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Abstract

Colloidal particles with two or more different surface properties (Janus particles) are of interest in catalysis, biological imaging, and drug delivery. Eccentric nanoparticles are a type of Janus particle consisting of a shell that envelops the majority of a core particle, leaving a portion of the core surface exposed. Previous work to synthesize eccentric nanoparticles from silica and polystyrene have only used microemulsion techniques. In contrast we report the solgel synthesis of eccentric Janus nanoparticles composed of a silica shell around a carboxylate-modified polystyrene core (Janus templates). In addition, we have synthesized nano-bowl-like structures after the removal of the polystyrene core by organic solvent. These Janus templates and nanobowls can be used as a versatile platform for site-specific functionalization or controlled theranostic delivery.

Introduction

Colloidal particles with two or more unique surface chemistries, commonly known as Janus particles named after the two-faced god of Roman mythology[1], are of interest because the combination of multiple surface chemistries can create a material with its own unique properties. These particles have a wide number of applications including catalysis, biomedical imaging[2], and drug delivery[3].

A wide variety of physical[4, 5] and chemical methods[6-9] have been used to synthesize Janus particles. Early Janus particle morphologies typically consisted of large spheres with different surface chemistries on each hemisphere. The past few decades have seen a large exploration of different Janus particle morphologies and synthesis techniques[10-15]. There is current interest in developing eccentrically encapsulated Janus nanoparticles[16, 17]. Such efforts have included the synthesis of eccentric nanoparticles where a silica shell is formed around a partially exposed polystyrene core[18, 19] or a polystyrene shell around a silica core[20-22]. Dissolving the core from this structure would create a nanobowl and a potential starting point for building a controlled drug delivery system.

There are several methods to synthesize eccentric particles with a polystyrene shell around a silica core. However, silica shells around a polystyrene core have required the precise tuning of reactants in a microemulsion. Wang and coworkers balanced concentrations of styrene, tetraethylorthosilicate (TEOS), and iron oxide nanoparticles in nano-micelles to create the necessary phase separation needed for synthesis of a magnetically responsive silica shell eccentrically encapsulating a polystyrene core[18]. Microemulsions however require the addition of a surfactant and require multiple wash steps to remove post-synthesis. A non-emulsion process would be more simple to scale up for future industrial use and have a simpler reaction chemistry.

Chen and coworkers recently demonstrated the eccentric encapsulation of silica around a carboxylate modified gold core using Stober's method. By varying the ratio of two carboxylate containing surface modification agents on the gold, they were able to control the degree to which silica would encapsulates the gold.[17] Feyen and coworkers also demonstrated eccentric encapsulation of silica around carboxylate modified iron oxide.[23] This literature thus suggests partial encapsulation of cores by silica can be accomplished more widely on different materials.

Here, we report a sol-gel, non-microemulsion method for controlled synthesis of a silica shell eccentrically encapsulating a carboxylate-modified polystyrene core (Janus template). The effect of polystyrene core size, surface functionalization, and tetraethylorthosilicate (TEOS) concentration on the Janus template-like particle morphology was examined. In addition, we synthesized nano-bowl-like structures after the removal of the polystyrene core by organic solvent. The nanobowls have a cavity that can be used for storage of therapeutics and capped with a biocompatible materials and can be used for efficient and controlled delivery and release of theranostics (imaging contrast molecules and therapeutics).

Experimental

Materials

Various polystyrene cores of different sizes and functional groups were purchased from Polysciences. The following nominal and actual diameters listed are those reported by the manufacturer. Spherical colloidal polystyrene with carboxylate (PS-COOH) modified surfaces of 50 nm (actual 45 ± 6.2 nm) diameters, 2.6% in water; 100 nm (actual: 85 ± 6.7 nm) diameters, 2.62% in water; and 200 nm (actual: 190 ± 6.5 nm) diameters, 2.65% in water were obtained. Polystyrene with amine (PS-NH$_2$) modified surfaces of 200 nm

(actual: 230 nm ±16.1) diameter, 2.5 % in water; sulfate (PSSO$_4$) modified surfaces of 200 nm (actual: 194 ± 9 nm) diameter, 2.65% in water; and hydroxyl (PS-OH) modified surfaces of 200 nm diameter (actual: 190 ± 16.1 nm), 2.6% in water were also purchased. Ammonium hydroxide (NH$_4$OH, 29.79%) was purchased from Fisher Scientific. Dimethylformamide (DMF) was purchased from Macron Chemicals. Tetraethylorthosilicate (TEOS, 98%) and anhydrous isopropanol (IPA) was purchased from Sigma. Deionized water used in all experiments was produced using a Millipore Advantage A10 system with a resistance of 18.2 MΩ.

Particle formation

All silica Janus templates were synthesized in 20 mL glass scintillation vials with 700 μL of H$_2$O, 4 mL of IPA and 1.3 mL of NH$_4$OH. To this mixture 100 μL of polystyrene spheres and 83 μL of TEOS (60 mM) were simultaneously added while stirring (unless stated otherwise). All solutions were allowed to react for 2 hours prior to reaction termination by centrifugation (unless stated otherwise). Reaction mixtures were centrifuged for 5 min at 500 g; the supernatant was transferred (the pellet discarded) to a fresh 15 mL centrifuge tube and centrifuged at 3221 g for 5 min. The resulting pellet was dispersed in ~15 mL of IPA. The particles were washed by centrifugation twice in IPA (at 3221g) prior to being redispersed and washed twice in H$_2$O (by centrifugation at 3221g).

Particle Diameter Determination

Particle diameters were measured using either dynamic light scattering (DLS) or by averaging 100 measurements from SEM images. A Brookhaven ZetaPlus DLS instrument was used to measure particle dimensions in solution. Each sample was measured five times to obtain an average signal. The largest majority peak is reported. Histograms were obtained from DLS or SEM measurements and plotted using OriginPro 7.0.

Imaging

Samples were sputter coated with palladium to improve imaging using an Emitech K575X Sputter Coater. SEM images were obtained using an FEI XL30 fitted with an FEI Sirion column to enable ultra-high resolution.

Results and Discussion

Janus templates were made by modifying Stöber's method with addition of carboxylated polystyrene nanoparticles at the start of the reaction. In a solution of ammonium hydroxide, IPA, DI water, TEOS, and PS-COOH, silica condensed around the PS-COOH in an eccentric fashion (**Fig. 1**).

An excess of PS-COOH yielded Janus templates with one or more cores embedded in the silica. The cores were removed using an organic solvent like DMF to create a silica nanobowl (an Janus template without the polystyrene core) (**Fig. 1**). The actual formation of the Janus templates occurred rather quickly; within the first 15-20 minutes, the reaction transitioned from a translucent solution to an opaque white one. Additional processing time did not affect the morphology of the Janus templates; it only allowed time to solidify the

particle and did not cover up the exposed polystyrene. Janus templates were reacted for as long as 18 hr and SEM images revealed no major changes in morphology between any of the reaction times tested (1, 2, 3, 18 hr). (**Fig. 2**). However the reaction was usually terminated and washed after 2 hr.

During the washing process, the reaction solution is first spun relatively slowly (500g) to separate out larger Janus template aggregates and enrich the supernatant with smaller, well-formed Janus templates. The supernatant was subsequently centrifuged at higher speeds (3221g) and washed as reported. Comparison of the Janus template aggregates with the Janus template supernatant by DLS showed enrichment of the supernatant with well-formed Janus templates consistent with sizes as observed with SEM (**Fig S1**).

Adjusting the TEOS concentration while holding everything else the same changed how much the silica enveloped the PSCOOH. As the TEOS concentration and silica coverage of the polystyrene increased, so did the particle size as measured by DLS (**Fig 3a**). At low TEOS concentrations (20, 40 mM), half to three quarters of the polystyrene surface was enveloped by the silica (**Fig 3 b-c**). At higher concentrations (80, 100 mM), the silica almost engulfed the polystyrene (**Fig. 3 d-f**).

Janus templates may have one or more PS-COOH cores incorporated with the silica. A rough survey of two wide-field SEM images revealed ~70-95% of all particles counted were Janus templates (**Fig. S2**). A closer examination of the wide field images in SEM (**Fig. S3**) and TEM (**Fig. S4**) also shows a heterogeneous population in regard to the number of cores incorporated into an Janus template. Counting the number of cores embedded in Janus templates also revealed similar results regardless of imaging modality (**Fig. S5**). Janus templates embedded with a single PS core represented only ~30% of the surveyed population. Janus templates with two cores represented the largest plurality (40%), and Janus templates with three or more cores made up the remaining ~30%. Attempts to improve homogeneity by varying ammonium hydroxide, water, and core concentration individually resulted in similar or worse distributions (data not shown). Therefore improving the yield of the single core Janus templates will require the changing of two or more reactants simultaneously. It seems reasonable that the formation process is driven by particle surface energies. An ideal recipe leading to the formation of predominately single core Janus templates of this size is no straight forward and requires more investigation. Otherwise, more advanced particle separations techniques are required to isolate single core Janus templates from the current mixture.

Three different sizes of PS-COOH were used to investigate the effect of core size on Janus template formation. Using 60 mM TEOS with the standard reaction conditions, particles were synthesized with no PS present, 50 nm, 100 nm and 200 nm diameter PS-COOH cores (**Fig. 4**). 50 nm and 100 nm PSCOOH cores successfully made Janus template nanoparticles. These Janus templates were smaller on average than a pure silica particle (**Fig 4e**). Attempting to make Janus templates with 200 nm PS-COOH resulted in poor silica encapsulation. From the SEM images, a large percentage of silica attempted to wrap around the PS-COOH unsuccessfully, leaving round indents and heavily agglomerated particles.

It may suggest that the interaction between the silica and the PS-COOH interact during formation with multiple weak molecular bonds. Comparing the diameter of the pure silica particle (350 nm) with the size of the 200 nm PS-COOH, suggests that core size in addition to surface functionality plays an important role in Janus template formation. Successful formation of an Janus template would thus hinge on growing enough silica to physically entrap the core. If the silica particle formed from Stöber's method alone is not larger than the core by a certain amount, Janus templates will not form properly.

Surface functionality of the core particle appeared to play a central role in Janus template morphology. The addition of 200 nm $PS-NH_2$, PS-OH, or $PS-SO_4$ into a 60 mM TEOS reaction solution yielded particles that were completely encapsulated by silica (**Fig. 5**). This was observed by an increase in the diameter of the resultant particles over the size of the polystyrene cores and by SEM images showing spherical particles with smooth morphology. Therefore, some undetermined interaction between TEOS and PS-COOH enabled the formation of Janus templates which did not occur with polystyrene cores containing other surface functional groups.

In a previous study by Lu *et al.*[24], silica was grown around polystyrene of different surface functionalities using Stöber's method. Uniform shells grew around amine-terminated polystyrene while silica islands grew around sulfate terminated polystyrene. The discrepancy between Lu *et al.* and our study is likely due to the relative amounts of water and ammonium hydroxide used. The previous study used 3.5 mL DI water and 0.5 mL ammonium hydroxide; 6 times more volume of water than ammonium hydroxide. In our study the volume of water used was about half the volume of ammonium hydroxide used. The diameter of silica nanoparticles formed with the Stöber method is highly sensitive to even small changes in reaction conditions[25] and the same is likely true for shell formation.

More insight into Janus template formation was acquired from Chen *et al.* who were able to create Janus template like structures using carboxylated gold cores and a silica shell.[17] In their study, they functionalized the gold core with mercaptophenylacetic acid (MPAA, a small carboxyl containing compound) and a polystyrene-polyacrylic acid block copolymer (PS-PAA, a large, carboxyl rich polymer). By changing the MPAA:PS-PAA ratio and thus the carboxylic acid surface density, they were able to achieve different types of silica encapsulation. The silica coverage ranged from concentric, to oblong, and finally Janus template like. In our study we believe the manufacturer's carboxylate polystyrene spheres have a carboxylate surface density such that our process can form Janus templates. However since the manufacturer does not titrate their polystyrene spheres, this surface density is currently unknown. For a better understanding of the formation process, experiments to monitor the silica formation as a function of carboxyl surface density will be required and are beyond the scope of the work presented here.

Because the Janus templates contain both silica and carboxyl groups on the same particle, chemical moieties like a targeting agent and a therapeutic can be attached independently in a spatially defined manner. The Janus templates may be of use as a multifunctional delivery platform because it can spatially organize the different chemical moieties on the nanoscale, a feature not commonly found in previous drug delivery systems like nanoliposomes[26] or

silica[27, 28]. Alternatively by removing polystyrene the Janus templates become a nanobowl with more surface area and internal carrier space for therapeutic or diagnostic agents. Nanobowls can then be capped with a sphere made of biocompatible materials, including PLGA[29], liposomes,[30] and chitosan[31]. For conditional and controlled release of the therapeutic from the bowl, such a cap could be released by specific interaction with DNA[32, 33], enzymatic processes, or environmental triggers like temperature and pH. Existing delivery systems usually have pores or open surfaces that allow passive and/or continuous release of their loads (imaging contrast molecules or therapeutic agents). Our nanobowls can be used for a controlled release of imaging contrast molecules and therapeutic (theranostics) agents.

Conclusion

The addition of a carboxylate modified polystyrene core added at the beginning of a modified Stöber's method resulted in polystyrene partially encapsulated in silica. Both the size and carboxylate surface groups of the polystyrene were found to be important in formation of an Janus template. The polystyrene core was dissolved from an organic solvent leaving a nanobowl behind. These Janus templates and nanobowl can be used as a versatile platform for site-specific functionalization or theranostic delivery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Notes and references

1. Kaewsaneha C, Tangboriboonrat P, Polpanich D, Eissa M, Elaissari A. ACS Appl. Mater. Interfaces. 2013; 5:1857–1869. [PubMed: 23394306]

2. Hu S-H, Gao X. J. Am. Chem. Soc. 2010; 132:7234–7237. [PubMed: 20459132]

3. Xu C, Wang B, Sun S. J. Am. Chem. Soc. 2009; 131:4216–4217. [PubMed: 19275156]

4. Ling XY, Phang IY, Acikgoz C, Yilmaz MD, Hempenius MA, Vancso GJ, Huskens J. Angew. Chem. Int. Ed. 2009; 48:7677–7682.

5. Nisisako T, Torii T, Takahashi T, Takizawa Y. Adv. Mater. (Weinheim, Ger.). 2006; 18:1152–1156.

6. Tang C, Zhang C, Liu J, Qu X, Li J, Yang Z. Macromolecules. 2010; 43:5114–5120.

7. Binks BP. Curr. Opin. Colloid Interface Sci. 2002; 7:21–41.

8. Landon PB, Mo AH, Zhang C, Emerson CD, Printz AD, Gomez AF, DeLaTorre CJ, Colburn DAM, Anzenberg P, Eliceiri M, O'Connell C, Lal R. ACS Appl. Mater. Interfaces. 2014

9. Hong L, Jiang S, Granick S. Langmuir. 2006; 22:9495–9499. [PubMed: 17073470]

10. Roh K-H, Martin DC, Lahann J. Nat. Mater. 2005; 4:759–763. [PubMed: 16184172]

11. Suci PA, Kang S, Young M, Douglas T. J. Am. Chem. Soc. 2009; 131:9164–9165. [PubMed: 19522495]

12. Nisisako T, Torii T, Takahashi T, Takizawa Y. Adv. Mater. (Weinheim, Ger.). 2006; 18:1152.

13. Liu B, Wei W, Qu XZ, Yang ZH. Angew. Chem.-Int. Edit. 2008; 47:3973–3975.

14. Walther A, Müller AHE. Chem. Rev. (Washington, DC, U. S.). 2013; 113:5194–5261.

15. Du JZ, O'Reilly RK. Chem. Soc. Rev. 2011; 40:2402–2416. [PubMed: 21384028]

16. Chen T, Yang M, Wang X, Tan LH, Chen H. J. Am. Chem. Soc. 2008; 130:11858–11859. [PubMed: 18707100]

17. Chen T, Chen G, Xing S, Wu T, Chen H. Chem. Mater. 2010; 22:3826–3828.

18. Wang Y, Xu H, Ma Y, Guo F, Wang F, Shi D. Langmuir. 2011; 27:7207–7212. [PubMed: 21539320]

19. Wang Y, Wang F, Chen B, Xu H, Shi D. Chem. Commun. (Cambridge, U. K.). 2011; 47:10350–10352.

20. Tan LH, Xing S, Chen T, Chen G, Huang X, Zhang H, Chen H. ACS Nano. 2009; 3:3469–3474. [PubMed: 19817393]

21. Ge X, Wang M, Yuan Q, Wang H, Ge X. Chem. Commun. (Cambridge, U. K.). 2009:2765–2767.

22. Meng Z, Xue C, Lu L, Yuan B, Yu X, Xi K, Jia X. J. Colloid Interface Sci. 2011; 356:429–433. [PubMed: 21324470]

23. Feyen M, Weidenthaler C, Schüth F, Lu A-H. J. Am. Chem. Soc. 2010; 132:6791–6799. [PubMed: 20420374]

24. Lu Y, McLellan J, Xia Y. Langmuir. 2004; 20:3464–3470. [PubMed: 15875883]

25. Stöber W, Fink A, Bohn E, Colloid J. Interface Sci. 1968; 26:62–69.

26. Ramachandran S, Quist AP, Kumar S, Lal R. Langmuir. 2006; 22:8156–8162. [PubMed: 16952256]

27. Kong SD, Lee J, Ramachandran S, Eliceiri BP, Shubayev VI, Lal R, Jin S. J. Controlled Release. 2012; 164:49–57.

28. Kong SD, Zhang W, Lee JH, Brammer K, Lal R, Karin M, Jin S. Nano Lett. 2010; 10:5088–5092. [PubMed: 21038917]

29. Xue JM, Shi M. J. Controlled Release. 2004; 98:209–217.

30. Pan J, Wan D, Gong J. Chem. Commun. (Cambridge, U. K.). 2011; 47:3442–3444.

31. Fu JK, Zhu YC, Zhao Y. J. Mat. Chem. B. 2014; 2:3538–3548.

32. Landon PB, Ramachandran S, Gillman A, Gidron T, Yoon D, Lal R. Langmuir. 2011; 28:534–540. [PubMed: 21875130]

33. Mo AH, Landon PB, Meckes B, Yang MM, Glinsky GV, Lal R. Nanoscale. 2014; 6:1462–1466. [PubMed: 24317092]
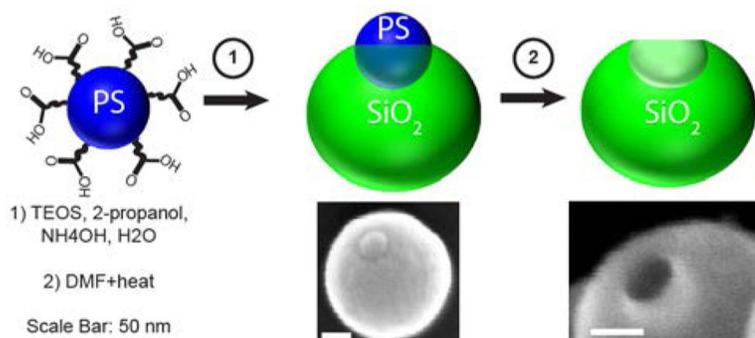
Fig 1.
A one pot aqueous synthesis scheme produces eccentric silica/polystyrene particles (Janus templates). A representative SEM image is shown (middle). Dissolving the polystyrene in DMF leaves an exposed cavity in the silica creating silica nanobowls (bottom right).
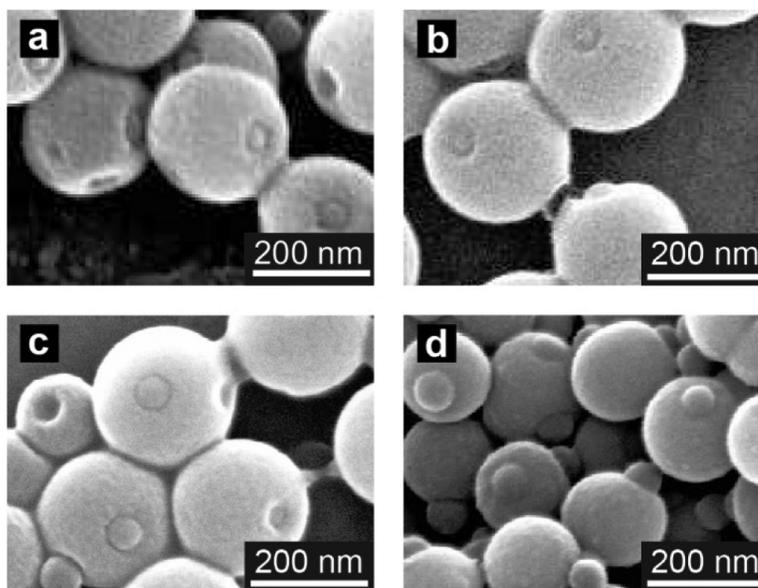
Fig 2.
Janus templates produced with 60 mM TEOS after **(a)** 1 hr, **(b)** 2 hr, **(c)** 3 hr, and **(d)** 18 hr in reaction solution. The polystyrene cores remains partially exposed at all times.
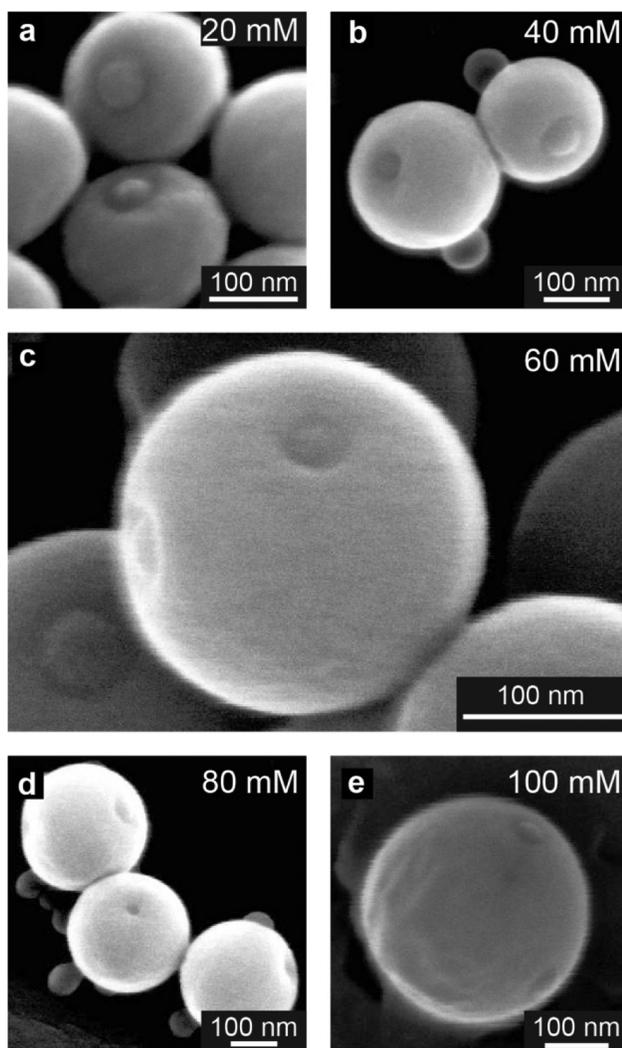
Fig 3.
Janus templates were formed using increasing amounts of TEOS (all other reactants constant) and two trends emerged: *i)* increasing Janus template diameter with more TEOS and *ii)* increasing encapsulation of the polystyrene by the silica. The following TEOS concentrations were used to form Janus templates. Each condition's average Janus template diameter and coefficient of variation were measured with DLS and reported in parentheses. **(a)** 20 mM (193nm, 0.22), **(b)** 40 mM (236 nm, 0.12), **(c)** 60 mM (244 nm, 0.15), **(d)** 80 mM (298 nm, 0.18), and **(e)** 100 mM (539 nm, 0.34) of TEOS. Multiple polystyrene cores may incorporate into an Janus template particle at different times during the reaction. If they incorporate near the beginning of the process (**3c** and **3e**) they can be well encapsulated. However if the polystyrene core incorporates much later in Janus template formation, the cores are poorly encapsulated as evidenced by the darker grey spheres in **3b** and **3d.**
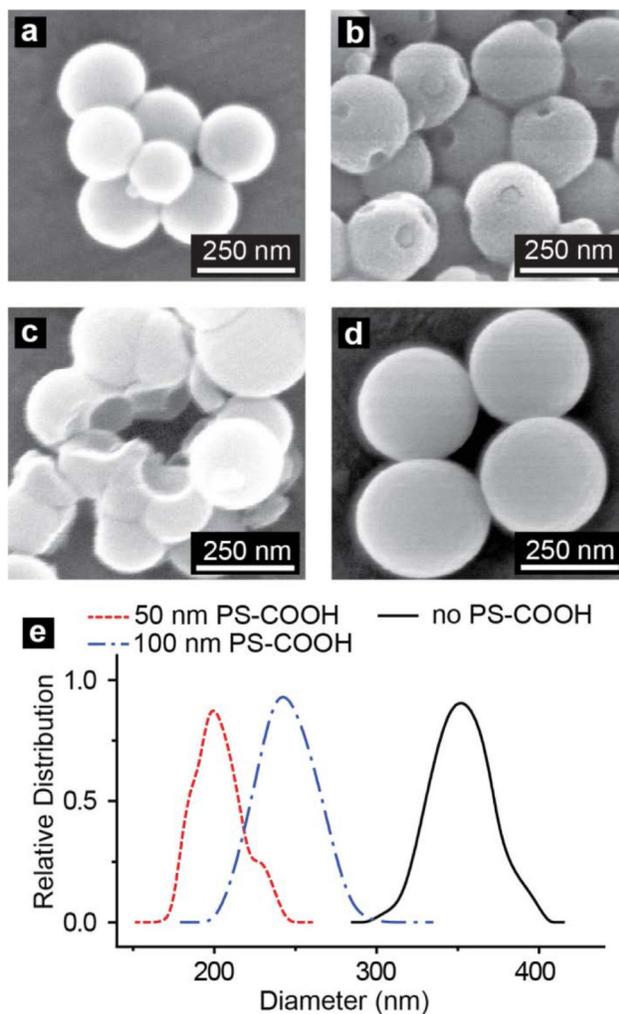
Fig 4.
Using 60 mM TEOS concentration, Janus template synthesis was attempted using PS-COOH cores of different diameters: **(a)** 50 nm, **(b)** 100 nm, **(c)** 200 nm in diameter, and **(d)** no core present in reaction. **(e)** Janus templates made with 50 nm and 100 nm cores show a smaller average diameter when compared to a silica sample made with no cores. No size distribution is reported for Janus template synthesis using 200 nm cores because the silica wrapped poorly around many of the 200 nm cores. They instead agglomerated leaving imprints where the polystyrene spheres once were. Size distributions were obtained by measuring the diameter of 100 distinct particles in SEM wide-field images.
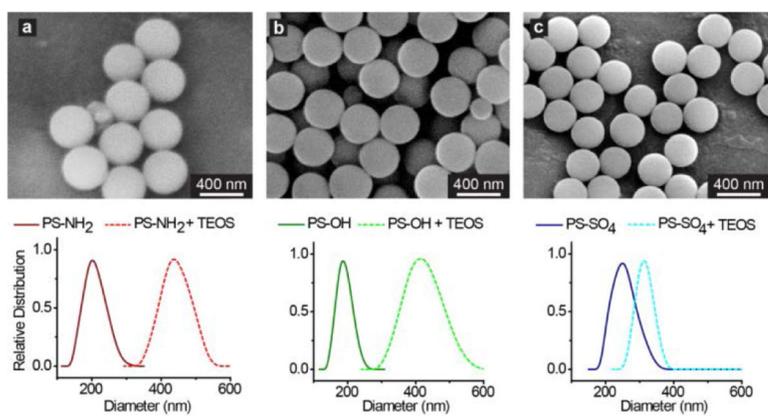
Fig 5.
200 nm polystyrene spheres functionalized with **(a)** amines, **(b)** hydroxyls, and **(c)** sulfates were added to a 60 mM TEOS solution. Unlike the carboxylate surface these polystyrene spheres were uniformly coated with silica as confirmed with SEM (top) and DLS (bottom).