

## RESS for the preparation of fluorinated porphyrin nanoparticles

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**Rapid Expansion of Supercritical Solutions (RESS) was used to produce clean, surfactant-free nanoparticles (average size = 60 nm) of a fluorinated tetraphenylporphyrin from supercritical solutions with CO<sub>2</sub>.**

When a supercritical solution that contains a dissolved solute is expanded across a micro-orifice, the solvent density decreases dramatically, and the solute is rejected from solution. As the characteristic speed of the expansion is the speed of sound, the process is quite rapid, with residence times in the orifice on the order of 1  $\mu$ s.<sup>1</sup> Because Rapid Expansion of Supercritical Solutions, or RESS, results in very high supersaturation ratios in the post-expansion environment, the process favors the formation of small particles with narrow size distributions.<sup>2</sup>

In recent years, there has been increasing interest in the production of organic and polymeric nanoparticles (*i.e.*, particles of 100 nm or less)<sup>3,4</sup> for both pharmaceutical and materials applications. Unfortunately, there are no good general methods for making such particles, particularly if a “clean” (*i.e.*, surfactant-free) product is desired.<sup>3,4</sup> In the late 1980s, RESS was proposed as a technique for producing fine powders,<sup>2,5</sup> but a perusal of the literature indicates that the consistent production of particles as small as even 1  $\mu$ m is typically not accomplished.<sup>6–8</sup> Recently, more encouraging results have been obtained by two groups. Ginosar and co-workers at INEEL<sup>9</sup> used an on-line technique to measure particle sizes and reported that the largest number fraction of phenanthrene particles produced by RESS was 10–40 nm in size; however, the largest mass fraction of the phenanthrene was in the form of micron-sized particles. Türk and co-workers<sup>10</sup> have produced the smallest particles to date by RESS, as they used an orifice with an  $L/D$  of 1 to produce submicron-sized particles (200  $\pm$  50 nm) of  $\beta$ -sitosterol from CO<sub>2</sub> solutions.

In this study we report on the rapid expansion of 5,10,15,20-tetrakis(3,5-bis(trifluoromethyl)phenyl)porphyrin (TBTPP), a novel fluorinated tetraphenylporphyrin synthesized in our laboratories, from supercritical CO<sub>2</sub> solutions. Our interest is in the production of nanoparticles of higher molecular weight organics, such as oligomers and polymers, by RESS. TBTPP was chosen because it is highly soluble in CO<sub>2</sub> and, with its strong color and fluorescence, is easy to characterize on the nanoscale.

As illustrated in Fig. 1, TBTPP was synthesized by a modified Rothmund reaction,<sup>11</sup> the condensation reaction between 3,5-bis(trifluoromethyl)benzaldehyde and pyrrole with an acidic catalyst. Details of the synthesis are described elsewhere.<sup>12</sup>

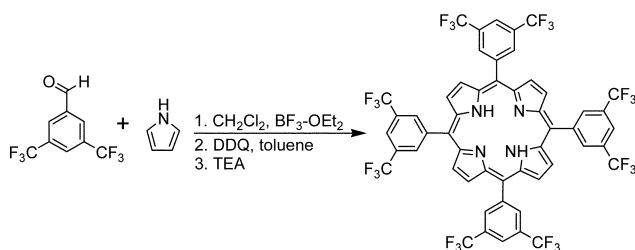


Fig. 1 The synthesis of TBTPP ( $M_w = 1159$ ,  $T_m > 350$  °C).

Before performing RESS experiments, the solubility of TBTPP in SC CO<sub>2</sub> was determined. Solubility isotherms at 40, 70, and 100 °C were measured at pressures ranging from 103 to 304 bar.<sup>12</sup> Because of the presence of the trifluoromethyl groups, TBTPP exhibits a relatively high solubility in SC CO<sub>2</sub> (*e.g.*, ~1.5 wt% at 300 bar), several orders of magnitude higher than nonfluorinated porphyrins.

RESS experiments with solutions of TBTPP in CO<sub>2</sub> were carried out using the apparatus shown in Fig. 2. For a typical experiment, the variable-volume equilibrium cell was loaded with 0.02–0.20  $\pm$  0.0005 g of TBTPP solid. The cell was then sealed, purged to remove all air, and charged with 20  $\pm$  0.05 g of CO<sub>2</sub> using the syringe pump (Isco 500 HP). After the mixture in the cell was heated to 40 °C in the isothermal bath, valve V2 was opened (while valves V1, V3 and V4 were closed), and the Isco pump was used to pressurize the mixture to the desired pre-expansion pressure (as measured by a pressure transducer, P). The mixture in the cell was then stirred for 2 h to obtain a homogeneous solution. Next, valve V2 was closed in order to isolate the cell from the rest of system. Valve V3 was then opened, allowing pure CO<sub>2</sub> to (1) flow from the syringe pump (being operated in the constant-pressure mode) to the 6-port switching valve (Valco Instruments 6C6UWEY), (2) bypass the equilibrium cell, and finally (3) expand across the nozzle (50  $\mu$ m dia.,  $L/D = 4$ ) into ambient air in the expansion chamber. The fluid in the tubing leading to the nozzle and nozzle assembly was heated to the desired pre-expansion temperature using cable heaters (Thermocoax 1Nc110). During this step, the pre-expansion temperature and pressure ( $T_{pre}$ ,  $P_{pre}$ ) were measured upstream of the nozzle, see Fig. 2. After steady-state conditions (as indicated by constant  $T_{pre}$  and  $P_{pre}$ ) were obtained, valve V4 was opened and the switching valve was switched to the position shown in Fig. 2 to divert the flow of pure CO<sub>2</sub> to the equilibrium cell, indirectly pushing the solution of TBTPP in SC CO<sub>2</sub> out of the cell by means of the movable piston in the cell. The solution was subsequently expanded through the nozzle into the expansion chamber. Samples were collected onto SEM stages located on the sampling device and characterized using Field Emission Scanning Electron Microscopy (FESEM, Hitachi S-4700). The average particle size and particle size distribution (PSD) were statistically determined from FESEM images using image analysis (Image-Pro Plus Version 4.0).

The goal of this work was to determine the key RESS variables that control the size and morphology of TBTPP

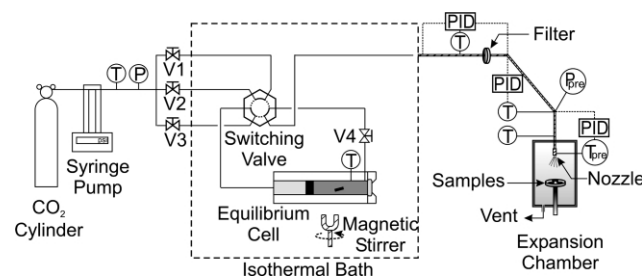
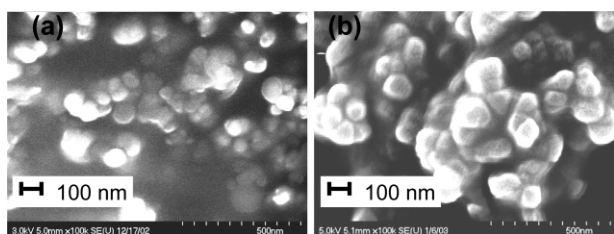


Fig. 2 Schematic of RESS apparatus.

particles. The process parameters selected for this investigation were the degree of saturation, concentration, and pre-expansion temperature and pressure. The degree of saturation,  $S$ , is defined as the ratio of the actual solute concentration to the equilibrium concentration at pre-expansion conditions ( $T_{\text{pre}}, P_{\text{pre}}$ ).

As shown in Fig. 3, the particles of TBTPP obtained from RESS are spherical, agglomerated, and, most importantly, unexpectedly small. Table 1 indicates that average particle sizes of 60 nm are reproducibly synthesized at a pre-expansion temperature of 70 °C, independent of the concentration, pre-expansion pressure, or degree of saturation employed. Only  $T_{\text{pre}}$  was found to affect particle size, as a pre-expansion temperature of 100 °C was found to consistently increase the average particle size to 80 nm (see Table 1 and Fig. 4). To our knowledge, these are the first reported results of the use of RESS to produce clean, template-free organic nanoparticles with an average size of less than 100 nm.

Similar trends of increasing particle size with increasing  $T_{\text{pre}}$  were previously reported for the precipitation of naphthalene,<sup>2,7</sup> salicylic acid,<sup>8</sup> and benzoic acid<sup>10</sup> from supercritical CO<sub>2</sub> solutions; however, those particles are much larger (*i.e.*, typically micron-sized) than our TBTPP nanoparticles. The observed relationship between  $T_{\text{pre}}$  and particle size is consistent with classical nucleation theory, as a higher  $T_{\text{pre}}$  would give a higher temperature and vapor pressure, and thus a lower degree of supersaturation, in the downstream expansion jet, resulting in larger particles and lower nucleation rates.<sup>1,13</sup> Classical nucleation theory also predicts that increases in concentration or  $S$  should produce smaller particles and increase

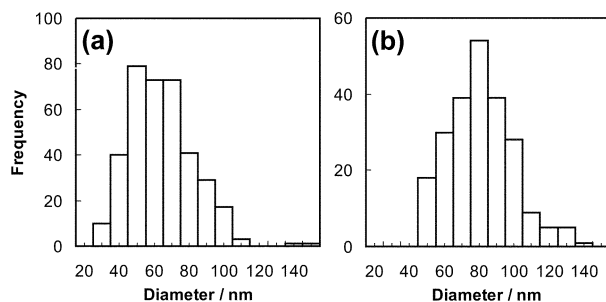


**Fig. 3** FESEM micrographs of nanoparticles obtained from RESS of a 1.0 wt% TBTPP solution in CO<sub>2</sub> with  $S = 0.9$ : (a)  $T_{\text{pre}} = 70$  °C,  $P_{\text{pre}} = 288$  bar, (b)  $T_{\text{pre}} = 100$  °C,  $P_{\text{pre}} = 303$  bar.

**Table 1** RESS process conditions and resulting particle sizes of TBTPP

Conc. (wt%)	$T_{\text{pre}}$ /°C	$P_{\text{pre}}$ /bar	$S$	Avg. Dia. /nm	Std. Dev. /nm
0.1	70	187	0.9	61	19
0.1	70	280	0.1	59	17
1.0	70	288	0.9	60, 54 <sup>a</sup>	18, 9
0.1	100	228	0.9	88	16
0.1	100	298	0.1	86, 82	23, 21
1.0	100	303	0.9	76	18

<sup>a</sup> Duplicate run.



**Fig. 4** PSDs of RESS products obtained from RESS of a 1.0 wt% TBTPP solution in CO<sub>2</sub> with  $S = 0.9$ : (a)  $T_{\text{pre}} = 70$  °C,  $P_{\text{pre}} = 288$  bar, (b)  $T_{\text{pre}} = 100$  °C,  $P_{\text{pre}} = 303$  bar.

the nucleation rate. However, Table 1 shows that no such effect occurred.

It is of interest to interpret our results in terms of the RESS modeling work done to date. In particular, calculations from both Weber *et al.*<sup>14</sup> and from Helfgen *et al.*<sup>15</sup> indicate that organic nanoparticles of 5–50 nm are formed upstream of the Mach disk in the supersonic free jet region. Both groups conclude that micron-sized particles are typically obtained by RESS because of the particle growth processes of condensation and coagulation that occur downstream of the Mach disk in the transonic and subsonic free-jet regions. Franklin *et al.*<sup>16</sup> performed computational fluid dynamics for the RESS of a perfluoropolyether diamide oil and arrived at similar conclusions, although the RESS product was a liquid, and not a solid particle.

Thus, theory predicts that RESS has the potential to be an effective technique for producing organic nanoparticles if the particle growth processes downstream of the Mach disk can be adequately controlled—as is the case in the work reported here. Investigations are underway to determine the relative importance of our system variables, such as nozzle configuration and the physical properties of TBTPP, on the particle formation process.

In summary, we have discovered that RESS can be used to consistently produce “clean” organic nanoparticles of less than 100 nm in diameter without the use of liquid solvents, surfactants, or other templating agents. In particular, rapid expansion of the fluorinated tetraphenylporphyrin TBTPP from supercritical CO<sub>2</sub> solutions was used to produce nanoparticles with diameters of  $56 \pm 16$  nm and  $83 \pm 19$  nm at pre-expansion temperatures of 70 and 100 °C, respectively. These surprising results indicate that RESS may yet have a role to play in the development of urgently needed alternatives to the established processes for preparing nanoparticles.

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