Particle Preparation and Morphology Control with Mutual Diffusion Across Liquid-Liquid Interfaces†

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Abstract

Advanced functional materials require sophisticated control of particle characteristics. The bottom-up process has been extensively used to produce functional materials for controlling the particle properties of composite particles. We propose crystallization at liquid-liquid interfaces as an advanced particle formation method. This review introduces crystallization at a liquid-liquid interface based on several case studies used in various applications. Conventional crystallization has been generally used to produce crystals and particles with homogeneous particle properties. Liquid-liquid interfacial crystallization makes it possible to create composite particles with hetero-phase structures and interfaces. Liquid-liquid interfacial crystallization with an inkjet technique can control the droplet size accurately, and the shape and particle size distribution are successfully controlled in inorganic-organic composite particles. In addition, we succeed in creating organic-organic composite particles using the interfacial crystallization by an ultrasonic spray nozzle. The coating efficiency of organic particles on the particles is enhanced using the ultrasonic spray nozzle in comparison with anti-solvent crystallization. In this study, the fabrication of inorganic-organic composite particles using a coaxial tube reactor on the liquid-liquid interfacial crystallization is proven successful. These findings suggest that liquid-liquid interfacial crystallization is a promising means of efficiently producing composite particles because of their applicability to infusion in various processes.

Keywords: composite particles, crystallization, liquid-liquid interface, morphology, supersaturation

1. Introduction

Fine particular material is employed in various industrial applications such as chemical, pharmaceutical, cosmetics, and food products. The physicochemical properties of particles originally affect the performance or features of products composed of powder. The ability to control particle properties such as shape, morphology, size, and size distribution is indispensable to developing industrial fields (Provis et al., 2010; Saallah and Lenggoro, 2018; Fuji et al., 2013). Particle-generation approaches that create fine particles can mainly be divided into two processes: break-down and bottom-up (Yokoyama and Huang, 2005; Tavares, 2017; Opalski et al., 2019). The bottom-up approach has been extensively used in producing composite materials in terms of controlling the particle properties of composite particles (Leon et al., 2014). Hetero-phase structures and interfaces in composite materials can provide additional functions to products and approaches that creation of interfaces and structures have been regarded as a driving force of new innovative product development (Shirakawa et al., 2006; Shirakawa et al., 2010). Several composite materials such as inorganic-organic and organic-organic products have been developed. Inorganic-organic composite materials have gathered attention for use in catalysts and photoelectronic materials, whereas organic-organic composite materials are currently being developed as biomaterial and pharmaceutical products (Alam et al., 2018; Lazzara et al., 2018).
Composite materials using inorganic-organic or organic-organic materials have been proceeded for delivering drugs and other bioactive molecules for over 30 years. Several products are ongoing or have been approved worldwide as nanocarriers of drug delivery systems (Natarajan et al., 2014). Most of these nanocarrier products have focused on target drug delivery such as cancer chemotherapy and effectively utilize the size advantage of nanocarriers to provide a favorable distribution of the drug carrier to the human body. Several researchers have previously succeeded in generating sustained-release products to nanocarrier applications (D’Souza and DeLuca, 2006; Washington, 1990). The accomplishment in sustained release of bioactive molecules has broken ground as nanotherapeutics. As a representative product of composite materials, nanocarriers that provide spatiotemporal control of drug release contributed to the improvement in the therapeutic efficacy of drugs and the reduction in toxicity. Among composite materials, nanocarriers confront tough and original challenges in drug-release kinetics control because of the large surface area per volume ratio and small diffusion. For development of nanocarriers such as composite particles with favorable release kinetics for drug delivery applications, understanding the mechanisms by which a carrier retains and releases a drug (Lee and Yeo, 2015) is crucial.

The silica nanoparticles with porous and hollow structures for controlling release kinetics of drugs were previously prepared using bottom-up approaches (Li Z. et al., 2004). Porous hollow silica nanoparticles with drugs were prepared through a sol-gel method and using a CaCO$_3$ template method (Nakashima et al., 2018). The prepared porous hollow silica nanoparticles were utilized as a carrier to investigate the controlled release kinetics of model substances. A drug injected into the inner core and fused onto the surfaces of the silica nanoparticles was released more gradually into a solution as compared to the general silica nanoparticles, exhibiting a typical sustained release without any burst phenomena. The results showed that porous hollow silica nanoparticles have a prospective potential in controlled drug delivery systems. Aw et al. (2012) also applied porous hollow silica as a biocarrier of drug delivery systems of indomethacin (IMC) as a model of a slightly water-soluble drug. The effectiveness of porous hollow silica as an oral-drug delivery system showed a high load capacity of drugs and sustained drug release over a long period. These natural materials based on silica can be successfully utilized as a biocarrier for both oral and implant drug delivery systems.

Except for silica, metal-organic frameworks (MOFs), which are hybrid materials formed by bottom-up approaches such as the self-assembly of polydentate bridging ligands and metal-connecting points, have been gathering attention as new drug delivery systems (Rocca et al., 2011). The MOFs have been reduced in size to nanometer sizes, and the nanoscale MOFs were developed as biomedical applications because of several attractive advantages over conventional nanomedicines, including their chemical and structural diversity, intrinsic biodegradability, and high loading capacity. Nano MOFs have been employed to deliver anticancer drugs and other chemotherapeutics. Nano MOFs are attractive as potential materials for the accurately effective delivery to targeted cells or organs in vivo. Murugan and Krishnan (2018) focused renewed attention on mesoporous silica for the application of “on-demand” drug delivery because the conception of targeted and sustained delivery of therapeutically compounds has been oriented into a more effective and attractive approach of drug release. These drug delivery systems have been extensively examined for site-specific delivery of single and multiple therapeutic agents. Although various types of external stimuli have been widely examined to bring about triggered and sustained drug release from mesoporous silica, chemo-responsive systems provide more therapeutic effectiveness with minimal collateral damage commonly associated with external stimuli. Therefore, these systems have been interpreted as “on-demand” drug release in mesoporous silica carriers and could achieve different strategies in response to various types of chemical stimuli.

This review introduces several case studies for crystallization with mutual diffusion across liquid-liquid interfaces used in various applications. Crystallization at a liquid-liquid interface was developed to synthesize asymmetric particles and composite particles. This liquid-liquid interfacial crystallization was applied to various advanced processes, which enabled finding a new possibility for creating advanced functional materials.

2. Crystallization at liquid-liquid interface

Crystallization at liquid-liquid interfaces was proposed as an advanced particle synthesis technique in our previous works (Kadota et al., 2007a; 2007b). This technique is a production method used to precipitate solute particles at the interface in partially miscible liquids. As a representative example, emulsions prepared as templates in liquid-liquid dispersion systems have been expanded in the biomedical applications as tissue engineering materials and drug carriers (Wu and Ma, 2016). Several studies conducted by Ramsden (1903) and Pickering (1907) revealed another means of stabilizing droplets using solid particles without surfactants (Fujii and Murakami, 2008). Pickering emulsions can be widely employed in various fields such as food, biomedicine, fine chemical products, and cosmetics (Linke and Drusch, 2018). We developed a liquid-liquid interfacial crystallization using mutual
diffusion phenomena between an aqueous solution and an organic solvent that occurs at a liquid-liquid interface. The techniques could be applied to various fields such as chemical engineering, food industries, and pharmaceuticals (Mori et al., 2019b). For example, different kinds of asymmetric particles were prepared through interfacial crystallization, and the preparation of glycine particles with porous structures was successful (Tanaka M. et al., 2011). Recently, Janus particles have been a unique class of multifunctional particles that combine two dissimilar chemical or physical functionalities at their opposite sides as asymmetric particles (Agrawal G. and Agrawal R, 2019).

An inkjet nozzle was installed to crystallization at liquid-liquid interfaces, because there is a possibility that an inkjet nozzle can control the shape and morphology of particles by preparing uniform spherical droplets (Tamura et al., 2014). The inkjet technique has garnered significant attention for universal particle production (Böhmer et al., 2006). Since the inkjet process can give narrow particle size distributions and control over particle morphology and precise dosage volume, this technique can be extended to manufacturing tablets for tailored medicine (Daly et al., 2015). Wijshoff (2010) fabricated polymer particles using an inkjet process. In another study, the size distribution and morphology of metal particles were successfully controlled (Böhmer et al., 2006). We applied the inkjet technique to liquid-liquid interfacial crystallization, and through an instillation, we present its effectiveness in controlling particle morphology and shape as compared with the batch process.

Glycine and alanine were selected as solutes, and 1-butanol and 2-butanone as solvents for crystallization at liquid-liquid interfaces. Alanine has no crystal polymorph, but glycine has three crystal polymorphs (Chen J. and Trout B.L., 2010). The organic solvents of 1-butanol or 2-butanone were set next to the liquid-liquid interface to contact with the aqueous solution. Fig. 1 depicts a schematic diagram of the experimental apparatus and an instillation of particle precipitation with an inkjet nozzle. In this apparatus, several droplets of the aqueous solution were discharged from the inkjet nozzle into the organic solvent with slight miscibility (Tanaka M. et al., 2011). Alanine or glycine immediately precipitated at the interface of droplets. For the batch process, particles of amino acids were obtained by mixing the aqueous solution with an organic solvent under fixed stirring. The emulsion including droplets of glycine or alanine solution in the organic solvent was stirred. The droplet size was estimated from SEM photographs. The crystal structure of both particles was measured through powder X-ray diffraction (XRD). The internal structure of both particles was also observed by SEM with cutting off particles using an ion milling apparatus.

Fig. 2 displays the relation between the mean particle size of alanine and the droplet size of instillation with the inkjet nozzle. The mean particle size of alanine was approximately 1.2-fold higher than aqueous droplet size in 1-butanol. Additionally, the mean particle size of glycine was larger than the corresponding droplet. The results suggest that the interface between the 1-butanol and aqueous solution expanded following their mutual diffusion during crystallization. The particle size of alanine was almost monodispersed as the coefficient of variation, and the control of the particle size was demonstrated to be feasible by controlling the droplet size using the inkjet nozzle.

Figs. 3 and 4 show SEM photographs of glycine and alanine particles produced by the batch process and by
instillation with an inkjet nozzle, respectively. In the batch process, most alanine particles were needle-like and most glycine particles were rod-like. In comparison with the batch process, glycine and alanine particles precipitated by instillation with an inkjet nozzle had a spherical shape. During this crystallization process by instillation with an inkjet nozzle, the interface part immediately reaches a supersaturated state once an aqueous solution contacts an organic solvent. Consequently, instillation process with an inkjet nozzle made spherical particles since nucleation and crystal growth of the solute material made progress along the spherical interface. Both particles prepared by the instillation exhibited more spherical and uniform particle size distribution than those by the batch process. The supersaturation ratio near the interface required a tiny gradient in the droplets due to the limitation to the crystallization area with the spherical interface of the droplets. Observation of the cross section of glycine and alanine particles by SEM emerged the presence of porous hollow structures. In the saturated aqueous solutions of alanine and glycine, the amount of glycine solute was greater than that of alanine solute in droplets. This difference in the amount of solute between alanine and glycine in saturated solutions may lead to hollow structures of alanine and porous structures of glycine.

The crystal structures of glycine particles prepared by instillation with the inkjet nozzle and by the batch process were evaluated by XRD. β-Glycine, which is an unstable polymorph, was identified in the instillation with inkjet nozzle, whereas the glycine particles prepared by the batch process were of the metastable α form (Matsumoto et al., 2019). In general, the α and β forms of glycine precipitate preferentially at lower and higher supersaturation ratios, respectively (Matsuoka 2005; Bouchard et al., 2008). Comparing the instillation to the batch process, the diffusion phenomenon within the strictly confined droplet generates regions of higher concentration at the interface. Consequently, several nuclei of glycine were homogeneously formed within the well-defined droplet by the inkjet nozzle. It is likely that the concentration of aqueous solution affects the size distribution and morphology of particles during interfacial crystallization (Fujii et al., 2007). According to Takiyama (2004), uniform crystals can be easily prepared from an unsaturated solution in anti-solvent or cooling crystallization. Concentration dependence of the amino acid solution on particle size, size distribution, and morphology was examined for the inkjet process. The size distribution of glycine and alanine particles moved toward larger sizes with an increase in concentration. The morphology of glycine prepared by instillation with an inkjet nozzle changed from spherical to ellipsoidal with an increase in glycine concentration. It is considered that the growth of glycine crystals proceeded along the minor and major axes depending on the crystal form.

The alanine particles were prepared by instillation using two types of anti-solvents: 1-butanol and 2-butanone. Here, the mutual solubility of 1-butanol and 2-butanone to water is different (Kitayama et al., 2009a). The surface morphology of alanine particles prepared using 2-butanone was coarser than that of particles prepared using 1-butanol. The difference in surface morphology derives from the mutual diffusion behavior following the organic solvent. Phase diagrams of water/1-butanol and /2-butanone were previously reported (Kitayama et al., 2009b; Kadota et al., 2013; Deki et al., 2016). In the solubility of 1-butanol in water, the amount of water diffusing into 1-butanol was much greater than that of 1-butanol diffusing into water at 25 °C. The diffusion of the solution from droplets could go ahead and performed with
maintaining the spherical shape. The converse phenomenon occurred in the usage of 2-butanone and water. The size of particles became larger than that of droplets because the diffusion of the organic solvent predominated in the mutual diffusion at the interface. This different behavior in mutual diffusion affected the particle formation with different shape and morphology.

3. Crystallization in a tube reactor

Another case study involved particle preparation of zirconia using a tube reactor (Kadota et al., 2016). Microchannels in tube reactors have attracted attention for preparing many types of particles since production in a single step is possible (Hattori et al., 2015). As part of an inexpensive and simplified approach, zirconia particles, which are widely used as a ceramic material with functional properties such as high mechanical strength, were prepared by neutralization reaction at the interface within a tube reactor. Micro reactors are generally applied to gas-liquid or liquid-liquid reactions (Sotowa et al., 2007; Asano et al., 2016). Many kinds of micro-reactors are utilized in various applications. A micro-channel reactor was used for the synthesis of monodispersed zirconium dioxide particles in a continuous flow process. Size distribution and morphology of zirconium dioxide particles were controlled by two types of coaxial tubular reactors.

Water and 1-butanol were prepared for applying interdiffusion in the liquid-liquid interface following their mutual solubility curves. Zirconium oxychloride was used as a starting ingredient. Ammonia solution and sorbitan monooleate were mixed into 1-butanol for neutralization with zirconium oxychloride. The flow rates of water and 1-butanol in the tube reactor with a single step were adjusted by syringe pumps connected to the microchannel. The crystal structure and morphology of zirconium dioxide particles were characterized by powder XRD and SEM, respectively. Most zirconium dioxide particles exhibited spherical shape with uniform size by the coaxial tubular reactor in the one-step process. In this synthesis, droplets in the tube reactor were stabilized by the addition of a surfactant. The cross section of the zirconium dioxide particle had a solid structure. Yamaguchi et al. (2004) revealed the flow dynamics and behavior of droplets in a micro-reactor through simulations. The simulation results demonstrated that the circulating flow occurred in the droplets. Suryo and Basaran (2006) also showed the circulating flow in droplets generated by the micro-reactor process. The particle size distribution of zirconium dioxide showed a monodispersed type. The mean particle diameter was nearly consistent with that of NaCl particles prepared by the coaxial tube reactor. This result indicated that the particle size strongly related to the size of droplets in the reactor. In addition, the selected solvents affected the particle size regardless of the species of solute substances. The design of liquid surface tension is necessary for further control of the particle size in the micro-reactor. The neutralization reaction between ammonia and zirconium oxychloride occurred in the liquid-liquid interface after ammonia was diffused into aqueous solutions from the solvent phase in the tube reactor. Concerning the morphology, the convected flow occurred in the droplet, resulting in solid zirconia particles being formed without a hollow structure.

A coaxial tube reactor of a two-step process was applied to synthesize zirconium dioxide particles with porous structures. One part involved the formation of droplets, and the other part involved the neutralization reaction in the liquid-liquid interface of the droplets. Schematic diagram of the experimental apparatus with the coaxial tubular reactor is shown in Fig. 5. The two-step process connected to reactors X and Y. Zirconium oxychloride solution was provided from the A side, 1-butanol that included sorbitan monooleate was supplied from the B side, and 1-butanol including ammonia solution was supplied from the C side. Most zirconia particles synthesized by the micro tube reactor in both the one- and two-step processes displayed a uniform size and spherical shape. SEM images of the cross section of the zirconia particles in the two-step process revealed their porous and hollow structure, resulting in the formation of zirconium dioxide particles along the spherical interface.


We introduced the synthesis of organic-organic composite particles by using an ultrasonic spray nozzle in the
interfacial crystallization. Glycine and starch were selected as model substances for the process (Gonda et al., 2015). Glycine and starch are commonly used as a model drug for pharmaceutical products and as an excipient, respectively. The composite particles prepared in the ultrasonic spray process were compared with those in a conventional anti-solvent crystallization process. The effect of using an ultrasonic spray nozzle on the polymorphism of glycine was also studied because the polymorphism had affected the particle properties, particularly its solubility.

The droplets from the aqueous glycine solution with starch particles were ejected from the ultrasonic spray nozzle into 1-butanol, which are slightly miscible with water. Ultrasonic atomization crystallization can be controlled by vibrating the spray nozzle with the ultrasonic oscillator. The contact or the operation time between 1-butanol and aqueous solution on the starch particles affects particle properties such as morphology and particle size distribution because the supersaturated ratio increases at the interface between aqueous solution and organic solvent (Kadota et al., 2007c).

In an analysis of SEM photographs, the composite particles produced with 1-butanol were spherical as shown in Fig. 6(a) and consisted of a starch core and glycine shell. Fig. 6(b) is a SEM photograph of a cross section of the composite particles. The cross section of the particles confirmed the appearance of coating particles or the core-shell structures of starch particles covered with fine glycine crystals. By contrast, composite particles of starch and glycine crystals produced by anti-solvent crystallization showed non-spherical particles with a wide particle size distribution. Moreover, many needle-like glycine crystals had already precipitated. From the comparison of results between ultrasonic atomizing crystallization and the anti-solvent method, we demonstrated that the production of the core-shell structure in the precipitation space was limited during liquid-liquid interfacial crystallization, as shown in Fig. 7. In addition, ultrasonic irradiation particularly affected the mean crystal size and size distribution of coating crystals. Consequently, the coating efficiency of fine crystals on starch would be affected.

Many studies on the effect of ultrasonic irradiation on crystal size have been studied (Kurotani et al., 2009; Kurotani and Hirasa, 2010; Guo et al., 2005; Hatkar and Gogate, 2012; Stelzer et al., 2013). Kurotani et al. (2009) investigated the relation between the ultrasonic irradiation and the generation of the primary nucleation of amino acids in supersaturated solutions. They succeeded in obtaining the demanded crystal size of products by optimally adjusting the conditions of ultrasonic irradiation and supersaturation. Furthermore, Yoshizawa (2004) classified microparticles into three structures from morphological control.

We reported the effect of operation time on the particle morphology by liquid-liquid interfacial crystallization (Kadota et al., 2007b), and succeeded in controlling the crystal growth rate and crystal shape by changing the operation time. The effect of operation time on the particle morphology during ultrasonic irradiation was examined under a constant glycine solution. The coating thickness of starch particles was calculated from the size difference between coated and bare particles. The shell thickness was independent of the operation time after several minutes. This was because nucleation was promoted by the effect of ultrasonic irradiation for a short time (Miyasaka et al., 2006). Ultrasonic irradiation enabled the fine crystals to enhance crystal generation in the initial stage of nucleation.

XRD patterns of the composite particles by the change in the glycine solution concentration were measured. Both α- and β-glycine crystals were coexistent on starch particles at lower glycine solution concentrations. However, only β-glycine crystals were covered on the starch particles at higher glycine solution concentrations. This phenomenon can be explained by the Ostwald step rule (Kitamura 1989; 2004). Initially, we investigated the variation of glycine polymorphism without starch particles because of clarifying the polymorphic transformation of glycine crystals on starch particles. XRD patterns of

![Fig. 6 SEM photographs of composite particles of starch with glycine prepared by ultrasonic spray nozzle: (a) composite particles; (b) cross section of composite particle framed by dot-line is the starch of the core particle. Reprinted with permission from Ref. (Gonda et al., 2015). Copyright: (2015) Elsevier.](image-url)

![Fig. 7 Schematic of the composite particle. Guest particles on the core particles precipitated through a liquid-liquid interfacial crystallization.](image-url)
Some research concerning IMC was previously investigated (Hattori et al., 2015). In the process, inorganic-organic composite particles precipitated at the liquid-liquid interface by individually feeding two different solute materials from 2-butanone and the aqueous solutions. The ability of composites strongly depends on the difference in precipitation rate between two solutes and is directly related to controlling the composite particle structures. NaCl has a relatively higher precipitation rate. Therefore, we selected IMC with a low precipitation rate into 2-butanone. IMC exhibiting analgesic activity is a non-steroidal anti-inflammatory. Some research concerning IMC was previously investigated to improve its poor solubility in water (Zhang et al., 1981).

The experimental apparatus for the coaxial tube reactor used in this process is shown in Fig. 8. The flow rate in the tube reactor was adjusted using a micro-syringe pump system. Water was run through the inner tube, and the organic phase flowed through the outer tube. As a preliminary experiment, the flow rate was varied to observe and comprehend flow patterns in the tube reactor. A previous study showed that when flow patterns form in a micro-reactor, the critical factors are the inertial force and the interfacial tension (Zhao et al., 2006). We used the Weber number for expressing flow patterns, and precipitated particles were observed by SEM. The quantitative amount of IMC was measured by Ultraviolet-visible (UV) spectroscopy.

Three types of flows (parallel, plug, and dispersed) were observed by flow visualization in the tube reactor. Dispersed flow consisted of water droplets suspended in 2-butanol that formed a spherical shape. The interfacial tension of water and the inertial force of 2-butanol were dominant in the dispersed flow with a high flow rate of 2-butanol. We produced NaCl crystals using the coaxial tube reactor by parallel, plug, and dispersed flow formed from the aqueous solution and 2-butanol. Precipitated NaCl crystals were cubic with a hollow dispersed flow. Channel blockages occurred in the parallel flow and were a major problem for continuous operations. The parallel flow was not appropriate for liquid-liquid interfacial crystallization using the tube reactor. The other two flows did not show any blockages.

We calculated the nucleation and crystal growth rates of precipitated crystals by the mass balance and number of crystals to clarify the behavior of crystal nucleation and growth in the tube reactor. The calculation results show that the crystal nucleation rate dramatically decreased at a residence time in the tube reactor. The crystallization growth rate moderately increased with increasing residence time and gradually decreased thereafter. These results correspond to the change in the degree of supersaturation. When NaCl solution reached a high supersaturated ratio or an unstable state, several nuclei of NaCl were generated in a short period of time. After nuclei were generated, NaCl concentration rapidly decreased and the solution reached a meta-stable state for a limited number of NaCl solutes in the droplet. This suggests that this crystallizer helped to control the particle shape with a narrow distribution by the residence time.

Crystallization at the interface of the NaCl aqueous and
IMC organic solutions was conducted in the tube reactor. Then, it had to facilitate nucleation for the crystals of IMC because the precipitation rate of IMC was very slow. Some researchers have reported that ultrasonic irradiation is effective at enhancing nucleation (Kudo and Takiyama, 2012; Guo et al., 2005; Kurotani et al., 2009; Miyasaka et al., 2006). The precipitation of IMC by ultrasonic irradiation to the liquid-liquid interface was examined. From the results of the crystallization of NaCl and IMC in separate operations, we expected that precipitation of composite particles consisting of NaCl and IMC would occur. The precipitation of NaCl/IMC composite particles in the dispersed flow was examined and composite particles were obtained. The obtained particles had a spherical shape and were aggregated particles consisting of many NaCl primary crystals. SEM photos revealed that IMC precipitated only on the surface of the aggregated NaCl particles. The aggregated composite particles of NaCl/IMC had a near mono-dispersion size distribution. We can propose that the precipitation mechanism of the composite particles in the dispersed flow can be expressed as shown in Fig. 9. The precipitation of IMC dominantly occurred on the surface of NaCl from the kinetic crystallization parameters (Mersmann, 1998; Kawashima et al., 2002).

NaCl crystals were first precipitated at the interface of 2-butane and the aqueous solutions and agglomerated during the flow of the droplet. Second, the droplet transferred to the area with ultrasonic irradiation, and IMC crystals were precipitated on the aggregated NaCl particle surface under ultrasonic irradiation. Then, NaCl/IMC composite particles were formed. This process in a dispersed flow can realize the fabrication of composite particles in one path continuously.

6. Preparation of a Pd-supporting TiO₂ catalyst using the inside surface

Capsulation is a basic technique for adding functions to particles (Kameta, 2014; Mori et al., 2019a). We introduced the synthesis of hollow titanium dioxide particles by using the inkjet process and showed the functionalization by charging Pd particles on the inside surface (Tanaka T. et al., 2016). We prepared the titania particles during the liquid-liquid interfacial sol-gel process with an inkjet nozzle and made an evaluation of the photocatalytic activity of the composite titania particles (Kadota et al., 2014).

Titanium tetraisopropoxide (TTIP) and hexane were used as a starting precursor of preparing titania particles in the sol-gel process and as an organic solvent to create the liquid-liquid interface with water, respectively. Acetonitrile was selected to vary the reaction rate of water because of being miscible with water but unfavorable for hexane. The aqueous solution was fed from the inkjet nozzle into the TTIP solution by controlling 1000 drops per second for 1 hour. The precipitated titania particles were a porous and hollow structure. For comparison of particle properties by inkjet nozzle, titania particles were also synthesized by using a pipette.

A photodeposition process of palladium on the porous hollow titania particles was performed (Ismail et al., 2013; Maicu et al., 2011; Camposeco et al., 2014). Porous hollow titania particles were added to an aqueous solution that included ethanol, and ultrasound was irradiated toward the suspension. Then, a palladium chloride solution was added to the suspension. The palladium chloride solution was charged into the particles under a low pressure to support palladium on the inner portion of the porous hollow titania particles. The palladium precipitated in the porous hollow titania particles. The suspension was irradiated with a black light in the dark, resulting in that palladium was supported on the titania hollow particles in a reduction of the number of palladium ions by the photocatalytic effect of titania. Prior to the examination of its photocatalytic effect, we examined the titania particle properties such as inner structure and pore characteristics. The element mapping state of Pd on the titania particles was evaluated by using an energy dispersive X-ray (EDX) analyzer. It was connected to a field emission type scanning electron microscope (FE-SEM). The photocatalytic performance between Pd supported on titania particles and non-supported titania particles was compared by evaluating the photocatalytic degradation of methylene blue solution (Nuno et al., 2015). Here, crystal structures of titania had three distinct polymorphisms (anatase, rutile, and brookite) and the photocatalytic activities were very sensitive to the crystal structures (Wen et al., 2015; Koelsch et al., 2004). The titania structure was controlled through the calcination of the particles.

The morphology and appearance of the titania particles prepared with and without the inkjet process were observed. Most titania particles prepared by the normal batch process without inkjet nozzle were irregular-shaped particles, whereas most of those prepared with the inkjet process displayed spherical particles with uniform size distribution. According to the observation of cross section, titania particles had porous hollow structures,
indicating that the crystal growth of titania particles occurred along the spherical interface. As described in section 4, the crystal growth of particles progressed along the interfacial droplet. This growth behavior of particles indicates the specific phenomena in liquid-liquid interfacial crystallization. Additionally, the particle size distribution of the titania prepared by the inkjet process was strictly narrower than that of the titania prepared by the batch process. The typical pore size distribution of titania particles prepared by the inkjet process was exhibited, whereas there were no peaks of the pore size distribution of titania particles prepared by the batch process.

The use of Pd supported on the surface of the porous hollow titania particles inside was expected to enhance the photocatalytic performance of titania. We compared the photocatalytic performances between the titania particles prepared by the non-inkjet and inkjet processes. Irrespective of preparing methods, the concentration of methylene blue gently decreased with increasing the irradiation time of ultraviolet-C (UV-C). In comparison of degradation rate, the titania particles synthesized by the inkjet process showed a slightly effective photocatalytic degradation than those by the non-inkjet process. This is because the photocatalytic activity of the titania particles by the inkjet process was advanced by increasing the specific surface area during photocatalytic degradation. This result could be supported by the specific surface area evaluated by BET.

Palladium element examination using EDX indicated Pd particles adhered on the inner surface of the hollow titania particles. The insertion of palladium onto the inner surfaces required the transmission of UV light to make a photocatalytic reduction of palladium chloride salt inside the hollow particle. Although the transmittances of titania generally show low values at wavelengths in the region of ultraviolet light (Chen X. et al., 2011), UV light can be transmitted through the titania shells with reduction of the electronic excitations. A previous study found that transmission through ultrathin films of anatase-type titania rapidly increased for ultraviolet light wavelengths of more than 350 nm (Rezaazadeh et al., 2015). In this study, titania particles by the inkjet process hardly showed any excited electrons because of having amorphous structures (Piccinini et al., 2013). UV light with 365-nm wavelength was irradiated on the porous titania particles relatively for the long time, and UV light was subsequently transmitted through the shell to the inner surface of the porous hollow titania particles with the reduction in electronic excitation. Then, the palladium could be supported on the inner surface of the titania particles.

Fig. 10 shows the degradation behavior of methylene blue with the Pd-supporting titania particles. The concentration of methylene blue in the Pd-supporting titania particles gently decreased with increasing of UVC irradiation time, whereas the concentration of methylene blue in the non-supported particles was an almost constant. The Pd-supporting titania particles showed a faster rate of photocatalytic degradation than the non-supported titania particles. The results indicated that the photocatalytic activity was improved by support of palladium to the titania particles, whereas the non-supported particles did not exhibit any photocatalytic activity. Camposeco et al. (2014) previously investigated that the photocatalytic activity of titania was enhanced by adding support palladium particles on titania with a photodeposition method. The palladium was supported onto the titania particles with an amorphous structure which electrons are hardly excited under solar irradiation. Fig. 11 shows that the porous hollow titania particles supported by palladium on the outer and inner surfaces exhibited a faster rate of photocatalytic degradation than that for the palladium-supported titania particles prepared by the non-inkjet process. The result was attributed to the increase of the specific surface area. Importantly, the synthesis of the titania particles with a high specific surface area was needed even when the palladium was supported onto the titania particles. We have succeeded in synthesizing the Pd-supported titania catalyst using the sol-gel process with the inkjet nozzle, resulting in the improvement of the photocatalytic activity of titania particles supported by palladium on the inner and outer surface of titania hollow particles.

7. Release properties of vitamins from TiO₂ porous hollow particles

Another example of functionalization by charging vitamins into the hollow particles was profiled (Tominaga et al., 2018, 2019). Titania particles with a porous hollow structure were prepared using the interfacial sol-gel processing preparation (Kadota et al. 2014) as described in the previous section. L-ascorbic acid encapsulated inside the porous hollow particles of titania by using two methods. The first
method was immersion preparation. Titania particles were added to the L-ascorbic acid aqueous solution. The supernatant solution was taken and dried in a desiccator until completely dry. The second method was the preparation by feed of a discharged solution containing L-ascorbic acid from the inkjet nozzle.

In vitro release study of L-ascorbic acid from the titania particles was conducted by using a dialysis bag method (Wang et al., 2008; Hanson 1982; Toomari and Namazi, 2016; Lasoń et al., 2016; Huang et al., 2017; Stebbins et al., 2017; Wei et al., 2010; Tanabe et al., 1988) in phosphate buffer saline as release media. A photostability test was conducted on the sample to investigate whether the effect of inhibiting degradation of L-ascorbic acid could be obtained by encapsulating L-ascorbic acid into the titania hollow particles. After irradiating UV, we conducted the same release test using the same amount of L-ascorbic acid as the encapsulated amount.

XRD analysis was performed on the obtained samples to confirm the crystal structural change by calcination treatments. From the XRD patterns, the samples without calcination were in an amorphous state, and those with calcination at 900 °C for 6 h were transferred to a rutile structure. The shape of titania particles was maintained in a uniform spherical shape even after the calcination treatment and encapsulation operations.

The cross sections of the samples and element mapping of the inner surface were evaluated using SEM and EDX, respectively. According to EDX evaluation, the samples derived from the encapsulating operation of L-ascorbic acid were detected. The results of element mapping revealed that L-ascorbic acid adhered to the inner wall surface of titania particles when prepared by this process.

The release profile of L-ascorbic acid from the titania particles was evaluated by using the UV-vis spectrophotometry. A peak of UV detection was observed within the absorption wavelength region from 244 nm to 265 nm (Liao et al., 2001). From the UV data, we found that L-ascorbic acid can be encapsulated using the immersion method. However, no peaks were observed for some samples in the absorption wavelength region of L-ascorbic acid. This causes the oxidation of L-ascorbic acid and the production of dehydroascorbic acid during the preparation of titania particles. The comparison of photostability results between pure L-ascorbic acid and encapsulated samples are shown in Fig. 12. The release rate of L-ascorbic acid reached approximately 94 % within 4 h and maintained a release rate of 90 % or more for a long time. However, pure L-ascorbic acid was completely released in 2 h. Accordingly, the release rate at that time was approximately 77 %. Therefore, it is considered that the remaining ~23 % was degraded by UV spectroscopy. Based on these circumstances, the degradation of L-ascorbic acid could be inhibited by encapsulation in the titania porous hollow particles.

8. Conclusion

Particle modification for functionalization and improved powder handling is a critical technique in powder technology. It can be realized by the sophisticated construction of composite structures in a wide range from nano- to micron-scale. In this study, we introduced the fabrication of composite particles with liquid-liquid interfaces and heterogeneous nucleation. The control of material transfer at liquid-liquid, liquid-solid, and solid-solid was a major factor in the production of complicated composite structures.

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