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Microchemical Plant in a Liquid Droplet: Plasmonic Liquid Marble for Sequential Reactions and Attomole Detection of Toxin at Microliter-Scale

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KEYWORDS: microchemical plant, plasmonic liquid marble, in-situ surface-enhanced Raman scattering, sequential reactions, enclosed microreactor, microsensing, Ag nanoparticles

ABSTRACT

Miniaturizing the continuous multi-step operations of a factory into a microchemical plant offers a safe and cost-effective approach to promote high-throughput screening in drug development and enforcement of industrial/environment safety. While particle-assembled microdroplets in the form of liquid marble are ideal as microchemical plant, these platforms are mainly restricted to single-step reactions and limited to ex-situ reaction monitoring. Herein, we utilize plasmonic liquid marble (PLM), formed by encapsulating liquid droplet with Ag nanocubes, to address these issues and demonstrate it as an ideal microchemical plant to conduct reaction-and-detection sequences on-demand in a non-disruptive manner. Utilizing a two-step azo-dye formation as our model reaction, our microchemical plant allows rapid and efficient diazotization of nitrobenzene to form diazonium nitrobenzene, followed by the azo coupling of this intermediate with target aromatic compound to yield azo dye. These molecular events are tracked in-situ via SERS measurement through the plasmonic shell, and further verified with in silico investigation. Furthermore, we apply our microchemical plant for ultrasensitive SERS detection and quantification of bisphenol A (BPA) with detection limit down to 10 amol, which is 50000-fold lower than the BPA safety limit. Together with the protections offered by plasmonic shell against external environments, these collective advantages empower PLM as a multi-functional microchemical plant to facilitate small-volume testing and optimization of processes relevant in industrial- and research-contexts.

INTRODUCTION

A microchemical plant is characterized by its ability to perform on-demand and sequential processes involving reagents transportation and integration, reaction initiation, and on-site reaction monitoring notably at the microliter-scale.^{1, 2} By miniaturizing the continuous multi-step operations in an actual factory, this strategy promotes high-throughput screening of novel (bio)chemical synthesis crucial for applications in drug discovery and industrial/environmental safety in a safe and cost-effective manner. In particular, liquid marbles (LM) are particle-assembled microdroplet platforms ideal for microchemical plant because they are mechanically robust and can merge easily to homogenize their respective enclosed contents.^{3, 4} Additional functionality such as magnetic and catalytic properties can also be easily incorporated to facilitate both microdroplet manipulation and reaction modulation required for microchemical plant's operations through the use of different active encapsulating particles.^{5, 6} While LM have been extensively applied for toxin degradation, blood profiling and nanoparticle synthesis, current liquid marble-based microreactors are mainly limited to single step reactions and serve only as simple proof-of-concepts.^{5, 7-9} These demonstrations do not reflect the actual synthetic protocols utilized in (bio)chemistry and nanotechnology, where step-by-step reactions are prevalent and necessary to avoid side reactions and incompatibility issues of conditions for activations of different reagents.

Another limitation restricting the potential of current liquid marble microreactor as efficient microchemical plant lies in the use of invasive and ex-situ reaction monitoring techniques which may not reflect the native reaction progress. Conventional monitoring method involving the extraction of an aliquot for ex-situ tracking of microliter-scaled reaction is particularly difficult because the droplet

is susceptible to extreme volume loss after multiple cycles, inadvertently affecting the concentration and reaction.^{10, 11} While “on-line” electrochemical detection of liquid contents using a magnetic shell have been reported, the need to open the shell exposes the liquid to the surrounding environment and is prone to contamination by extraneous interfering species.¹² A straightforward solution to these issues is to coat reaction droplets with plasmonic nanoparticles to form plasmonic liquid marble (PLM), thus enabling ultrasensitive surface-enhanced Raman scattering (SERS) monitoring of enclosed reaction across plasmonic shell.¹³ Combining the benefits of its mechanical robustness and ability to track reaction in situ, we envisage the immense potential of PLM to realize the concept of microchemical plant where multi-step reactions can be programmed and monitored on-demand in a non-disruptive process.

Herein, we develop the concept of an enclosed microchemical plant capable of performing sequential reaction-and-detection, akin to having “multiple process units within a miniaturized chemical plant”, using droplets as individual components. Using multi-step aryl azo synthesis as the model reaction, chemical reactions are initiated by mixing PLMs individually encapsulated with sodium nitrite and nitroaniline (NA) followed by bisphenol A (BPA) sequentially. We optimize and characterize the SERS performance of the PLM, and acquire direct, non-destructive and real-time tracking of the mixing efficiency and reaction progress at each step. The model reaction also highlights our strategy as a microsensory platform whereby the conjugation of diazonium cation with small phenolic toxins like BPA enables their sensitive and quantitative detection, and drastically improves the detection limit to 10 amol, 50000-fold lower than the BPA safety limit. Furthermore, we showcase the robustness of our system by demonstrating that the plasmonic shell can protect light-sensitive or volatile reactants from ambient light, and improve reaction efficiency by inducing hydrodynamic flow

when merging the PLMs, which excels over existing microfluidics systems. These demonstrations showcase the practical feasibility of liquid marbles in terms of on-demand sequential reactions with in-situ monitoring, and move one step closer towards our endgoal of a liquid marble-based all-in-one microchemical plant.

PLMs are typically generated via spontaneous assembly of HCl-treated Ag nanocubes (edge length $\sim 115 \pm 6$ nm, Figure S1) onto the surface of 2- μ L water droplets immersed in decane (Figure 1A). We employ Ag nanocubes as building blocks for fabrication of plasmonic liquid marbles due their strong SERS activities, excellent monodispersity, as well as well-controlled morphology.¹⁴ These properties are advantageous over other plasmonic two dimensional materials and non-shape-controlled Ag nanoparticles (Supporting Information 1),^{15, 16} and are essential to ensure ultrasensitive and uniform SERS performance required for subsequent application as microchemical plant. As-fabricated PLMs are robust and able to move freely in decane when placed on a substrate/container surface due to effective isolation of the liquid microdroplet (Figure S2). PLM provides an analytical enhancement factor of $\sim 4.5 \times 10^8$,^{13, 17} as well as excellent homogeneity (10% relative standard deviation) across an extended area of $\sim (10 \times 60) \mu\text{m}^2$ (Figure S3). Such high SERS enhancement is mainly attributed to the closely packed 3D Ag nanocubes shell on the water/oil interface, which comprises approximately 3-4 layers of Ag nanocubes (Supporting Information 2, Figure S4). Furthermore, the aqueous-based liquid marbles submerged in decane also exhibit superior stability even after storage at ambient condition for at least 6 days (Figure S5).

Figure 1. (A) Scheme depicting PLM-based microchemical plant for sequential microreactions and in-situ SERS detection. (B) Optical images demonstrating the merging of two neighbouring 2- μ L PLMs containing methylene blue (MB) and crystal violet (CV), respectively. Scale bar, 1 mm. (C) SERS spectra collected from PLMs containing MB only, CV only and a mixture of MB (503 cm^{-1}) and CV (919 cm^{-1}) upon merging. (D) SERS intensity of MB and CV before and after merging of various PLMs.

We first study the merging behaviour of two PLMs and evaluate the consequential mixing of their encapsulated contents for latter application as microchemical plant. Upon intimate contact between two 2- μ L PLM containing methylene blue (MB, 10^{-4} M) and crystal violet (CV, 10^{-4} M), respectively, we observe rapid merging of the particle shells and their enclosed microdroplets within 40 ms with no visible leakage or distortion to the liquid marble's structure (Figure 1B; S6). After rolling the as-merged PLM for a duration of 30 s to induce efficient homogenization, SERS measurement on the newly-formed PLM demonstrates a multiplex spectrum containing fingerprints signals of both MB and CV (Figure 1C; Table S1). Using

vibrational modes at 503 and 919 cm^{-1} unique to MB and CV,¹⁸ respectively, we observe a 50% intensity reduction to these SERS bands relative to the pre-merged PLMs (Figure 1D) which is attributed to the associated 50% decrease to dyes' concentrations upon merging. This result indicates the efficient and rapid (< 30 s; Figure S7, S8) mixing of two enclosed microdroplets, as well as the consistent SERS performance of PLM even after a two-fold expansion in its volume. Manipulation of individual liquid marble and their merging can be further extended to multiple marbles. Such on-demand merging and rapid homogenization of PLMs are crucial for efficient microchemical plant, where multi-step reactions and reaction monitoring are performed without disrupting the encapsulated reagents.

A two-step azo-dye formation is employed as our model reaction to demonstrate PLM as an efficient microchemical plant for sequential and in-situ reaction-detection processes without needing post-reaction extraction/treatment.¹⁹ Azo-dye synthesis involves an initial in-situ diazotization of aromatic amine (nitroaniline; NA) in the presence of sodium nitrite (NaNO_2) and HCl to form highly-reactive diazonium intermediates ($-\text{N}_2^+$; reaction 1), followed by their transformation into azo-dyes via coupling with another aromatic molecule in an alkaline sodium carbonate (Na_2CO_3) environment (reaction 2, Figure 2A; S9). Notably, the synthesis of azo-dyes in two separate steps is important as the initial diazotization reaction and subsequent azo coupling reaction are favorable under acidic and alkaline environments, respectively.

Figure 2. (A) Schemes illustrating the use of PLM-based microchemical plant for sequential two-step synthesis of azo-dye and concurrent SERS monitoring. (B) SERS spectra recorded from the reactants and products involved in the 1) diazotization and 2) azo coupling reaction. (C, D) SERS intensity-time correlation of vibrational modes involving NH₂ (1630 cm⁻¹) and N=N (1406 cm⁻¹) during diazotization and azo coupling reaction, respectively.

In the first reaction, diazonium nitrobenzene (dNB) cations are rapidly produced within 60 s when we merge two different PLMs, where one comprises an aqueous solution of HCl and NA, and the other containing excess NaNO₂ (Figure 2A, C).²⁰ Successful dNB formation is affirmed by the disappearance of NH₂ bending modes (Figure 2C), as well as the emergence of a new peak at 1187 cm⁻¹ indexed to C-N (C-N₂⁺) stretching. Evident red-shift of C-N (C-NO₂) and NO₂ stretching modes from 1155 to 1110 cm⁻¹ and 1360 to 1340 cm⁻¹, respectively, further support the formation of electrophilic -N₂⁺, which is anticipated to induce electronic

delocalization of the entire molecule (Figure 2B). The evolutions to the experimental SERS spectra are also in close agreement with DFT-simulated SERS spectra of NA and dNB, indicating the oxidation of $-\text{NH}_2$ (of NA) into $-\text{N}_2^+$ by NaNO_2 under acidic condition (Figure S10; Table S2). We note that constant SERS intensity of 1340 cm^{-1} (NO_2 modes) is observed beyond 60 s (Figure S11). It again demonstrates the rapid completion of the diazotization reaction in < 1 min, which is 10-fold faster than laminar mixing in microfluidic channel.^{21, 22} We also observe no apparent morphological changes to Ag nanocubes on the PLM shell (Figure S12).

Sequential initiation of reaction 2 is achieved by merging the PLM from reaction 1 with another PLM that contains bisphenol A (BPA) in 2% Na_2CO_3 solution as the model aromatic molecule. The excess 2% Na_2CO_3 aqueous solution (0.2 M) in PLM is critical to neutralize the excessive acid produced in the first step and concurrently provides an alkaline environment for azo coupling reaction. In the absence of azo coupling, BPA is colourless and reveals no distinguishable SERS feature due to its weak Raman cross section and poor affinity with plasmonic shell (Figure 2B). As we merge the two PLMs, azo coupling between BPA and dNB yields coloured BPA-NB as the final dye product. It exhibits an absorption peak (476 nm) that is in resonance with the 532-nm excitation laser used (Figure S9). The combination of SERS and resonance Raman scattering (RSS) into surface-enhanced resonance Raman scattering (SERRS) is strategic to enable ultrasensitive molecular detection, as evident from > 30 -fold intensity boost of the NO_2 stretching mode as well as C-N stretching mode of C- NO_2 (1120 cm^{-1}) and C- N_2 (1164 cm^{-1} ; nitrobenzene ring ring) (Figure 2B; S10, S13). More importantly, the emergence of three distinct vibrational bands unique to N=N stretching mode at 1406, 1446,

and 1456 cm^{-1} is a direct confirmation to the formation of BPA-NB, and closely matches with DFT-simulated spectra of BPA-NB (Table S2). Using azo-dye's characteristic N=N stretching mode at 1406 cm^{-1} , we also reveal rapid formation of BPA-NB as PLMs merge whereby their SERS intensity plateau beyond 180 s. Collectively, molecular-level monitoring of entire azo-dye formation reaction using PLM indicates an efficient initial diazotization reaction that transforms NH_2 (NA) into N_2^+ ions (dNB), followed by rapid coupling of dNB with Raman-insensitive BPA to form a resonant azo-dye that allows ultrasensitive SERRS. Our results emphasize the immense potential of PLM-based microchemical plant for swift reaction-detection sequences that can be programmed and transited smoothly without the need for inter-step treatment and/or extraction. This advantage is especially vital in high throughput screening of reagents and reaction parameters for development of novel (bio)chemical reactions. The demonstration using the generation of extremely reactive diazonium species also highlights the importance of isolated PLM microreactor to avert potential safety concerns pertaining to the use of hazardous/explosive reagents, intermediates and products.

Synergizing our microchemical plant with azo-dye formation reaction, we further demonstrate the application of this ensemble for accurate, ultrasensitive and quantitative SERRS detection of BPA, a toxic phenolic estrogen linked to diseases such as breast cancer.^{23,}

²⁴ In our method, two PLMs encapsulated with BPA of varying concentrations and dNB, respectively, are merged to produce azo-dyes for in-situ SERRS molecular sensing (Figure 3A). All SERRS spectra collected exhibit vibrational signatures of BPA-NB. Utilizing the N=N stretching mode at 1406 cm^{-1} , we observe a linear decrease of SERRS intensity with BPA concentration between 2 nmol to 100 amol, which is apt for quantitative molecular detection

(Figure 3B). More importantly, our PLM platform is able to achieve a detection limit down to 10 amol (or 1 pg/mL) which is 50000-fold lower than the BPA safety limit (~ 50 ng/mL) and $> 10^7$ -fold better than UV-vis method (Figure 3C; S14). Exploiting the simple-yet-efficient synthesis of azo-dye in PLM-based microchemical plants, we also demonstrate versatile azo coupling reaction using a library of diazonium intermediates to produce and optimize azo-dye complexes for improved detection of toxic phenolic compound (Figure S9). Additional resonant enhancement to azo-dye vibrational responses using this method also allows accurate toxin sensing by discriminating against other chemical interferences/precursors, especially vital for measurement in highly diluted samples and/or samples that are susceptible to contamination.^{25, 26} Combining the advantages of microchemical plant with SERRS enabled by azo-dye formation, our detection scheme is attractive for ultrasensitive BPA sensing and can be potentially extended to other heteroatom-substituted aromatic toxin prevalent in the food industry.

Figure 3. (A) Illustration on the ultratrace detection of BPA using PLM. (B) SERRS spectra of BPA-NB synthesized with various BPA concentrations. The characteristic peak, $\nu(\text{N}=\text{N})$, are highlighted in purple. cps denotes counts/s. (C) Plot of SERRS intensity of BPA-NB (1406 cm^{-1}) at various BPA concentrations. Control experiment utilizing UV-vis detection is also included for comparison.

We further demonstrate the ability of PLM's plasmonic shell to effectively isolate and protect enclosed aqueous microdroplet from potential detrimental effects arising from the environment, such as photobleaching and unwanted molecular diffusion to contacting liquid phase. To evaluate this, we compare the azo-dye reaction performance of three different microreactors; PLM and naked reaction microdroplets in both air and decane (Figure 4A). Matching vibrational spectra from these microreactors denote successful formation of BPA-NB regardless the differences in experimental configurations (Figure 4A). Using the 1406 cm^{-1} band of BPA-NB as reference (Figure 4B), PLM exhibits strongest SERRS intensity of 910 counts/s which is > 1000 -fold higher than the RRS spectra from naked reaction droplets in both decane (0.73 counts/s) and air (0.81 counts/s). Notably, SERRS using PLM yields strong vibrational spectra even with lower laser powers and shorter exposure times (PLM, 1 s; naked droplets, 10 s), which is ideal to minimize analyte photodecomposition.²⁷ PLM platform is also able to preserve as-synthesized azo-dye using a protective Ag shell that functions as an effective shield against direct exposure to ambient light/laser, and the closely-packed Ag nanocubes shell also slows down water-to-oil molecular diffusion by decreasing the contact area of liquid droplet with outer oil phase (Figure S15).^{28,29} This is evident from the $< 10\%$ change in vibrational intensity even after prolonged laser exposure during Raman measurement or extended storage in ambient condition for 6 days. In contrary, control platform involving naked reaction microdroplet in air experiences significant photobleaching where Raman intensity decreases by $> 50\%$ after laser exposure for 180 s or storage in ambient condition for 30 min (Figure 4B; Figure S16). Control microdroplet immersed in decane also demonstrate $> 40\%$ loss of azo-dye through its diffusion to external oil phase after storage for 3 days in the dark (Figure 4B; Figure S16). Building from the

microchemical plant concept, PLM is an ultrasensitive SERRS platform that excels over traditional set-ups based on colloidal solution and substrate pre-deposited with Ag nanocubes (Figure 4C, D) by 45-fold and 900-fold, respectively.

Figure 4. (A) SERRS spectrum and RRS spectra of BPA-NB recorded from PLM and control naked microdroplets (in decane or air), respectively. Insets are schemes depicting the respective experimental set-up. (B) Comparison of the stability of as-synthesized BPA-NB in PLM and control naked microdroplets in decane or air. N=N stretching at 1406 cm^{-1} is employed as the reference. (C) SERRS spectra and corresponding (D) SERS intensities of BPA-NB collected from three detection platforms involving PLM, Ag nanocubes deposited on Si wafer, and Ag colloidal.

In conclusion, we showcase PLM as a viable microchemical plant to perform sequential and multistep chemical reactions as well as in-situ SERS tracking, using a two-step azo-dye synthesis as model reaction. The combination of our microchemical plant with azo-dye formation allows

ultrasensitive detection and quantification of toxic BPA down to 10 amol, which is 50000-fold lower than regulatory limits. Furthermore, PLM's plasmonic shell also protects enclosed microdroplet from external environment influences such as photobleaching. The ensemble benefits offered by PLMs demonstrate their tremendous potential as microchemical plant for programmable, isolated and non-disruptive reaction-detection cycles. Our microchemical plant is potentially applicable for small-volume testing of industrial processes as well as large-scale screening of parameters for reaction optimization/development relevant in synthetic (bio)chemistry and nanotechnology.

ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization of as-synthesized HCl-treated Ag nanocubes, characterization of the mobility of PLM in decane, evaluation of SERS performance of PLM, estimation of PLM shell layer thickness, characterization of Ag nanocubes on PLM shell, evaluation of PLM stability in decane, time-dependent optical characterization of two liquid marble merging together, SERS characterization of mixing efficiency after merging two PLM, versatile azo coupling chemistry, comparison of experimental SERS spectra with DFT-simulated SERS spectra, table of Raman band assignments, morphological characterization of Ag nanocubes after diazotization reaction, detection limit of BPA by UV-vis spectra, comparison of SERS performance from PLM and naked droplet for the same reaction, exposure of naked droplets in ambient environment and molecular diffusion from water to oil. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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Table of Contents