Pressure Regulator-cum-collector

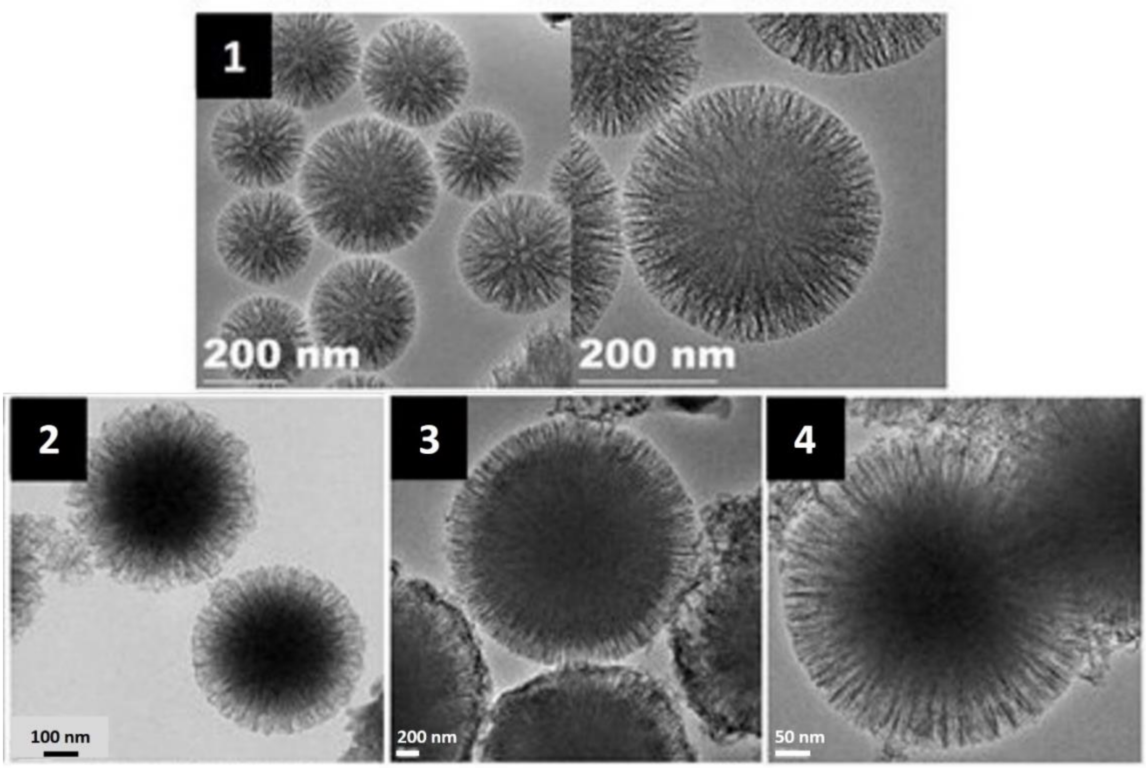


Figure S6: Transmission Electron Microscopy (TEM) Characterization Data of (1) Synthesized through Continuous Flow, Emulsion, using Decalin, at 150 °C for 60 minutes; (2) Synthesized through Continuous Flow, Emulsion, using Cyclohexane, at 150 °C for 30 minutes; (3) Synthesized through Continuous Flow, Emulsion, using Cyclohexane, at 150 °C for 45 minutes; (4) Synthesized through Continuous Flow, Individual solutions for *in-situ* emulsification, Cyclohexane, at 150 °C for 90 minutes

Table S1*:* A compilation of all the equipment used in this work, notes on their characteristics, and ways to address their drawbacks

No.	**Equipment**	**Usage in**	**NOTES AND COMMENTS** **(Trials in experiments, addressing the various issues encountered and solutions)**
1	**STIRRER** To maintain homogeneity in emulsion concentration	Lab-scale process	No stirrer employed initially, but visualized phase separation of emulsion when involving longer reaction times
		Intensified process	No stirrer was required since homogeneous solutions were individually pumped
		All emulsion-containing experiments in this work employed the use of an IKEA stirrer at 500 rpm to ensure concentration homogeneity while pumping; No stirrer was used in the process intensification experiments	
2	**PUMP** To ensure accurate and controlled reagent delivery that will contribute to maintaining the correct residence time and stoichiometry of the reaction constituents	Lab-scale process involving low-boiling solvents	SF-10 Vapourtec Peristaltic Pump – ✓ Ability to tolerate a maximum of 10 bars ✓ Suitable for the pumping of biphasic reagents (here, emulsion)
			Knauer Single-Piston Pump – ✓ Ability to tolerate high pressures, but unsuitable for solid-biphasic pumping
		Lab-scale process involving high-boiling solvents	HPLC Jasco Piston Pump – ✓ Ability to tolerate high process pressures ✓ Efficient at high flow rates
			Vapourtec E-series Double-Piston pump – ✓ Ability to tolerate a pressure up to 50 bars
		All the above pumps were tried with the experiments performed in this work; there was no issue observed with the versatility or reproducibility in any case	
		Intensified process	HPLC Jasco Piston Pump – ✓ Robust hence, suitable for scale-up ✓ Ability to tolerate high pressures up to 200 bars; hence enhanced safety
			Vapourtec R-series double piston pump – ✓ Suitable for scale-up ✓ Ability to tolerate pressures up to 50 bars; hence enhanced safety

		The scale-up experiments in this work involved both the above pumps	
3	**REACTOR** The core unit of reaction progress	Lab-scale process	PTFE coils of 1/8” and 1/16” dimensions – ✗ Possibility of degradation at temperatures above 150 °C ✗ Not suitable for long reactions at elevated temperatures ✗ High instances of Clogging
			PTFE coils of 1/4" dimensions – ✓ No clogging ✗ Poor pressure-withstanding capacity at higher temperatures ✗ Poor heat efficiency (heat transfer)
			SS coils of 1/8” and 1/16” dimensions – ✓ Robust at high temperatures and pressures, ✓ Excellent heat transfer in comparison to the PTFE ones, ✗ High instances of Clogging
			SS coils of 1/4" dimensions – ✓ No clogging experienced ✓ Good heat transfer
		All experiments performed in this work employed SS coils of 1/4” dimension, volumes ranging from 70-140 ml	
		Intensified process	Agitated Tube Reactor (ATR) ✓ Very good heat transfer ✓ Absolutely no clogging ✓ Enhanced scalability ✓ High reproducibility
		All the scale-up experiments performed in this work employed the ATR (tube diameter of 7/8”, 350 ml volume	
4	**TEMPERATURE CONTROLLER**	Lab-scale process	Oil-bath ✗ Suitable only for PTFE coils of small volume, ✗ Heat efficiency decreases with increased volume capacity of the coils
			Column oven ✓ Better heat efficiency than a coil, ✗ Decreased efficiency with increased coil thickness; particularly poor for SS coils

	To maintain reaction temperature		High-temperature alumina furnace ✓ Focussed heat transfer ✓ Good process to process reproducibility ✓ Easy maintenance and use
		All the experiments performed in this work employed the High-temperature alumina furnace	
		Intensified process	Julabo A-45 Chiller ✓ Excellent heat control (A maximum ΔT of 2 °C) ✓ Attainability of a wide range of temperatures
		All the process intensification experiments performed in this work employed the Julabo A-45 as the temperature controller	
5	**QUENCH** To terminate the reaction	*All the experiments performed in this work were thermally quenched (as reported in literature). A long coil, also known as the cooling loop (dimensions corresponding to the actual reactor coil employed) was used to connect the reaction zone with the BPR so as to promote non-abrupt heat dissipation to quench the reaction.*	
6	**BACK-PRESSURE REGULATOR** To maintain the reaction mixture in liquid state even above the boiling points of reagents	Variable and fixed Aldrich, Idex and Vapourtec BPRs ✗ Clogging	
		Stainless Steel (SS) Swagelok BPR ✓ BPR with a collection vessel of 1 L capacity ✓ Ideal for particulate products ✓ Absolutely no clogging	
		All the experiments performed in this work employed the Swagelok Metal BPR	

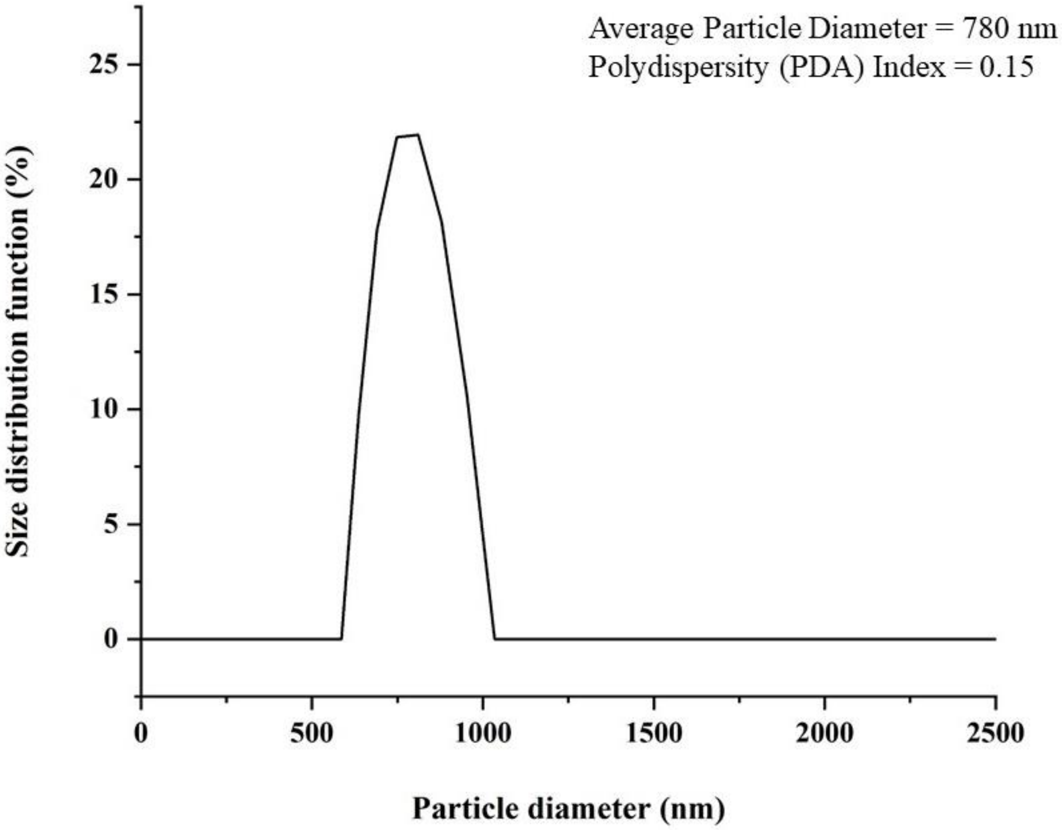
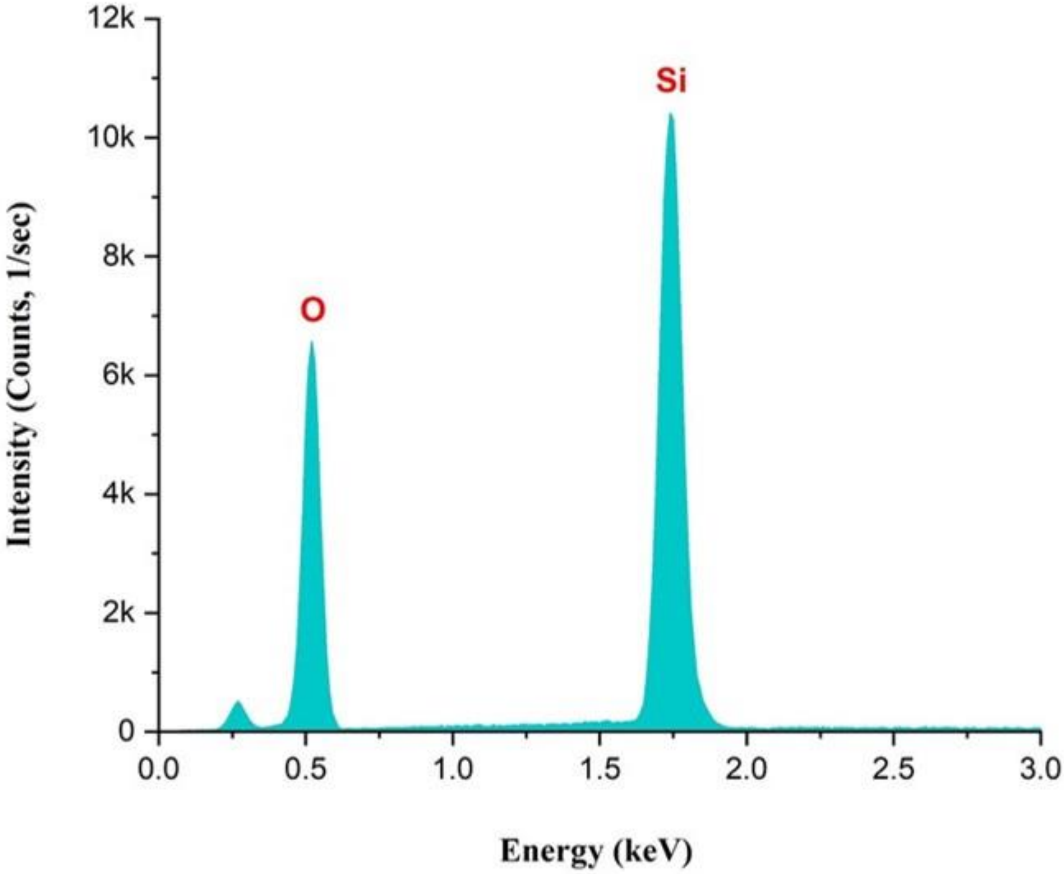
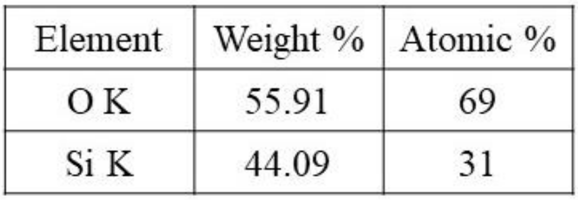


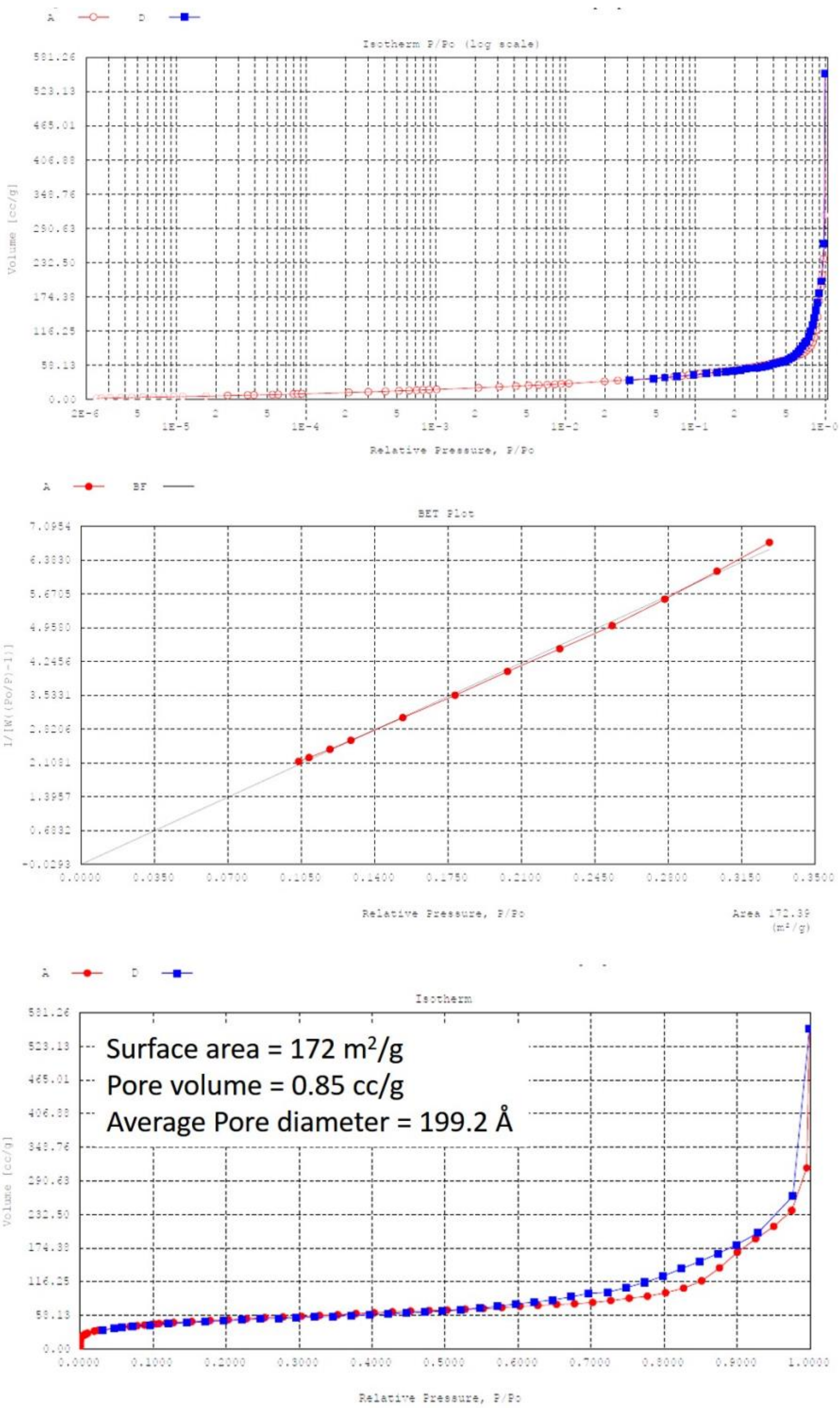
Figure S7: The Dynamic Light Scattering (DLS) data of scaled-up DFNS obtained through process intensification using the continuous flow dynamically agitated ATR





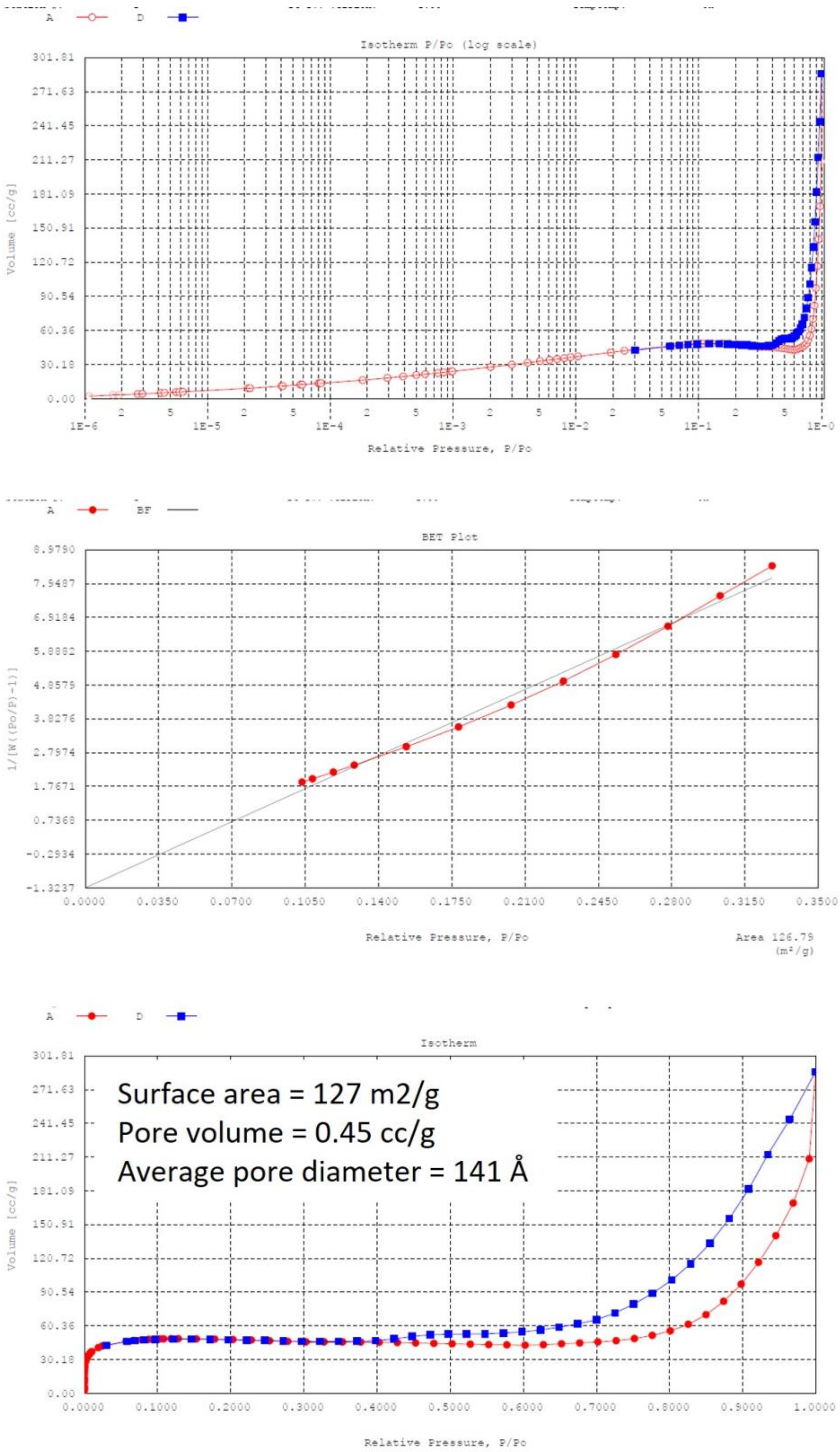
Element	Weight %	Atomic %
O K	55.91	69
Si K	44.09	31

Figure S8*:* The Energy Dispersive Spectroscopy (EDS) spectrum of the scaled-up DFNS obtained through process intensification using the continuous flow dynamically agitated ATR shows the presence of only two elements viz. Silicon (Si) and Oxygen (O). The minute hump at 0.25 keV is presence of Carbon from the Carbon-tape used in SEM sample preparation



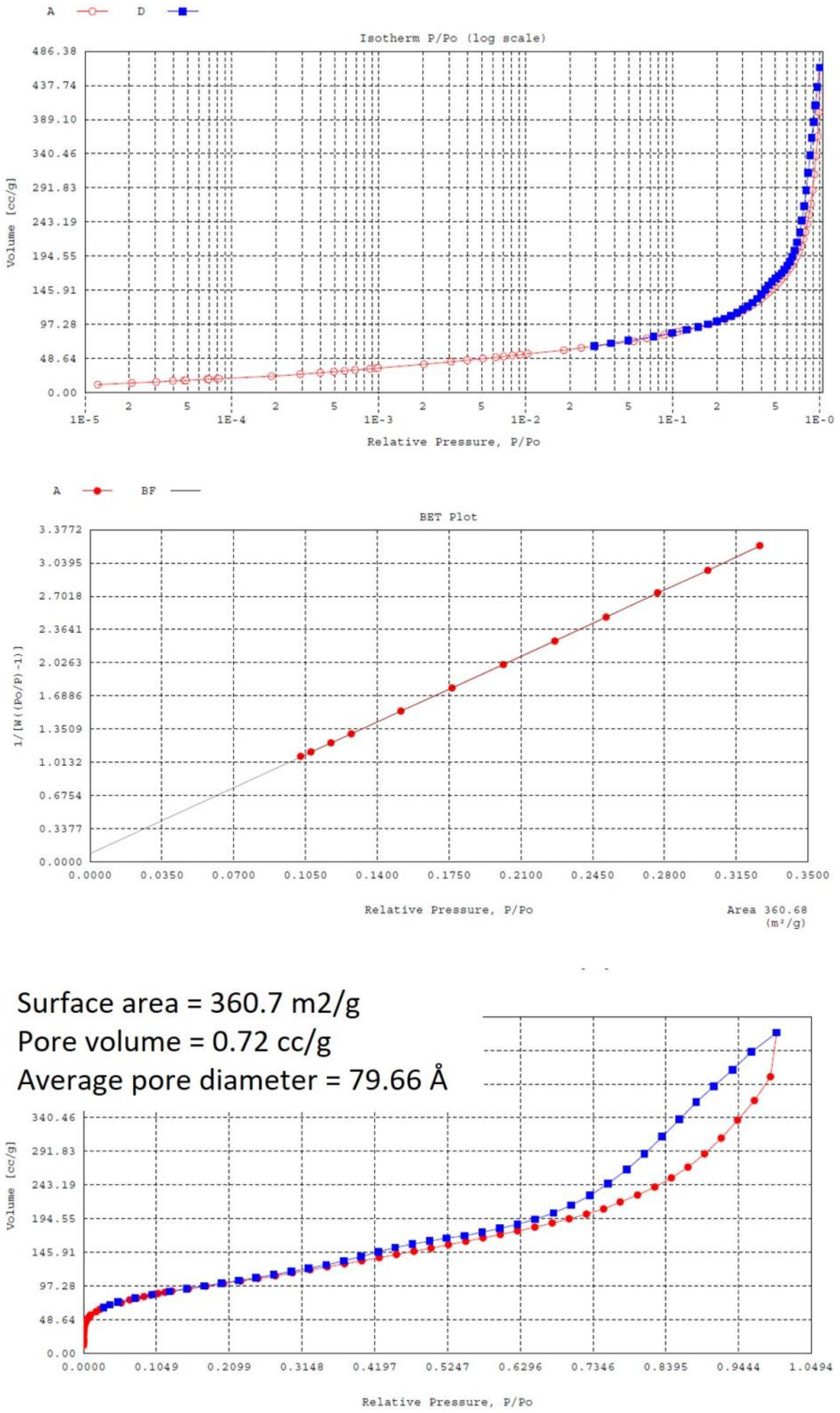
Surface area = 172 m^2/g
Pore volume = 0.85 cc/g
Average Pore diameter = 199.2 Å

Figure S9: The Brunauer-Emmett-Teller (BET) Surface Area measurement of the DFNS synthesized through continuous flow using Cyclohexane as the solvent, at 150 °C for 30 minutes



Surface area = 127 m2/g
Pore volume = 0.45 cc/g
Average pore diameter = 141 Å

Figure S10*:* The Brunauer-Emmett-Teller (BET) Surface Area measurement of the DFNS synthesized through continuous flow using Cyclohexane as the solvent, at 150 °C for 45 minutes

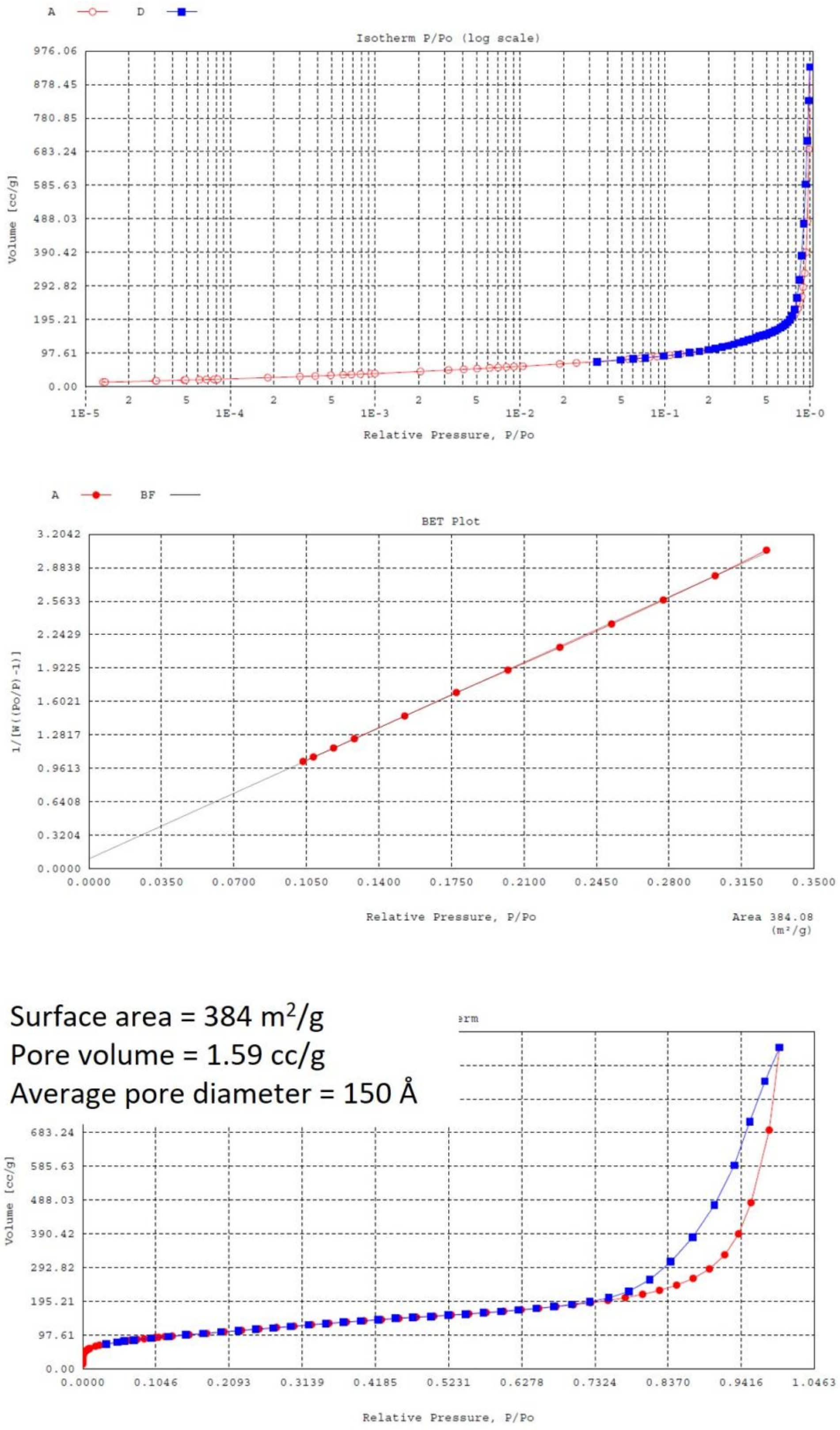


Surface area = 360.7 m2/g

Pore volume = 0.72 cc/g

Average pore diameter = 79.66 Å

Figure S11*:* The Brunauer-Emmett-Teller (BET) Surface Area measurement of the DFNS synthesized through continuous flow using Decalin as the solvent, at 150 °C for 60 minutes



Surface area = 384 m^2/g

Pore volume = 1.59 cc/g

Average pore diameter = 150 Å

Figure S12: The Brunauer-Emmett-Teller (BET) Surface Area measurement of the DFNS synthesized through batch for comparison using Xylene as the solvent, at 140 °C for 120 minutes

Throughput and Space-Time-Yield (STY) calculations for the scaled-up synthesis of DFNS obtained through process intensification using continuous flow dynamically agitated ATR

TEOS is the precursor for the formation of DFNS; hence, the conversion of TEOS into DFNS needs to be measured.

TEOS ≡ DFNS (a form of SiO_2)

208.33 units ≡ 60.08 units (based on molecular weight)

As per the formula employed in the flow experiments, 1000 ml of the total emulsion contains 100 ml of TEOS.

And,

Emulsion collected from the process intensified synthesis of DFNS (after carrying out for 7 hours) = 1005 ml

1000 ml original Emulsion ≡ 100 ml TEOS

Hence, 1005 ml collected Emulsion (post reaction aka reaction mixture) = x ml TEOS

= 100.5 ml TEOS = 94.47 grams TEOS = 0.453 moles TEOS

Theoretical Yield of DFNS

= (Number of moles of TEOS) * (Molecular weight of DFNS)

= (Weight of TEOS / Molecular weight of TEOS) * (Molecular weight of DFNS)

= (94.47 / 208.33) * 60.08

= 27.21 grams

Practical Yield of DFNS

The experimental (practical) amount of DFNS obtained = 15.67 g (from the 1005 ml reacted mass collected)

Calculation of % yield

= (Actual Yield / Theoretical Yield) * 100

= (15.67 / 27.24) * 100

= 57.5 %

Calculation of Throughput and Space-Time-Yield (STY)

- ⇒ Throughput = (Flow rate of the reagent medium; ml/h) * (Molecular weight of DFNS; g) * (Number of moles of TEOS) * (Residence Time; min) * (% Yield)
- ⇒ STY = Throughput (g/h) / Volume (L)

Reactor	Volume (L)	Throughput (g/h)	Space-Time Yield (STY, g/h/L)
[*] ATR (Single tube)	0.35	5.48	15.65
[$] ATR (10 tubes)	10	156.5	156.57
[$] RTR	100	1565.7	1565.71

[*] Demonstrated in this manuscript; [$] Theoretically calculated

Table S2: The Throughput and Space-Time-Yield (STY) calculations for scaled up process.

REFERENCES

(1) SpinPro R10 (https://www.flowid.nl/spinpro-reactor/)

(2) Coflore ATR (https://www.amt.uk/coflore-atr)

(3) Benjamin J. Deadman, D. L. B., Ian R. Baxendale, Steven V. Ley. Back Pressure Regulation of Slurry-Forming Reactions in Continuous Flow. *Chem. Eng. Technol.* **2015**, *38* (2), 259–264.