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A Green and Facile Approach to Obtain 100nm Zeolitic Imidazolate Framework-90 (ZIF-90) Particles via Leveraging Viscosity Effects

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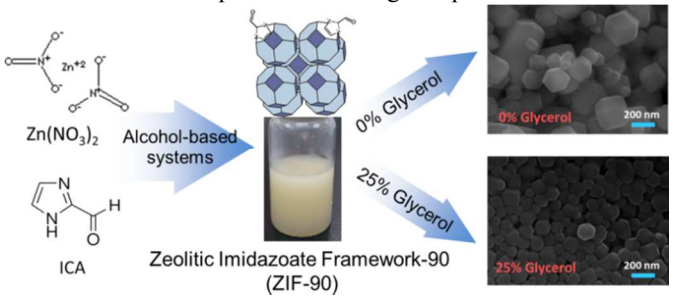
For the first time, ~100 nm zeolitic imidazolate framework-90 (ZIF-90) particles were produced by a water–alcohol-based system, taking advantage of viscosity effects using an optimized H_2O/*tert*-butanol/glycerol/PVP system. Furthermore, an *in vitro* cytotoxicity assay revealed the half-maximal effective concentration (EC_{50}) of ZIF-90 nanoparticles to be ~92 μg/ml.

In past decades, porous materials such as metal–organic frameworks (MOFs)[1] have attracted immense attention owing to their potential for producing a large variety of unique structures. In particular, porous materials offer sustainable solutions for issues, such as greenhouse gas reduction,[2] industrial catalysis,[3] pollutant treatment,[4, 5] disease diagnosis and therapy,[6] and efficient electronics[7] and gas fuel storage,[8] owing to a variety of superior properties including a unique pore structure and large specific surface area.[9] For the realization and advancement of more demanding applications such as sensors,[10] catalysis,[11] and drug delivery,[12] porous materials miniaturized to the nanoscale, or even smaller, may offer significantly altered properties, such as higher reactivity, compared with bulk material. This shift occurs since increasing textural porosity and external surfaces removes or diminishes mass transfer limits.[13] Therefore, strategies for the synthesis of nanosized porous materials, *i.e.*, nanoMOFs, are attracting steady interest in the materials science field.[14] In general, most conventional protocols for nanoMOF synthesis require minimal chemical reaction control (addition of modifiers or surfactants, or altering reactant ratios), but solely rely on growth control via physical parameters, such as the type of energy supply, reaction time, and temperature.[14] Although a number of methodologies have been reported[9, 14] for the synthesis of nanosized MOFs, routes for their efficient synthesis with desirable size, shape, and surface morphology are still under investigation. Furthermore, most nanoMOFs are usually synthesized by systems containing toxic organic solvents such as dimethylformamide (DMF)[15] and tetrahydrofuran (THF).[16] However, in addition to reduced particle size, the use of porous solids for industrial or biomedical applications also requires a more environmentally friendly synthesis or biocompatible composition —i.e., a low-toxicity system for synthesis and less cytotoxicity. So far, unfortunately, such routes for synthesizing nanoMOFs are very scarce.

Currently, our research is focused on the development of an efficient, rapid approach and environmentally friendly synthetic methods for precisely miniaturizing zeolitic imidazolate framework (ZIF) to realize particles with sizes from the micrometer to nanometer scale.[17] In addition, we investigate their potential biomedical applications.[18] ZIFs, a subclass of MOFs, have an extended 3D structure consisting of tetrahedral metal ions (M = Zn or Co) bridged by imidazolate. Moreover, the M–Im–M angle is similar to the Si–O–Si angle (145°) preferred in zeolites. ZIF-90, zinc(imidazolate-2-carboxyaldehyde(ICA))$_2$, is with the carbonyl group in the 2-position of the imidazole linker and the resulting structure has also been reported to have a high thermal and solvent stability.[19] Therefore, it is an ideal composition for use in gas separation or structural patches[20] composed of thin films or membranes.[21]

Water-miscible alcohols (as trigger solvent in the synthetic precipitation method), *e.g.*, ethanol (C = 2), propan-2-ol (C = 3), and *tert*-butanol (C = 4), have been used in the water-based synthetic system, and their effects on synthesized ZIF-90 were studied in our recent report.[17] Remarkably, we found that a smaller ZIF-90 particles were produced with increasing viscosity (i.e., increased number of carbons in the alcohol of the synthetic solution). More specifically, the synthetic system of *tert*-butanol + water/polyvinyl-pyrrolidone polymer (PVP, MW = 40,000) produced ~280 nm ZIF-90 particles. Thus, the alcohol viscosity of the applied water-based system appears to

be a vital factor for controlling the particle size of ZIF-90. In order to further reduce particle size, in this study, we adopted a water-alcohol-based system primarily modeled on that of the aforementioned study. In this case, for obtaining smaller ZIF particles as well as for the study of viscosity effects on particle size, we examined the volume-ratio change with glycerol (OH=3) as a modifier. We then applied a synthetic system using a mixed *tert*-butanol/H_2O/PVP solvent. It is worth noting that ZIF-90 nanoparticles (denoted as nanoZIF-90 hereafter) were well-dispersed and had a narrowed particle size distribution, ~100 nm, when they were produced by this high-viscosity synthetic system with the concentrations of glycerol at 25 v/v% and that of PVP at 0.2 wt% (Scheme 1). In addition, *in vitro* toxicity of nanoZIF-90 was also established around 90 μg/ml of half-maximal effective concentration (EC_{50}).To the best of our knowledge, this is the smallest-diameter ZIF-90 particles synthesized by a water-related system so far as well as this nanoscaled material obtained here is with low cytotoxicity. Notably, although some reports[22, 23] had shown that ZIF-90 particles with sizes of one hundred nanometers or less can be successfully synthesized, those nanoscaled ZIF-90 particles produced by using the DMF solvent carry the risk of the toxic solvent still being present within the particles. Thus, we should note once again that a particle size distribution in this range (~100 nm) as well as nanoscaled ZIF-90 synthesized by water-related systems are needed for improved membrane-type patches[20] such as transdermal patches[20] or for applications as nanocarriers for cell penetration[24] or gas-separation films.[19]



Scheme 1. Synthesis of ZIF-90 nanoparticles with ~100 nm particle size prepared by changing the viscosity using glycerol in a water–alcohol-based system

The detailed experimental procedure is described in the Experimental Section (Electronic Supplementary Information, ESI). Briefly, nanoZIF-90 were synthesized as follows: zinc nitrate ($Zn(NO_3)_2$) was added to the *tert*-butanol solution termed the trigger solution (solution A). Another aqueous solution containing ICA and 0.2% polyvinylpyrrolidone (PVP, MW = 40,000) was also prepared as a glycerol modifier (in varying amounts) (solution B). In general, the volume ratio of solution A to B was fixed at 1. The reactant molar ratio of Zn to ICA was maintained at 1:4 in the final solution. After mixing solutions A and B at ambient temperature for a few minutes, the resultant powder was collected by centrifugation, washed with excess methanol, and vacuum dried at 50°C.

To evaluate effects of viscosity on particle size, we performed a series of nanoZIF-90 syntheses from mixtures with a range of viscosities, by using different percentages of glycerol. In other words, we precisely tuned the particle size by controlling the glycerol modifier in a range of volume ratios from 0% to 25% in the final solution (Fig. 1). As expected, the particle size decreased from 280 nm to 110 nm as the volume ratio of glycerol increased from 0% to 25%. This trend is consistent with our assumption that the viscosity of the applied water-alcohol-based system solution is a key factor for controlling the nanoZIF-90 particle size. Additionally, the SEM images in Fig. 1b and 1c show that particles obtained with higher viscosity have a regular morphology. This indicates once again that glycerol plays an important role in the control of particle size and shape by controlling the viscosity of the synthetic solution.

However, it is worth noting that particle size increased dramatically when the volume ratio of glycerol modifier was greater than 25% in the synthetic solution (*i.e.*, 30% glycerol; Fig. S1, ESI). We believe that glycerol is not homogenously dispersed throughout the solution if the volume ratio of the modifier is greater than 25%. Therefore, under this condition, the viscosity is no longer a dominant factor determining particle size.

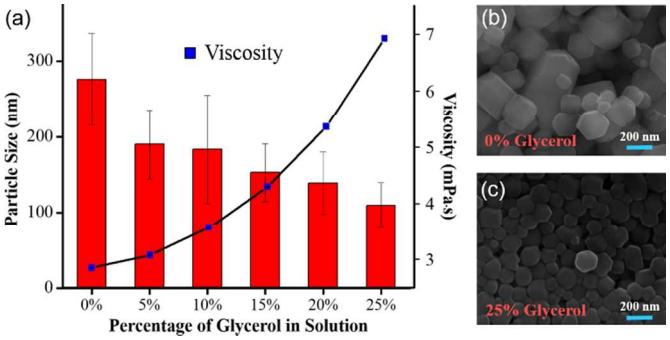


Fig. 1. ZIF-90 materials synthesized at different volume ratios of glycerol modifier. a) The corresponding particle sizes of the ZIF-90 materials synthesized in different systems and the measured viscosity of each system, shown as a solid line. b) SEM image of particles synthesized in a system with 0% glycerol c) SEM image of particles synthesized in a system with 25% glycerol. All systems had 0.2 wt% PVP polymer.

The crystallinity and functional group of as-synthesized nanoZIF-90 obtained using this water–alcohol-based system were examined using power X-ray diffraction and FT-IR, respectively. As evidenced in the XRD and FT-IR patterns, they exhibit the same functional group and crystallinity, respectively, as those synthesized in solvothermal systems with *N,N*-dimethylformamide (DMF) as the solvent[25] (Fig. 2a and b, Fig. S2 and S3). This indicates that our new method can also produce phase-pure nanoZIF-90. The structure of the nanoZIF-90 particles was also investigated by the N_2-adsorption isotherm method; these results are summarized in Fig. 2c and Table 1. Remarkably, the nanoZIF-90 particles (size ~ 100 nm) had a Langmuir surface area (S_L) of about 1183 $m^2 g^{-1}$, and total pore volume of 0.52 cm^3 g^{-1} when produced at ambient temperature. The N_2 adsorption isotherm shown in Fig. 2c indicates a typical type-I isotherm.[26] The increase in the volume

adsorbed at very low relative pressures is due to the presence of micropores; a second uptake at high relative pressure with a very small adsorption–desorption hysteresis loop indicates the existence of textural meso-/microporosity, caused by the packing of crystal particles.[27] Additionally, the thermal properties of nanoZIF-90 were investigated by using thermogravimetric analysis (TGA). The TGA curves in Fig. 2d and Fig. S5 were found to be different from those reported for the synthesis of micrometer-sized ZIF-90 crystals prepared using DMF. However, this result is similar to one in our previous report,[17] as the TGA trajectories of the sample prepared in DMF show a deep drop at two steps in the 50–320°C range, which resulted from the entrapment of DMF within the synthesized ZIF-90.[12, 17]

In order to gauge the potential of nanoZIF-90 for biomedical applications, their *in vitro* toxicity was established by the AlamarBlue assay, using a cell line of HEK-293 (Fig. 3). In order to maintain high dispersity in the high ionic strength of the cell medium,[28] the nanoZIF-90 were capped with cetyltrimethylammonium bromide (CTAB) before performing the assays (Fig. 3a; Fig. S6). As seen in Fig. 3b, the EC_{50} of our nanoZIF-90 was determined to be approximately 92 μg/ml. This value is comparable to the reported EC_{50} values for gold nanoparticles (varies from 5 to 1000 μg/ml), mesoporous silica nanomaterials (from 30 to 500 μg/ml), ZIF-8 (from 100 to 140 μg/ml), and MILs (57 ± 11 μg/ml).[29-32] The representative images in Fig. 3c and 3d show a cell line incubated with and without nanoZIF-90, respectively. This indicates that the HEK-293 cell line experienced cell death after incubation with 90 μg/ml nanoZIF-90 in 2 days.

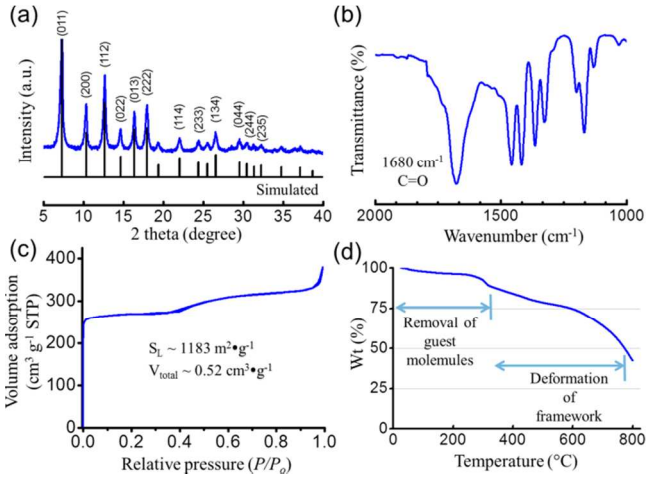


Fig. 2. Characterization of nanoZIF-90, synthesized in an optimized water-alcohol-based system to achieve the smallest-possible particle size. a) XRD pattern, b) FT-IR spectrum, c) Nitrogen adsorption–desorption isotherm, and d) TGA curve.

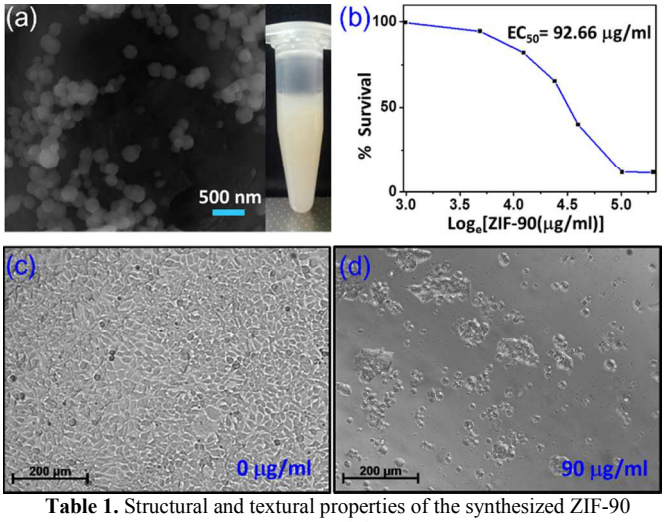


Table 1. Structural and textural properties of the synthesized ZIF-90 materials

System[a]	S_L (m^2/g)[a]	S_{BET} (m^2/g)[b]	V_{total}[c]	V_{micro}[d]	Particle size [nm][e]
DMF[25]	1320	1270	0.58	0.48	1430±311
H_2O /*tert*-butanol[17]	1011	766	0.45	0.33	276±60
H_2O/glycerol(25%)/ *tert*-butanol	1183	897	0.52	0.38	110±30

[a] Langmuir surface area. [b] BET surface area. [c] Total pore volume. [d] t-Plot micropore volume. [e] Particle size calculated from SEM images.

Fig. 3. Cytotoxicity: a) SEM of nanoZIF-90 capped with CTAB in a fine distribution. b) Cell viability when incubated with nanoZIF-90 material. c) Representative image of cell viability before the nanoZIF-90 was added. d) Representative image of cell viability with the concentration 90 μg/ml of nanoZIF-90 after 48 h incubation.

In summary, we report the first synthesis of 110-nm–size ZIF-90 nanoparticles, using a water–alcohol-based (H_2O/PVP/glycerol/*tert*-butanol) system under ambient conditions. The effects of viscosity observed by the variation of glycerol concentrations on the properties of the synthesized ZIF-90 were also investigated. Further, the cytotoxicity of the nanoZIF-90 is moderate and comparable to that of other organic and inorganic drug carriers. This green-synthesis strategy is fast and reliable, compared to conventional organic-solvent-based systems. Thus, our water/polymer/alcohol system allows for the reduction in the size of ZIF-90 particles to ~100 nm and the particles have a potential for use in industrial and biomedical applications owing to their less toxically synthetic method and low cytotoxicity.

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A Green and Facile Approach to Obtain 100nm Zeolitic Imidazolate Framework-90 (ZIF-90) Particles via Leveraging Viscosity Effects

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100nm ZIF-90 nanoparticles with low cytotoxicity are obtained by utilizing glycerol for the control of viscosity effects in water-alcohol-based system