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Microgels | Very Important Paper | Hot Paper

Sprayed Aqueous Microdroplets for Spontaneous Synthesis of Functional Microgels

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Abstract: The development of sustainable synthesis route to produce functional and bioactive polymer colloids has attracted much attention. Most strategies are based on the polymerization of monomers or crosslinking of prepolymers by enzyme- or cell-mediated reactions or specific catalysts in confined emulsions. Herein, a facile solution spray method was developed for spontaneous synthesis of microgels without use of confined emulsion, additional initiators/catalysts and deoxygenation, which addresses the challenges in traditional microgel synthesis. The polarization of air-water interface of the microdroplets can spontaneously split hydroxide ions in water to produce hydroxyl radicals, thereby initiating polymerization and crosslinking in air environment. This synthesis strategy is applicable to a variety of monomers and enables the fabrication of microgels with tunable chemical structures and variable sizes. Importantly, the synthesis route also allows for the preparation of enzyme- or drug-loaded microgels *via* the *in situ* encapsulation, which also display high enzymatic activity and stimuli-triggered drug release. Therefore, this work not only is of great significance to macromolecular science and microdroplet chemistry, but also may bring new insights into cellular biochemistry and even prebiotic chemistry due to the prevalence of microdroplets in the environment.

With the unique properties, like high porosity and swelling in water, tailored chemical structure and functionality, biocompatibility and stimuli-responsiveness, microgels (MGs) have achieved the exciting applications in various fields including catalysis,[1] agriculture,[2] sensing,[3] and medicine.[4] Typically, the synthesis of MGs (a few microns to hundreds of microns) is based on the two-phase batch emulsion or microfluidic emulsion strategy.[4b,5] In the conventional water-in-oil or oil-in-water emulsions, MGs can be formed by free radical polymerization and crosslinking.[6] During this process, specific initiator decomposition conditions (e.g., high temperature, UV irradiation, or pH) are usually unfavorable to the chemical stability of the payload (biomolecules or drugs) and colloidal stability of emulsions[7]. Moreover, the surfactants (e.g., Sodium dodecyl sulfate, Triton X-100) and the unreacted initiators (e.g., Ammonium persulphate, superoxide) are environmentally unfriendly.[8] In addition, the initiator radicals integrated to polymers as "impurities" cannot be removed through purification and will affect their properties and applications.[4c,9] Therefore, it is extremely important to develop a convenient and sustainable strategy for free radical-mediated synthesis of functional and bioactive MGs.

In recent years, the emerging field of water microdroplet chemistry has gained many exciting achievements.[10] These researches indicate that aqueous microdroplets act as a powerful microreactors able to spontaneously trigger hard-to-occur chemical reactions, significantly increase reaction rates ($>10^3$), and precisely control reaction selectivity, compared to the reactions in bulk water.[11] This is because microdroplets possess some unique surface properties, such as ultrahigh polarization (about 10^9 V/m), extreme pH conditions, and partial solvation.[12] Remarkably, the polarization of the microdroplet surface can ionize hydroxide ions (OH^-) in water into hydroxyl radicals ($^\bullet OH$) and electrons, endowing them with both oxidation and reduction.[13] With these excellent properties, microdroplet chemistry has been used to conduct many challenging chemical reactions. However, the existing reports show that microdroplet chemistry has been limited to the synthesis and degradation of low molecular weight compounds.[14] Excitingly, in a very recent work,[15] the "top-down" strategy based on micro-

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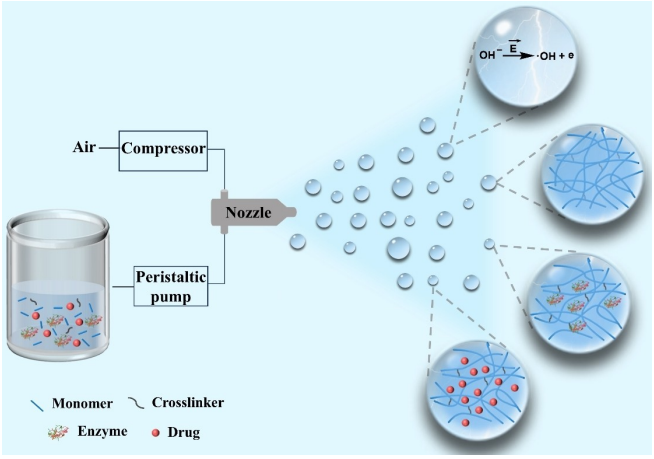
droplets was developed for spontaneously decomposing natural minerals to form nanoparticles. This work will be important for weathering and soil formation. However, the complementary process, i.e., the "bottom-up" strategy based on microdroplets for the synthesis of polymer colloids, has not yet been explored. This process may bring new insights into cellular biochemistry and even prebiotic chemistry.

Previous work has indicated that the "bottom-up" self-assembly process enables the transition from molecular to nanoscale or macroscale. The unique molecular behavior of the air-water interface of microdroplets has been studied to explain the origin of life, such as cell membrane lipid layer formation, molecular polymerization, peptide bond synthesis, and DNA/enzyme adsorption.[16] Given the prevalence of microdroplets in natural environment (e.g., bubble-aerosol-droplet cycles in atmosphere, water droplet circulation in pore space of volcanic rocks), aqueous microdroplet-mediated spontaneous molecular polymerization and enzyme encapsulation may have hosted a process of molecular evolution, for example membraneless organelles,[3a,17] providing a pathway for the emergence of cellular processes in life.

Herein, we report for the first time a facile solution spray strategy for spontaneous synthesis of functional and bioactive MGs without confined emulsion, additional initiators/catalysts and deoxygenation (Scheme 1). During solution spray, the resulting microdroplets not only can spontaneously produce hydroxyl radicals, which can initiate monomer polymerization and crosslinking, but also provide an emulsion-free confined microreactors for the formation of MGs. First, the size and corresponding hydrogen peroxide (H_2O_2) content of microdroplets formed at different spray pressures and different number of spray events as well as in the nitrogen or air environment are explored. Notably, microdroplets produce free radicals even in air environment, enabling oxygen-resistant radical polymerization. Subsequently, the size and morphology of MGs are adjusted by increasing the number of spray events. Moreover, we demonstrated that microdroplet chemistry is applicable to the synthesis of MGs from a variety of monomers. More importantly, enzyme- and drug-loaded MGs can also be obtained through the *in situ* encapsulation during solution spray, and they display high enzymatic activity and stimuli-responsive drug release. Overall, this work offers a convenient and sustainable strategy for oxygen-resistant, emulsion- and initiator-free synthesis of functional MGs, which is of great significance for the fields of both polymer science and microdroplet chemistry.



Scheme 1. Aqueous microdroplet-mediated "bottom-up" synthesis of functional and bioactive MGs based on radical polymerization in air environment. Aqueous solution containing monomers, crosslinkers, and enzymes or drugs is processed using the spray droplet generator to obtain microdroplets. Polarization at air-water interface of microdroplets can spontaneously split hydroxy ions (OH^-) in water to produce hydroxy radicals (•OH), thereby initiating polymerization and crosslinking of MGs in the absence of emulsion, initiators, catalysts and deoxygenation. Meanwhile, the strategy also allows the *in situ* encapsulation of active molecules within MGs to achieve enzyme- or drug-loaded MGs.

The spray droplet generator was adopted to achieve water microdroplets by solution spray (Figure S1). In this process, the peristaltic pump transports aqueous solution to the nozzle, subsequently transforming solution into microdroplets through high-speed spray. To clearly show the size and morphology of the resulting microdroplets, the aqueous solution containing sodium fluorescein was sprayed onto the slide surface and then observed using fluorescence microscopy (Figures 1a-c). As the spray pressure increased, the size of the obtained microdroplets decreased. At the spray pressures of 0.1 and 0.2 MPa (Figures 1a,b), the microdroplets maintained a regular spherical shape, and their diameters were mainly distributed at 10–40 μm and 1–10 μm, respectively. However, higher spray pressure (0.4 MPa) leads to the aggregation of microdroplets and the formation of droplets with irregular shapes (Figure S2). Moreover, at the spray pressure of 0.2 MPa, the size of microdroplets increased with the increase of number of spray events. The number of spray events refers to the number of sprays in a consecutive spray process. After two consecutive sprays (Figure 1c), the microdroplets still remained an independent and regular morphology with a diameter of 5–25 μm. Predictably, after three consecutive sprays (Figure S3), some microdroplets fused with each other and could not form a regular morphology.

Some previous work has revealed that the air-water interface of microdroplets exhibit an ultrahigh polarization, which can ionize OH^- in water to produce •OH, subsequently rapidly re-combining to form H_2O_2.[18] The lifespan of •OH is extremely short, and their content is usually expressed by the detection of final product H_2O_2. Next, we used potassium titanium oxalate (PTO) to quantitatively measure the concentration of H_2O_2 in the resulting microdroplets. The titanium ions of PTO can form a stable orange complex with H_2O_2, and its absorption at 400 nm in UV-vis spectra is proportional to the content of H_2O_2. Clearly, as the decrease of spray pressures or the increase of numbers of spray events (Figure 1d,e and Figure S4), the concentration of H_2O_2 in microdroplets decreased due to their size increase. An almost equal concentration of H_2O_2 was achieved in air environment compared to that in nitrogen environment. These results showed that at the spray

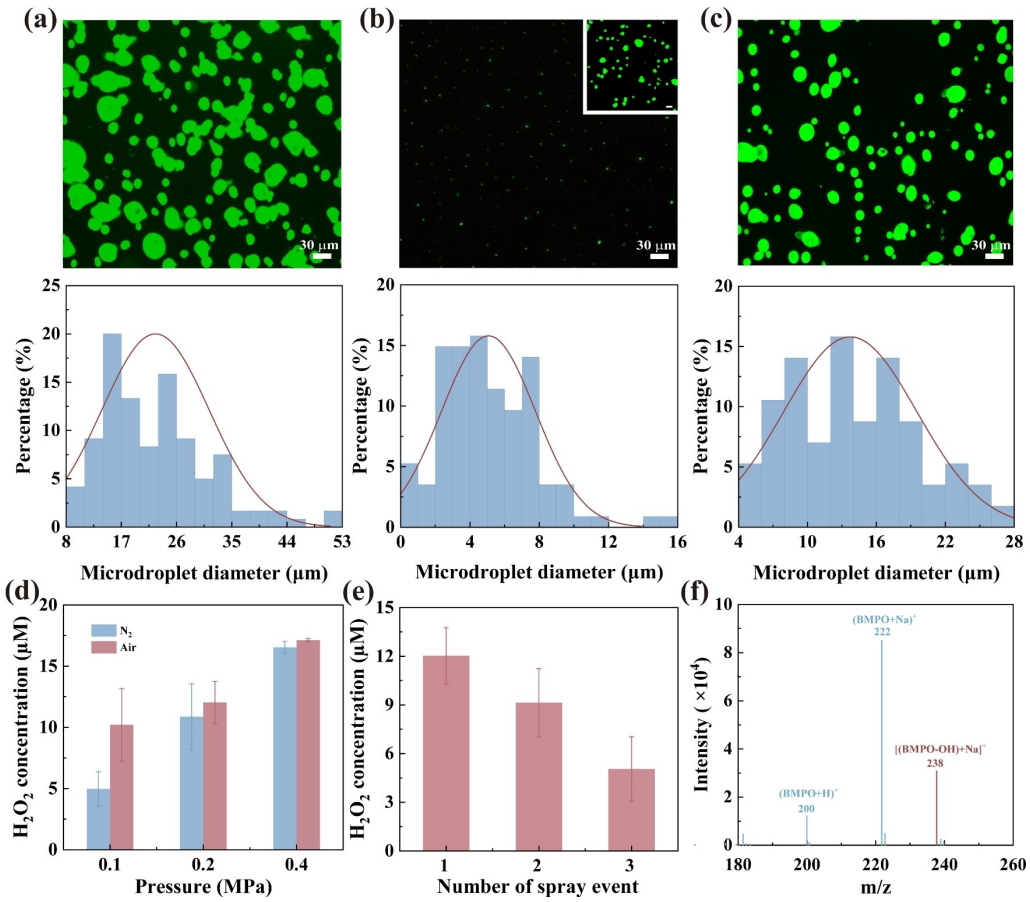


Figure 1. Fluorescence imaging and diameter statistics of microdroplets obtained at different spray pressures and different number of spray events: (a) 0.1 MPa, 1 time; (b) 0.2 MPa, 1 time (Inset: A partial enlargement, scale bar: 10 μm); (c) 0.2 MPa, 2 times. H_2O_2 concentration of microdroplets obtained at different conditions: (d) 0.1–0.4 MPa, 1 time; (e) 0.2 MPa, 1–3 times. The statistical data are represented as mean ± SD (n = 3 independent experiments). (f) Mass spectrometry of •OH spontaneously produced in microdroplets captured by BMPO.

pressure of 0.2 MPa with one spray time, the formed microdroplets possess regular spherical and high concentration of H_2O_2. This is consistent with previous literature that microdroplets with a diameter of 1–10 μm are capable of generating a higher concentration of H_2O_2.[13a] Therefore, the spray parameter will also be used for subsequent experiments. To observe the generation of •OH in microdroplets more intuitively, 3,4-dihydro-2-methyl-1,1-dimethylethyl ester-2H-pyrrole-2-carboxylic acid-1-oxide (BMPO, radical scavenger) was employed to capture •OH in air environment. In mass spectrometry (Figure 1f and Figure S5), the peak at m/z of 238 is $[(BMPO–OH)–Na]^+$ formed after the radical capture, indicating that microdroplets indeed are able to spontaneously produce •OH in air environment. These resulting radicals will initiate polymerization of polymers and further formation of crosslinked polymer networks.

Next, we investigated the feasibility of solution spray for MG synthesis based on free radical polymerization. The monomer *N*-vinylcaprolactam (NVCL) is first chosen because it is widely used to synthesize stimuli-responsive and biocompatible MGs by free radical polymerization.[19] The aqueous solution containing only monomer NVCL and crosslinker *N*, *N*'-methylenebis(acrylamide) (BIS) without deoxygenation was sprayed to obtain PNVCL MGs in air environment. Some work has revealed that the electrons spontaneously generated in microdroplets can quickly combine with dissolved oxygen to produce superoxide anions, thereby depriving them of the ability to quench free radicals.[20] SEM image suggested that PNVCL MGs can be prepared by facile solution spray in air environment (Figure S6). With the increase of the number of spray events, the size of MGs increased and their morphology became more regular spherical. This indicated that the growth mechanism of MGs may be through aggregation to form large colloidally stable polymer particles.[21] After the first spray, the polymerization and crosslinking in the microdroplets is taken place to form polymer particles which are further grown to obtain MGs through the droplet fusion in the subsequent spray process. Additionally, the statistical result showed that the average diameter of MGs is 1.52 μm (Figure S7). Dynamic light scattering (DLS) data indicated that the hydrodynamic diameter (D_h) and polydispersity index (PDI) of MGs are about 1.71 μm and 0.269, respectively. The result suggested that the homogeneity of MGs is relatively poor. Moreover, the size from DLS is larger than

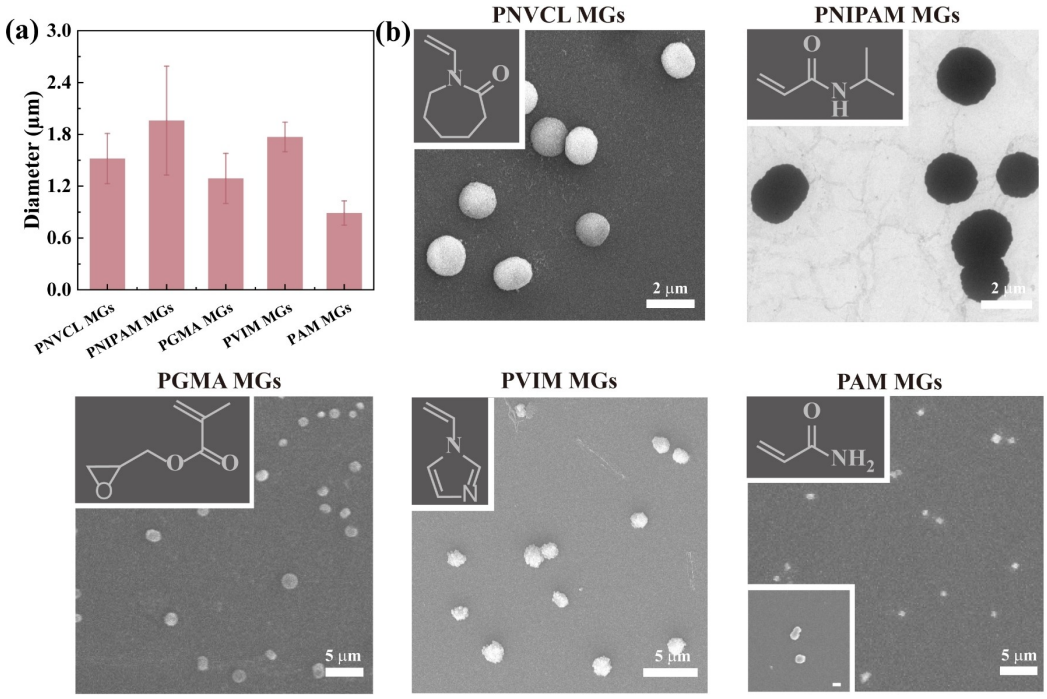


Figure 2. (a) Average diameters of various MGs and (b) their corresponding SEM images. The inset is the high-magnification SEM image of PAM MGs (scale bar: 2 μm). The statistical data are represented as mean ± SD (n = 30 MGs).

that from SEM image due to the swelling of MGs in aqueous solution. These results demonstrated that microdroplet chemistry enables oxygen-resistant radical polymerization-mediated synthesis of MGs without the confined emulsion and additional initiator. Furthermore, the applicability of the developed strategy to different monomers was explored (Figure 2). We observed that several commonly used monomers, such as *N*-isopropylacrylamide (NIPAM), glycidyl methacrylate (GMA), 1-vinylimidazol (VIM), and acrylamide (AM) can be also successfully polymerized to form MGs by solution spray. SEM images demonstrated that the morphologies of obtained MGs are spherical and their sizes are varying.

Some research work from our group and others demonstrated that high water content and crosslinked network structure of MGs provide the biologics with the possibility of resisting harsh environments and avoiding deactivation.[4b,22] This has led to exciting advances in enzyme-loaded MGs for the fields of biocatalysis and biomedicine.[23] Based on the microdroplet chemistry, we tried to spray the aqueous solution containing NVCL, BIS, and enzymes to obtain enzyme-loaded MGs through the *in situ* loading. The enzymes are catalase (CAT) and horseradish peroxidase (HRP) respectively, and they can be used to catalyze the decomposition of H_2O_2. SEM images showed that CAT-loaded MGs and HRP-loaded MGs also have a regular morphology (Figures S8 and S9). Furthermore, the bioactivity of CAT-loaded MGs was determined through the conversion of H_2O_2 (Figures 3a,b). Apparently, the characteristic peak of H_2O_2 at 236 nm decreased after treatment with CAT-loaded MGs. To determine the bioactivity of

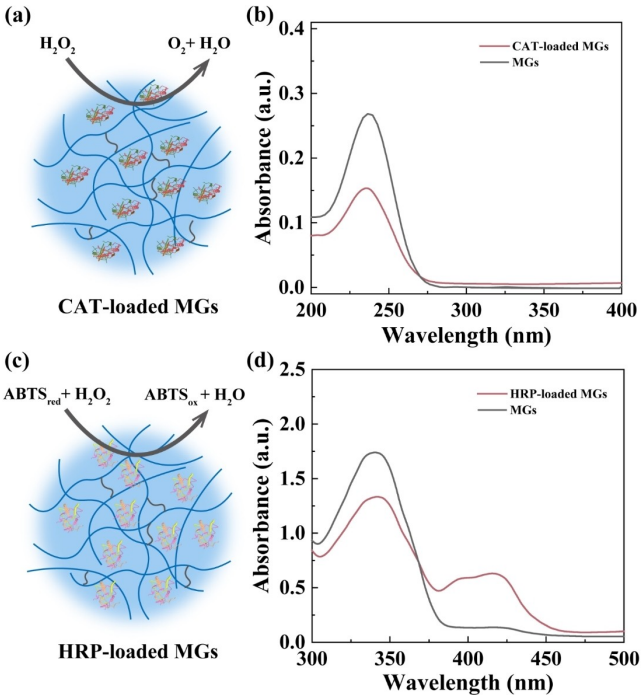


Figure 3. (a) Schematic illustration of CAT-loaded MGs for the catalysis of H_2O_2. (b) UV-vis spectra of H_2O_2 treated with MGs and CAT-loaded MGs. (c) Schematic illustration of HRP-loaded MGs for the catalysis of ABTS with the action of H_2O_2. (d) UV-vis spectra of ABTS solution treated with MGs and CAT-loaded MGs.

HRP-loaded MGs, $ABTS_{red}$ was oxidized with H_2O_2 to form $ABTS_{ox}$ (Figures 3c,d). Clearly, after treatment with HRP-

loaded MGs, the absorption peak of $ABTS_{red}$ at 340 nm decreased, while an enhanced adsorption at 380–450 nm from $ABTS_{ox}$ was observed.[24] According to the calculation, the enzyme activities of CAT-loaded MGs and HRP-loaded MGs are 77.6 U/mg and 135.0 U/mg, respectively. As a contrast, the activities of free CAT and HRP are 200 U/mg and 300 U/mg, respectively. The result indicated that the enzyme activity is reduced during the process of*in situ* enzyme encapsulation, which may be due to the influence of the ·OH and H_2O_2 formed in microdroplets. Nevertheless, the *in situ* enzyme encapsulation within MGs based on microdroplet chemistry can retain enzyme activity, which will provide the possibility for their further applications in biocatalysis and biomedicine.

Besides, MGs as ideal carriers are also promising for targeted delivery and controlled release of drug.[25] Among them, temperature-responsive PNVCL MGs have attracted much attention because of their unique volume phase transition temperature.[26] They exhibit a reversible swelling and shrinkage above or below the volume phase transition temperature. Similarly, we sprayed aqueous solutions containing NVCL, BIS, and doxorubicin (DOX, an anti-cancer drug) to obtain DOX-loaded MGs. In the fluorescence spectrum, DOX-loaded MGs emerged a characteristic absorption peak of DOX at 580 nm (Figure 4d), indicating that DOX is successfully encapsulated into MGs. Moreover, DLS results suggested that the D_h of DOX-loaded MGs reduce from 1.20 µm to 0.62 µm when the temperature increased from 25 °C to 50 °C (Figures 4a,c). The temperature responsiveness of DOX-loaded MGs enabled controlled drug release, which was observed in fluorescence imaging (Figure 4b), that is, a red corona from the released DOX was formed around the MGs at 50 °C. Furthermore, the decrease of absorption peak of DOX at 50 °C also proved that DOX-loaded MGs possess temperature-responsive drug release behavior (Figure 4d).

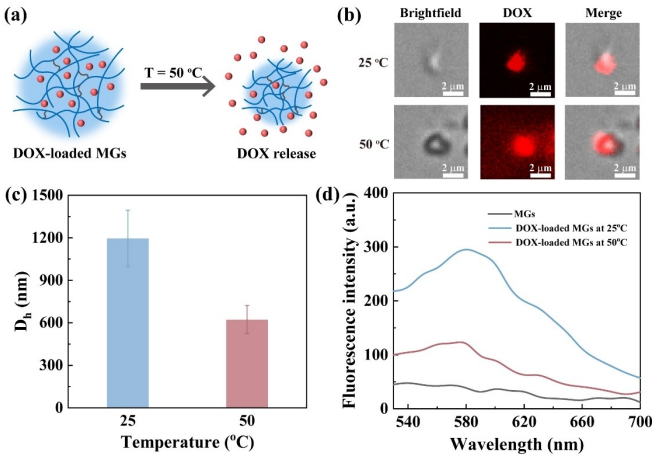


Figure 4. (a) Schematic illustration of temperature-responsive drug release of DOX-loaded MGs. (b) fluorescence imaging, (c) hydrodynamic diameter, and (d) fluorescence spectra of DOX-loaded MGs at 25 °C and 50 °C. The statistical data are represented as mean ± SD (n = 3 independent experiments).

We compared the developed method with other existing methods for synthesis of MGs. In batch emulsion or microfluidic emulsion,[19a,27] the dispersed droplets act as confined reactors to provide a space for monomers, prepolymers, initiators and/or crosslinkers. Subsequently, light or heat is required to initiate polymerization and/or crosslinking, and sometimes additional catalysts are added to increase the reaction rate. Batch emulsion exhibits the advantages of simple operation and high yield for MG preparation, but its main limitation is the polydispersity and heterogeneous size of formed MGs. In contrast, microfluidic emulsion can well control the formation of MGs, including morphology and size, and even obtains compartmentalized MGs. Nevertheless, the throughput of this method is relatively low and it is difficult to synthesize smaller MGs (< 10 µm). Furthermore, for the encapsulation of biologics, removal of oil and surfactant (i.e., oil and alcohol washing) is necessary to obtain biologic-loaded MGs in these methods, which may damage the activity of biologics. Although electro-demulsification chip and antistatic gun technologies have been developed to break the emulsion rapidly and gently,[28] these strategies cannot completely avoid the contact between biologics and oil/surfactants, as well as the equipment and operation required are relatively complex. Additionally, MGs can also be prepared using lithographic method,[29] this is, adding prepolymers into the templated mold and photoinitiating polymerization and/or crosslinking. The size and shape of MGs are determined by the mold without additional emulsion. Therefore, this method exhibits broad compatibility for biologic encapsulation within MGs.

In summary, a facile strategy of solution spray was developed for spontaneous synthesis of functional and bioactive MGs. This strategy eliminates the need for confined emulsion, additional initiators/catalysts and deoxygenation. The resulting microdroplets act as confined reactors spontaneously producing ·OH to initiate polymerization and crosslinking of polymers in air environment. The size and morphology of MGs can be adjusted by the spray pressure and the number of spray events. Moreover, we demonstrated the applicability of a variety of monomers for the synthesis of MGs by microdroplet chemistry. Furthermore, this strategy also allows the *in situ* encapsulation of biologics into MGs, enabling enzyme catalysis and controlled drug release. The *in situ* capture of the bioactive substances during the spontaneous polymerization may be a pathway for the origin of early lifeforms. This work is of great significance to the fields of both macromolecular science and microdroplet chemistry. Notably, the developed synthesis strategy gets rid of the limitations of emulsion, initiators, catalysts, and deoxygenation in the synthesis of polymer colloids.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Functional Microgels · Spontaneous Synthesis · Water Microdroplets · Enzyme Loading · Controlled Drug Release

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