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Microparticles and Microcapsules from the Solvent Extraction of Deep Eutectic Solvent-Based Emulsion

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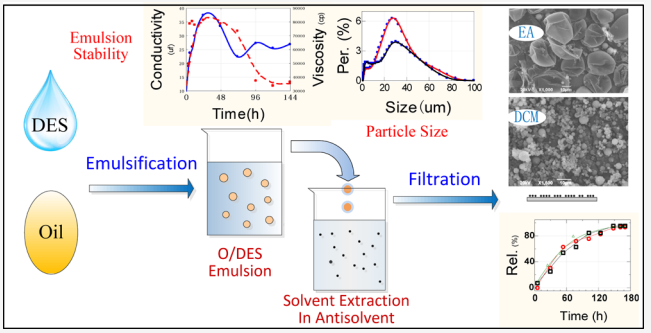
ABSTRACT: The microparticles of poly(lactic-*co*-glycolic acid) (PLGA) and poly(methyl methacrylate) (PMMA) and microcapsules of ibuprofen-PLGA, ibuprofen-polylactic acid, and ibuprofen-PMMA were successfully prepared using the solvent extraction of oil-in-deep eutectic solvent (O/DES) emulsions with dichloromethane or ethyl acetate as the solvent of the oil phase, [ChCl] [DL-malic acid] or [ChCl] [malonic acid] as the DES, and water, 1 wt % poly(vinyl alcohol) solution in water, or ethanol as the antisolvent. The morphologies of the product microparticles and microcapsules were characterized by scanning electron microscopy and found to be dependent on the solvent of the oil phase in the O/DES emulsions rather than the other surfactants, which was essentially the outcome of interplay between polymer solution phase separation and polymer chain mobility. The encapsulation efficiencies and drug loading efficiencies of the microcapsules were determined experimentally in the ranges of 14.5−16.4% and 87.1−98.9%, respectively. The in vitro test confirmed the slow release characteristics of the product microcapsules. Additionally, the information on the miscibility of various organic solvents with DES was collected and presented as fundamental information for the formation of O/DES emulsions. The stability of O/DES emulsions was also monitored by measuring the variations of viscosity and electrical conductivity with time of the emulsion, and the results showed that the stability could be as long as 72 h. Compared to the traditional methods such as solvent evaporation of O/W emulsion and solvent extraction of O/O emulsion, the application of solvent extraction of O/DES emulsion could provide a surfactant-free route and reduce the use of harmful organic solvents, respectively.



1. INTRODUCTION

The emulsion-based methods are of great importance in preparing both the polymeric microparticles and polymer-coated microcapsules including the solvent evaporation,[1−3] solvent extraction,[4,5] and their modifications,[6] which have been extensively used in pharmaceutical industry, flavor industry, pesticide industry, and so on.[7,8] As shown in Figure 1, both the solvent evaporation and solvent extraction of emulsion could be roughly divided into two stages: (1) formation of emulsion and (2) removal of solvent. The first stage determined the size of the polymer solution droplet, and thus the size of product polymer microparticles during the solvent removal of the polymer solution droplet decided the shape of the microparticles, which could also be applicable for spray drying, electrospraying, and so on.[9,10] The removal of solvent could be evaporation or extraction during which the surface shrinking of polymer solution droplets took place and the polymer concentration increased. After the polymer concentration reached the phase boundary, the solid−liquid (S-L) or liquid−liquid (L-L) and solid−liquid phase separation occurred to form the polymer particles. However, the practical processes were much more complicated since the mass transfer and heat transfer between the droplets and environment happened simultaneously. The heat transfer would lead to a temperature gradient along the radius of each droplet and thus result in convection flow in the droplet. It was extremely difficult to predict the morphology of the product microparticles. Recently, some researchers made simplifications and adopted the Peclet number, the ratio of the solvent removal rate to polymer diffusion coefficient, to evaluate the interplay of phase separation with polymer chain mobility so that to predict the morphology of product particles in spray drying and electrospraying.[11]

Recently, the deep eutectic solvent (DES) proposed by Abbott and his co-workers[12] as a novel green solvent has been widely used in reaction,[13] microextraction,[14,15] material processing,[16] and electrochemical applications[17] due to its characters of low vapor pressure, biodegradability, low cost,

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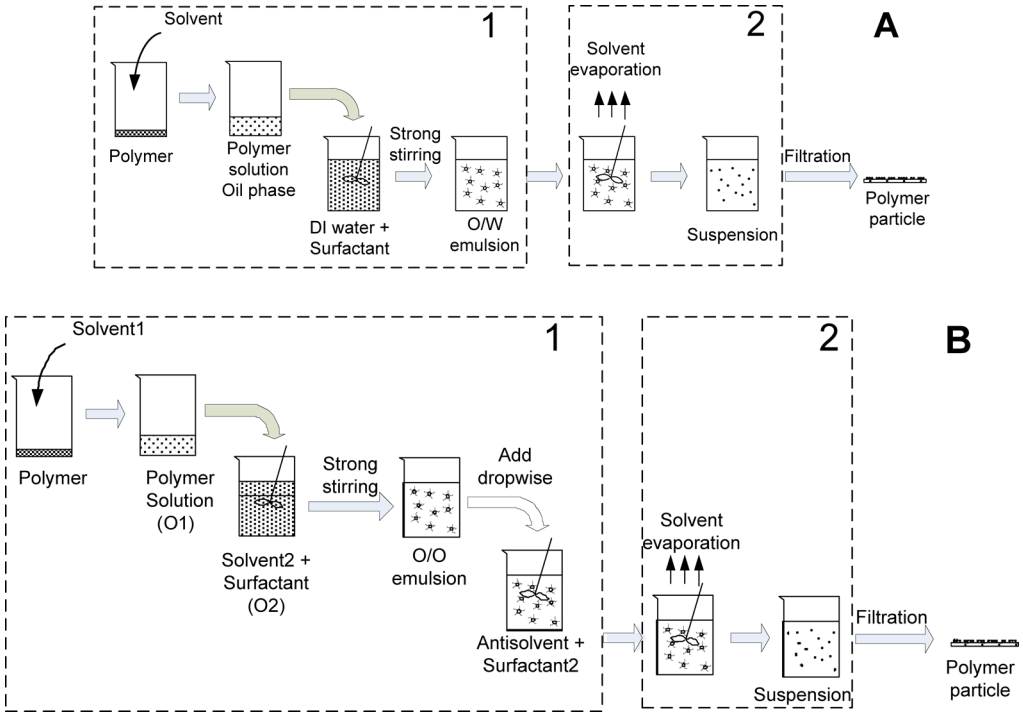

Figure 1. (A) Solvent extraction method and (B) solvent evaporation method of emulsion to prepare polymeric microparticles.

and sustainability. Based on its miscibility with organic solvents, Pal and co-workers proposed the concept of DES-based emulsion and prepared the cyclohexane-in-DES microemulsion of [ChCl] [urea] with sodium dodecyl sulfate as the surfactant.[18] The DES-related emulsions, especially the oil-in-DES (O/DES) emulsions with polymer solution as the dispersed oil phase, could be used to prepare polymeric microparticles and microcapsules. The relatively high viscosity of the DES that resulted from the hydrogen-bond effect could be a drawback of the solvent evaporation of O/DES emulsion; however, it could be helpful to increase the stability of emulsion and thus provide an opportunity for a surfactant-free solvent extraction method. Meanwhile, the replacements of the water phase and continuous oil phase with the DES in the O/W and O/O emulsions could offer an anhydrous method and avoid or reduce the use of harmful organic solvents, respectively.

In this study, the feasibility of preparing microparticles and microcapsules with the solvent extraction of O/DES emulsion was testified by using poly(lactic-*co*-glycolic acid) (PLGA), polylactic acid (PLA), or poly(methyl methacrylate) (PMMA) as the model polymer, DCM or EA as the solvent of the oil phase, [ChCl] [malic acid] or [ChCl] [malonic acid] as the model DES, and ibuprofen as the model drug. The morphologies of product samples of PLGA and PLA microparticles and ibuprofen-PLA, ibuprofen-PLGA, and ibuprofen-PMMA microparticles were characterized by scanning electron microscopy (SEM) and dynamic light scattering (DLS). The encapsulation efficiency (EE) and drug loading efficiency (DLE) were determined experimentally, and the in vitro test was conducted to measure the release kinetics of the microcapsules. In addition, the information on miscibility of different DESs with organic solvents was collected and presented as a basis and guide to form the emulsions. The O/DES emulsion of 2.5 wt % PMMA and 0.5 wt % ibuprofen in EA/[ChCl] [DL-malic acid] was prepared, and its stability was characterized with measurements of viscosity and electrical conductivity with time.

2. EXPERIMENTAL SECTION

2.1. Chemicals and Reagents. The choline chloride (ChCl) (≥98.0%), DL-malic acid (>99.0%), malonic acid (≥98.0%), dichloromethane (DCM) (≥99.8%), ethyl acetate (EA) (≥99.8%), ethanol (≥99.8%), and PLA (M_w = 60 kDa, PDI = 2) were purchased from Sigma-Aldrich. PMMA samples (M_w = 80 kDa, PDI = 1.06) were obtained from Scientific Polymer Products, Inc., while 50:50 ester-terminated PLGA with an inherent viscosity of 1.15 dL/g was purchased from Lactel Absorbable Polymers Corp. All the chemicals and reagents were used without further purification.

2.2. Preparation of DES-Based Emulsion and Stability Characterization. The 2.5 wt % PLGA, PMMA, or PLA solutions in DCM and EA were prepared and used as the oil phase, while the DESs of [ChCl] [DL-malic acid] or [ChCl] [malonic acid] were prepared and used as the DES in the O/DES emulsions. Typically, 28.0 g of ChCl and 26.9 g of DL-malic acid were accurately weighed, well mixed, and put into a 100 mL screw bottle before it was placed in an oven at 393.15 K for 12 h to prepare the DES of ChCl/DL-malic acid with a molar ratio of 1:1.[12,19] The water content in the DES was measured and determined to be lower than 500 ppm using the titration method.[20] The O/DES emulsions were prepared by dispersing 5 g of the polymer solution into 50 g of the DES using a high-speed homogenizer (T25, IKA) with a speed rate of 8000 rpm and a homogenization time of 90 s.

The stability of the O/DES emulsions was monitored by measuring the variations of their viscosity (DV2T, Brookfield) and conductivity (76652-03, Ransburg) with time.

2.3. Preparation of Microparticles and Microcapsules. After approximately 55 g of the O/DES emulsion was added dropwise with a rate of 10 g/min into 500 g of the antisolvent of water, which was stirred at the rate of 200 rpm, the stirring

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Table 1. Miscibility of DES with an Organic Solvent[a]

solvent	ChCl/EG	$ZnCl_2$/EG	ChCl/PA	ChCl/glycerol	ChCl/MA	betaine/MA
DCM	◎	×	×	√	×	×
EA	×	×	◎ and ⊙	×	×	×
PA	√	√	× and ⊙	◎	×	×
DMF	× and ⊙	⊙	⊙	√ and ⊙	√	√ and ⊙
ACN	√	√	√	√	√	× and ⊙
ethanol	√	√	◎	√ and ⊙	√	√
n-hexane	×	×	×	×	◎	×
cyclohexane	×	×	×	× and ⊙	×	×
paraffin	×	×	×	◎	×	×
pyridine	√	√	√	◎ and ⊙	×	× and ⊙
ether	×	×	√	√	◎	×
MB	×	×	×	×	×	×
THF	×	×	√	⊙	×	× and ⊙

[a] √: soluble, ×: insoluble, ◎: partly soluble, ⊙: white solid precipitated; PA: propanedioic acid, MA: malic acid, DCM: dichloromethane, EA: ethyl acetate, DMF: *N*,*N*-dimethyl formamide, PA: pyruvic acid, ACN: acetonitrile, MB: methylbenzene, THF: tetrahydrofuran.

of the resultant solution was kept for 2 h to evaporate the solvent of the oil phase. After the evaporation, the suspension was filtered and washed with deionic water three times to obtain the microparticle sample, which was then stored in a vacuum for further characterizations. For some experiments, 1 wt % poly(vinyl alcohol) (PVA) was added into water as the surfactant. The similar procedure was used to prepare the microcapsule except that the ibuprofen was added and dissolved in the oil phase.

2.4. Characterizations of the Microparticles and Microcapsules. The morphology, particle size, and size distribution of the microparticles and microcapsules were characterized using a scanning electron microscope (JSM-6490LV, JEOL) and dynamic laser scattering (MS-2000, Malvern), respectively.

The encapsulation efficiency (EE) and drug loading efficiency (DLE) were measured by dissolving the microcapsules in THF and determining the concentration of ibuprofen with a UV−vis spectrophotometer (CARY 5000, Agilent).[21] The in vitro test of the ibuprofen microcapsules was carried out to obtain their release kinetics.[22] Typically, approximately 0.2 g of microcapsules that was accurately weighed was added into a dialysis bag (M_w = 10000 g/mol) before being placed into 60 mL of pH 7.4 buffer solution and shaken at 37.5 °C. Samples of 4.0 mL were taken every 12 h, and the concentrations of ibuprofen were determined. After each sampling, the same volume of the fresh medium was added to maintain the volume.

3. RESULTS AND DISCUSSION

3.1. Miscibility of DES with an Organic Solvent. The miscibility of DES with an organic solvent was determined experimentally and is listed in Table 1. It was worth noting that the miscibility information above was based on organic solvent−DES systems with a mass ratio of 1:10.

3.2. Stability of DES-Based Emulsion. According to the information on miscibility of DES with organic solvents, which iss provided in Table 1, the O/DES emulsion of (2.5 wt % PMMA and 0.5 wt % ibuprofen in EA)/[ChCl] [DL-malic acid] (molar ratio of 1:1) with a mass ratio of 1:10 between the oil phase and DES phase was prepared. The variations of viscosity and electrical conductivity with time for the emulsion at 298 K were measured to characterize its stability, as shown in Figure 2. The stable terms of the emulsions were around 60 and 72 h

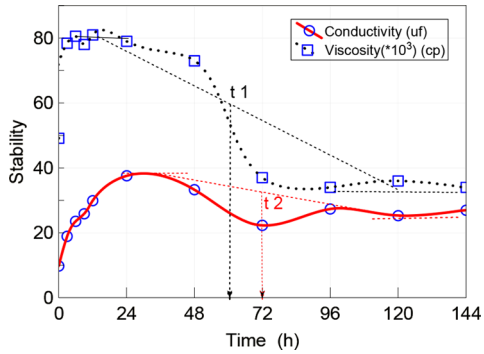

Figure 2. Variations of viscosity and conductivity with time for the O/DES emulsion of (2.5 wt % PMMA and 0.5 wt % ibuprofen in EA)/[ChCl] [DL-malic acid] (molar ratio of 1:1). The emulsion was prepared with a homogenization rate and time of 8000 rpm and 90 s, respectively.

according to the viscosity and conductivity, respectively. It should be pointed out that the stable terms of the emulsions were long enough for the preparation of microparticles and microcapsules using the solvent extraction method.

3.3. Microparticles. The polymer microparticles were prepared using the solvent extraction method by adding the O/DES emulsion into the antisolvent of water with PLGA or PMMA as the model polymer, DCM or EA as the solvent for the oil phase, [ChCl][malic acid] as the DES, and water as the antisolvent.

3.3.1. PLGA. Figure 3 shows the SEM photos of PLGA microparticles prepared with the solvent extraction of O/DES emulsion with solution of PLGA in DCM or EA as the oil phase, [ChCl] [malic acid] as the DES, and water with/without addition of 1 wt % PVA as the antisolvent.

As shown in Figure 3A, solid spherical PLGA particles with smooth surface were prepared from the solvent extraction of (PLGA/DCM)/[ChCl] [malic acid] emulsion in water. The diameter of the particles was in the range of 0.5−5 μm. When the O/DES emulsion was added into the antisolvent of water, the DES was readily extracted by water. Meanwhile, considering the solubility of DCM in water to be closed to 1 wt %,[23] which was larger than their proportion in the experiment, DCM was also fully extracted so that the PLGA particles were obtained. Although the fast solvent removal would lead to fast surface shrinking of the polymer solution

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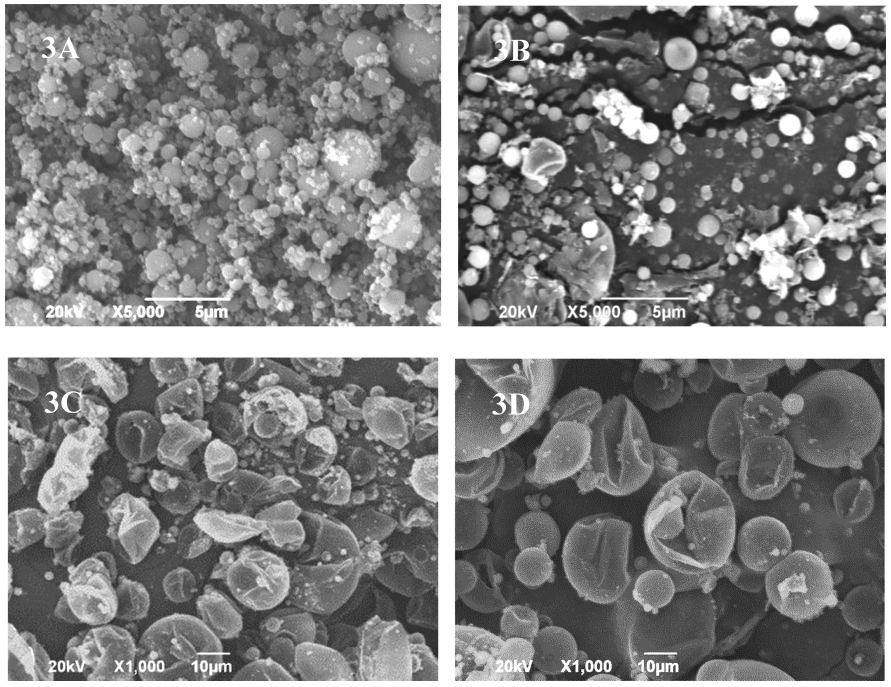

Figure 3. SEM photos of PLGA microparticles prepared from the solvent extraction of O/DES emulsion. The DES was [ChCl] [malic acid]. (A) PLGA solution in DCM as the oil phase and water as the antisolvent. (B) PLGA solution in DCM as the oil phase and 1 wt % PVA solution in water as the antisolvent. (C) PLGA solution in EA as the oil phase and water as the antisolvent; (D) PLGA solution in EA as the oil phase and 1 wt % PVA solution in water as the antisolvent. The mass ratio of the polymer solution to DES was 1:10. The O/DES emulsions were prepared with a homogenization rate and time of 8000 rpm and 90 s, respectively.

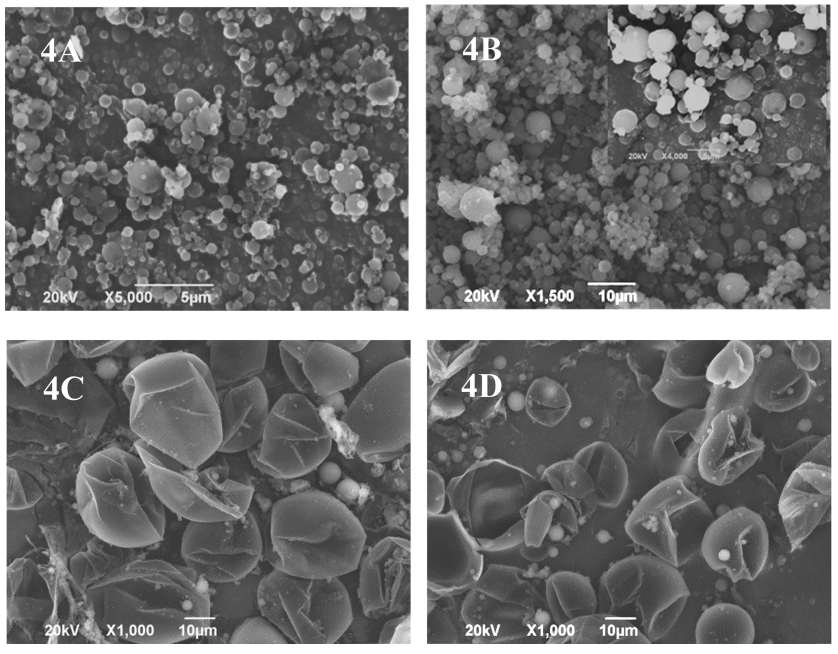

Figure 4. SEM photos of PMMA microparticles prepared from the solvent extraction of O/DES emulsion. The DES was [ChCl] [malic acid]. (A) PMMA solution in DCM as the oil phase and water as the antisolvent. (B) PMMA solution in DCM as the oil phase and 1 wt % PVA solution in water as the antisolvent. (C) PMMA solution in EA as the oil phase and water as the antisolvent. (D) PMMA solution in EA as the oil phase and 1 wt % PVA solution in water as the antisolvent. The mass ratio of polymer solution to DES was 1:10. The O/DES emulsions were prepared with a homogenization rate and time of 8000 rpm and 90 s, respectively.

droplet, the relatively high mobility of PLGA polymer chains in the solvent of DCM could prevent the local polymer concentration enhancement in the droplet. Therefore, the solid spherical PLGA particles were prepared. In addition, the extraction of DES and DCM into the aqueous phase was so fast that the addition of 1 wt % PVA into the antisolvent of water would not alter the morphology of the product particles, as shown in Figure 1B. When the solvent of the oil phase was changed from DCM to EA, the size of product PLGA particles was increased to the range of 10−50 μm (Figure 3C),

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suggesting the formation of PLGA/EA droplets with larger sizes than those of PLGA/DCM droplets using the same homogenization condition and time. Meanwhile, the morphology of the PLGA particles became bowel-like or irregularly shaped particles with wrinkled surface, which might be due to the much higher extraction rate of EA in water than that of DCM and/or the PLGA chain mobility in EA was lower than that in DCM. It was reported that the solubility of EA in water at 298 K was approximately 8%,[24] which was much higher than that of DCM. The fast removal of EA combined with the relatively low molecular mobility of the polymer chain would lead to an increase in the polymer concentration in the outer shell of the dispersed droplets. The solid−liquid phase separation could take place to form a "soft" polymer shell when the concentration exceeded the solid−liquid phase boundary. The EA and PLGA and EA solution that was trapped in the polymer shell would penetrate through the PLGA shell to form a whole so that the bowel-like particles were prepared. If the thickness of the shell was so small that its mechanical strength was weak, deformation of the particles would take place and wrinkles would be found on the surface of the particles. Similar to Figure 3B, for the EA system, the addition of 1 wt % PVA in the water phase did not change the morphology of the product polymer particles, as shown in Figure 3D. It was interesting to find out that the microparticles could be prepared even without the addition of a surfactant, which could be attributed to the high viscosity of the DES as a continuous phase. The addition of a surfactant into the DES phase could be more effective than that into the antisolvent water phase, and the molecular design was needed to identify the surfactant for DES phase, which required further study.

3.3.2. PMMA. The SEM photos of PMMA microparticles prepared with the solvent extraction of O/DES emulsion with solution of PLGA in DCM or EA as the oil phase, [ChCl][malic acid] as the DES, and water with/without addition of 1 wt % PVA as the antisolvent are shown in Figure 4. Similar to Figure 3, PMMA particles prepared from emulsions with EA as the solvent for the oil phase were larger than those with DCM. The shape of the latter particles was solid spherical particles with a smooth surface, while the former was bowel-like or irregularly shaped particles with wrinkles on the surface. The addition of the PVA surfactant in the antisolvent water did not change the morphology of the product PMMA particles.

Even though the antisolvent used above was water, it was worth noting that other anhydrous solvents such as ethanol could also be used as an antisolvent, which might provide an anhydrous route to prepare polymer microparticles or microcapsules compared to the solvent evaporation of O/W emulsion. Figure 5 shows the SEM photos of PMMA microparticles prepared from the solvent extraction of O/DES emulsion with a solution of 1.5 wt % PMMA in EA as the oil phase, ChCl/malic acid as the DES, and ethanol as the antisolvent.

3.4. Microcapsules. The microcapsules were prepared using the solvent extraction of O/DES emulsion with ibuprofen as a representative of pharmaceutical to be encapsulated and PLA, PLGA, or PMMA as the barrier material.

3.4.1. Particle Morphology. Figure 6 shows the SEM photos of the ibuprofen microcapsules using the solvent extraction of O/DES emulsions with 1 wt % PVA solution in water as the antisolvent. The conditions for preparing these microcapsules are listed in Table 2.

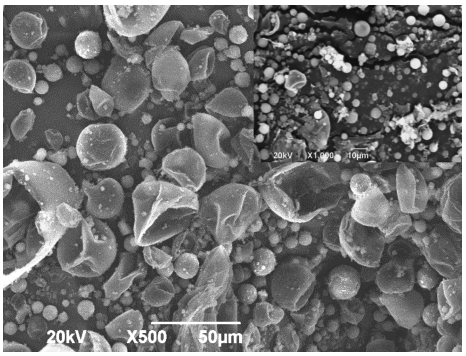

Figure 5. SEM photo of PMMA microparticles prepared from the solvent extraction of O/DES emulsion with a solution of 1.5 wt % PMMA in EA as the oil phase, ChCl/malic acid as the DES, and ethanol as the antisolvent.

As shown in Figure 6A, solid spherical ibuprofen-PLA microcapsules with a diameter less than 10 μm were prepared when DCM was used a solvent for the oil phase, which was similar to the PLA particles, as shown in Figures 3A,B and 4A,B. As shown in Figure 6B−E, when EA was used, the sizes of product ibuprofen microcapsules were getting much larger, and the shape shifted into bowl-like or irregularly shaped particles and wrinkles appeared on the surface regardless of the polymer and DES used, which was similar to the case of PLGA particles and PMMA particles, as shown in Figures 3C,D and 4C,D, respectively. In addition, the particle size distribution of the product microcapsules was measured using dynamic laser scattering (DLS), and the results for sample 6B and 6E were illustrated in Figure 6F. The particle sizes of the product suspensions were in the range of 20−40 μm, which was basically consistent with the microcapsule size shown in Figure 6B,E.

3.4.2. Encapsulation Efficiency (EE) and Drug Loading Efficiency (DLE). The encapsulation efficiency (EE) and drug loading efficiency (DLE) of the microcapsule samples of 6B, 6C, and 6E were determined experimentally and are listed in Table 2. The EEs were in the range of 14.5−16.5%, which might suggest that the amount of ibuprofen used were too much for the barrier polymers. The DLEs fell into the range of 87.1−98.9%, suggesting high loading of ibuprofen in the microcapsules.

3.4.3. In Vitro Test. The in vitro test of microcapsules for samples of 6B, 6C, and 6D was carried out, and the release kinetics of ibuprofen out of the microcapsules in buffer solution within 180 h is demonstrated in Figure 7. The three microcapsule samples showed close release kinetics, and the release term was extended to about 150 h.

4. CONCLUSIONS

The solvent extraction of O/DES emulsion has been successfully used to prepare PLGA and PMMA microparticles and ibuprofen-PLGA, ibuprofen-PLA, and ibuprofen-PMMA microcapsules. The replacements of the outer water phase in O/W emulsion and the outer oil phase in O/O emulsion with the DES phase provided an opportunity for a surfactant-free, anhydrous route and reduction in use of harmful organic solvents, respectively. The stable term of the O/DES emulsion was determined to be 60 and 72 h based on the measurements of viscosity and electrical conductivity, respectively. The solvent of the inner oil phase was found to be crucial in

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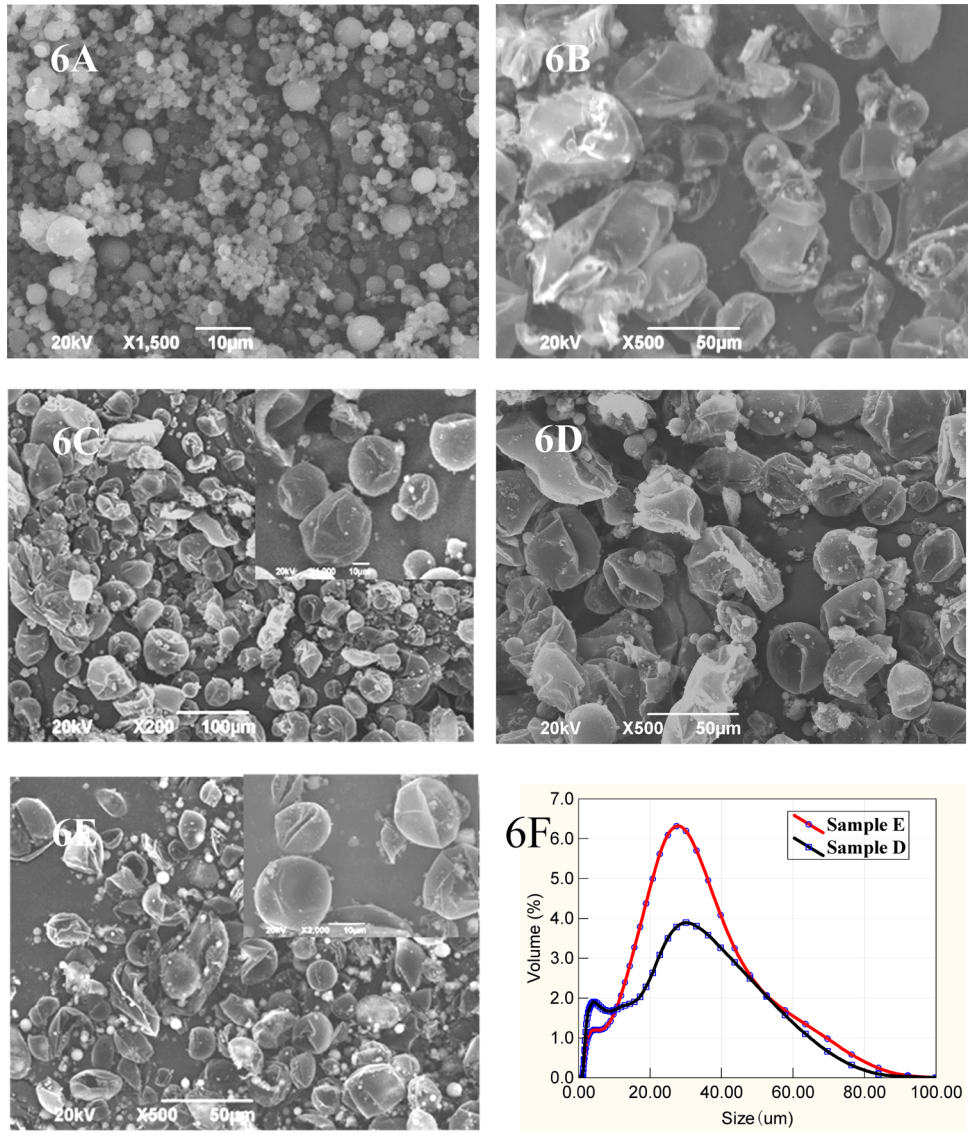

Figure 6. (A–E) SEM photos of ibuprofen microparticles prepared from the solvent extraction of O/DES emulsion with 0.5 wt % ibuprofen and 2.5 wt % polymer in the oil phase and 1 wt % PVA solution in water as the antisolvent. The mass ratio of polymer solution to DES was 1:10. The O/DES emulsions were prepared with a homogenization rate and time of 8000 rpm and 90 s, respectively.

Table 2. Conditions for Preparation of Microcapsules[a]

sample no	oil phase solvent	polymer	DES (molar ratio)	EE (%)	DLE (%)
6A	DCM	PLA	ChCl/malic acid (1:1)		
6B	EA	PLA	ChCl/malic acid (1:1)	16.5	98.9
6C	EA	PLGA	ChCl/malic acid (1:1)	14.5	87.1
6D	EA	PLA	ChCl/malonic acid (1:1)	16.4	98.2
6E	EA	PMMA	ChCl/malic acid (1:1)		

[a]The oil phase was a solution of 0.5 wt % ibuprofen and 2.5 wt % polymer in oil phase solvent. During the preparation of emulsion, the homogenization speed rate was 8000 rpm and homogenization time was 90 s.

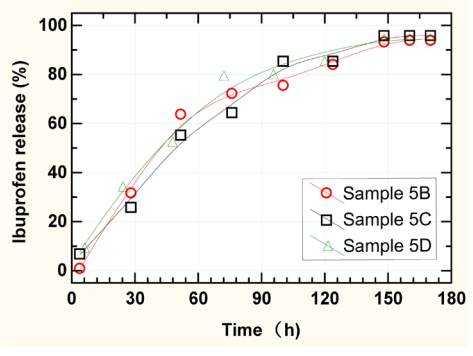

Figure 7. Release kinetics of the microcapsule samples.

determining the morphologies of the product microparticles and microcapsules. The solid spherical microparticles and microcapsules were prepared when DCM was used, while the bowel-like or irregularly shaped microparticles and microcapsules with wrinkles on their surfaces were obtained when EA was used. The EEs and DLEs of the microcapsules were in the ranges of 14.5–16.5% and 87.1–98.9%, respectively, while

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the in vitro test showed that the release terms were around 150 h.

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Notes

The authors declare no competing financial interest.

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