Pickering Emulsions and Antibubbles Stabilized by PLA/PLGA Nanoparticles

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INTRODUCTION

Microencapsulation is one of the most widely employed techniques for the protection of pharmaceuticals or food-grade ingredients against harsh environments. Among the several existing microencapsulation techniques, those relying on emulsions have become the most used ones in pharmaceutical, cosmetic, and food industries. Commonly, the stabilization of oil-in-water (O/W) emulsions can be achieved using low-molecular-weight molecules and/or polymeric surfactants. However, coalescence of emulsion droplets still occurs over long periods of time. Moreover, surfactants can have toxic effects on cells, which is detrimental in the above-mentioned applications. A promising alternative is the use of particles to stabilize emulsions. Recently, these so-called Pickering emulsions have gained much attention because they nearly stop coalescence and display low or negligible toxicity. The Pickering emulsion technique can effectively stabilize water-in-oil (W/O), O/W, or water-in-oil-in-water (W/O/W) emulsions depending on the physicochemical characteristics of the emulsifying particles. Many different types of micro- and nanoparticles (NPs) have proven to be good emulsifiers.

Particles made of poly(lactic acid) (PLA) or its copolymers with glycolic acid (PLGA) represent a class of Pickering emulsifiers that has been barely studied so far. Yet, these particles have several important advantages for potential applications. First, they are biocompatible, therewith having the potential to enable a wide range of medical and pharmaceutical applications of Pickering emulsions. Second, these particles offer environmental advantages in agrochemical or any other application that demands biodegradability after service. Third, these kinds of particles can present tunable physicochemical features and surface activity as a function of the employed synthetic route and monomer composition of polymers, as well as post-synthesis treatments. PLGA NPs have already been studied for the stabilization of oil-in-water emulsions. However, these particles were surface-modified using surfactants. Therefore, they may not possess low toxicity, which is one of the advantages of the use of Pickering stabilization over the use of surfactants. Also, there is limited information about the use of hydrophobic PLA NPs to stabilize water-in-oil Pickering emulsions and even less about water-in-oil-in-water emulsions. In this work, we report the synthesis...
of bare (not surface-modified) PLA and PLGA particles, focusing on characterization of the more hydrophobic PLA particles, and we investigate the formation of oil-in-water, water-in-oil, and water-in-oil-in-water emulsions stabilized by these particles. This approach for the production of Pickering (double) emulsions based on PLA/PLGA NPs has the advantage of not requiring potentially toxic additives (e.g., polymers or surfactants) and of allowing the control of the surface activity and wettability in different oil–water media.

Recently, a new method for the effective encapsulation and release of bioactive ingredients was proposed, which consists in the production of antibubbles based on Pickering emulsions. Antibubbles were first described as liquid droplets confined inside air bubbles in water (Figure 1A). The production of antibubbles in a controlled manner has been reported using surfactants. The latter adsorb at the inner and outer interfaces of antibubbles in a controlled manner has been reported using surfactants instead of surfactants. Recent studies have demonstrated that colloidal silica nanoparticles (Figure 1B) can stabilize antibubbles when introduced between the oil and water phases (A/B interface). This approach enables the production of antibubbles with a release mechanism triggered by temperature.

![Figure 1](https://example.com/figure1.jpg)

**Figure 1.** (A) Schematic picture and (B) optical micrograph of an antibubble stabilized by Pickering stabilization using PLA and PLGA nanoparticles.

## MATERIALS AND METHODS

**Reagents.** Lactide polymers, poly(lactic acid) (PLA) (Resomer R 202 H, 10–18 kDa), and poly(lactic-co-glycolic acid) PLGA (Resomer RG 502 H, 7–17 kDa) were supplied by Sigma-Aldrich, Germany. To prevent degradation, polymers were preserved in a closed bag at 6 °C. Acetone (99.5%, Macron Fine Chemicals, Germany), cyclohexane (ACS, 99+%, Alfa Aesar, Germany), maltodextrin (DE 13.0–17.0, Sigma-Aldrich), PBS (phosphate buffer solution tablet, Sigma-Aldrich, Switzerland), sodium azide (99.8%, Sigma-Aldrich, the Netherlands), calcine (C₂₆H₃₂N₃O₁₈, Mₑ = 622.53 g/mol, Sigma-Aldrich, Japan), and D₂O (99.9% D, Mₑ = 20.03 g/mol, Sigma-Aldrich, Canada) were purchased and used as received.

**Synthesis of PLA and PLGA Nanoparticles.** PLA and PLGA nanoparticles were synthesized by the anti-solvent technique (Figure S1). In a typical procedure, an acetone solution (10 g) containing 4 wt % polymer (PLA or PLGA) was prepared. The solution containing the polymer was poured into 20 g of MilliQ deionized water under magnetic stirring. This rapid mixing leads to spontaneous precipitation of polymers into nanoparticles due to anti-solvent diffusion. After precipitation, acetone was removed from nanoparticles using a rotary evaporator under reduced pressure at 37 °C, during 30 min. The degree of removal of acetone from the nanoparticle suspension was evaluated by 1H NMR spectroscopy, measured on a Varian Mercury Plus 400 MHz apparatus (Agilent, Santa Clara, CA) using D₂O as the solvent. After that, PLGA NPs were kept in a water solution at 6 °C and the PLA NP solution was frozen in liquid nitrogen and freeze-dried with a condenser temperature of −81 °C and a chamber pressure of 0.1 mbar during 48 h. The resulting dried PLA NPs were stored at 6 °C for further use and analysis. An additional thermal treatment was performed on PLA NPs inside an oven at 30 °C during 14 days to tune the NP wettability in organic solvents and the affinity for the aqueous phase. The temperature was chosen according to the onset point of the glass transition (Tg) for NPs as determined by differential scanning calorimetry (DSC) analysis (Figure S14). The effect of the thermal treatment was studied using contact angle measurements and Fourier transform infrared (FTIR) spectroscopy (Cary 630, Agilent Technologies). PLGA NPs were used without any further treatments since they perfectly emulsified oil-in-water emulsions, as required for this work (for more characterization information, see Table S1 and Figures S13, S18, and S19).

The size, polydispersity index (PDI), and ζ-potential (ZP) of NPs were determined by dynamic light scattering (DLS) experiments over five different measurements of each NP sample (in MilliQ water) using a Zetasizer 5000 instrument (Malvern Instruments, UK). The thermal history of NPs was analyzed by differential scanning calorimetry (DSC) performed on a PerkinElmer Pyris Diamond (Shelton, Connecticut) under the N₂ atmosphere. The samples were weighed (10–17 mg) in an aluminum pan, which was then sealed. Hereafter, the samples were heated from 20 to 100 °C and then cooled to 20 °C. Three heating–cooling cycles were performed at a rate of 10 °C/min. Transmission electron microscopy (TEM) was used to characterize the morphology of NPs. PLA NPs were loaded on copper grids, negatively stained with 2% ammonium molybdate and the images were recorded on a Philips CM12 transmission electron microscope operating at an accelerating voltage of 120 keV. Scanning electron microscopy (SEM) morphology analysis of PLA NPs was performed using a Regulus8230 cold field emission scanning electron microscopy (CFE-SEM) without metal coating and low voltage (0.1 to 1 kV) to avoid damaging the samples. Secondary electron and backscattered-type detectors were used to acquire the images.

The contact angle of water or cyclohexane in air on a layer of PLA NPs coated on carbon tapes was measured using a Theta Lite Optical Tensiometer (Attension, from Biolin Scientific, Gothenburg, Sweden), using the software OneAttension v3.2 using the Young–Laplace equation. The dried PLA NPs were placed directly on the carbon tape by pressing the tape on the NP powder repeatedly and gently removing the excess NPs using a brush until a homogeneous...
layer of nanoparticles was obtained (Figure S17). The equipment was set in sessile drop mode with 10 µL droplets of water or cyclohexane using a 100 µL syringe needle (Hamilton, Switzerland). Pictures of the droplets were captured with an ultrafast camera (10 FPS) immediately after the drop was deposited. The reported contact angle values are the average of three measurements for each sample.

**Nanoparticle-Stabilized W/O/W Emulsion.** The formation of W/O/W emulsions occurs in two steps. First, an aqueous solution containing 25% maltodextrin and 0.02% calcein was adjusted to pH 5.5 using minimum amounts of NaOH (0.01 M) and HCl (0.01 M) and monitored by pH meter (SevenGoTM pH meter, Mettler Toledo, the Netherlands). Calcein was chosen as a model drug due to its use as a labeling molecule and its easy monitoring by spectroscopy (UV–vis and fluorescence) in particle and emulsion-controlled release systems. 41,42 The aqueous solution was emulsified in cyclohexane containing 5% PLA nanoparticles using an Ultra Turrax at 17 krpm (IKA, T25, digital, Ultra Turrax) during 30 s aiming at a final 25/75% water-in-oil emulsion. Second, 20% of the resulting W/O emulsion was emulsified in an 80% water solution containing 25% maltodextrin and 2% PLGA nanoparticles using an Ultra Turrax at 4 krpm for 30 s. At the end of the process, a double emulsion was obtained. Next, the double emulsion was frozen in liquid nitrogen during 10 min and then freeze-dried at 0.1 mbar, −81 °C for 48 h. The characterization of W/O and W/O/W emulsions was carried out using a Leica optical microscope (microscopy systems, Type DM-LM, U90-250V, 50-60Hz, Germany).

**Formation and Analysis of Antibubbles.** Freeze-dried double emulsions were reconstituted in water to form antibubbles. The freeze-dried product (5 wt %) was suspended in a water solution containing 0.001 wt % sodium azide (to avoid bacterial spoiling) and 25 wt % MD (for osmotic equilibrium between the core of the antibubbles and the continuous phase). The stability of the antibubbles in suspension was monitored in time either at room temperature or at 37 °C.

### RESULTS AND DISCUSSION

**Synthesis of PLA and PLGA Nanoparticles.** PLA and PLGA polymeric nanoparticles were synthesized by the antisolvent technique (SI1). After the evaporation of acetone, the resulting wt % of NPs was calculated based on the initial weight of the polymer sample. A longer evaporation time led to larger degree of water removal and hence to a more hydrophilic, with a relatively large, negative ζ-potential and thus gives a stable dispersion in water. In a further step, PLA NP suspensions were freeze-dried to remove the water. This procedure was carried out to increase the hydrophobicity of NPs to allow their dispersion in organic solvents. The resulting PLA NPs were analyzed by SEM (Figure 3). SEM micrographs display NPs with size in the nanometer scale, in agreement with DLS and TEM results. However, a NP network was observed, probably due to the pressure of water crystals, which increased cohesive interactions between NPs during freezing and freeze-drying steps.

After freeze-drying, PLA NPs cannot be resuspended in water but are effectively suspended in an apolar solvent as cyclohexane (Figure 4). This suggests that freeze-drying increased the hydrophobicity of PLA NPs. It has been observed before that hysteresis effects take place when dispersing micro-/nanoparticles in fluids. 46 In our case, we attribute the hypothesized increase in hydrophobicity to the formation of the colloidal-gel NP network observed by SEM, which probably stems from strong cohesive interactions between terminal groups of PLA chains. 47,48

**Contact Angle Measurements of the PLA NP Surface.** Contact angle measurements of PLA NPs coated on the carbon tape were taken over time to monitor the change of hydrophobicity of NPs after the synthesis in water, freeze-drying, and thermal treatments (Figure 5). The carbon tape alone was used as the reference of the surface and displayed a contact angle average of 86°. The presence of PLA NPs without any treatment on the carbon tape led to a decrease of the contact angle to 67°, denoting their hydrophilic character after synthesis and evaporation. Interestingly, previous reports indicated that PLGA nanoparticles prepared by an antisolvent technique were hydrophilic, displaying a contact angle of 120° after drying during 15 h at 25 °C. 26 The difference may lie in the thermal treatment procedure and the fact that in the literature work, the polymer presented higher molecular weight (based on its inherent viscosity, 0.7–1.0 dL/g) and only 25% glycolic acid groups. Also, the polymer solution in acetonitrile was slowly added to the water phase, which could allow polymers to orient their hydrophilic groups away from water. A contact angle value between 0 and 90°, as in the case of untreated PLA NPs, means that the surface is wetted by water at the air–water interface (Figure 5B). Contrarily, in the presence of freeze-dried PLA NPs, the surface was very hydrophobic, as shown by the high contact angle of 123° (Figure 5C). Also, a thermal treatment was performed on the probably formed during the rotary evaporation of residual acetone from PLA NPs (Figure 2).

The antisolvent technique yielded NPs, which are hydrophilic, with a relatively large, negative ζ-potential and thus gives a stable dispersion in water. In a further step, PLA NP suspensions were freeze-dried to remove the water. This procedure was carried out to increase the hydrophobicity of NPs to allow their dispersion in organic solvents. The resulting PLA NPs were analyzed by SEM (Figure 3). SEM micrographs display NPs with size in the nanometer scale, in agreement with DLS and TEM results. However, a NP network was observed, probably due to the pressure of water crystals, which increased cohesive interactions between NPs during freezing and freeze-drying steps.

The PLA and PLGA nanoparticles have a homogeneous size distribution as denoted by the low PDI values (≈0.1), which implies monodisperse particles in water suspension (Figure S13). 43 TEM images (Figure 2) corroborated the particle size determined by the DLS analysis. TEM images also indicate the formation of aggregates of two or three nanoparticles, which

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**Table 1. DLS Analysis of PLA and PLGA NPs Synthesized by the Antisolvent Technique**

<table>
<thead>
<tr>
<th>Nanoparticles</th>
<th>Size (nm)</th>
<th>Polydispersity Index</th>
<th>ζ-Potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLA</td>
<td>232 ± 5</td>
<td>0.085 ± 0.007</td>
<td>−45 ± 3</td>
</tr>
<tr>
<td>PLGA</td>
<td>182 ± 2</td>
<td>0.095 ± 0.011</td>
<td>−48 ± 1</td>
</tr>
</tbody>
</table>

“The standard deviation was calculated after five measurements.”
PLA particles. This treatment decreased the contact angle to 105° (Figure 5D), possibly due to partial degradation of the PLA, which could increase the number of terminal groups and thus the hydrophilicity.46,49,50 The same trends in the hydrophobic behavior were observed by measuring the contact angle of cyclohexane on the freeze-dried PLA NPs (Figure 5E) and on the freeze-dried and thermally treated freeze-dried PLA NPs (Figure 5F).

**FTIR Analysis on PLA NP films.** FTIR spectroscopy is commonly used to characterize PLA.51,52 The spectra of the freeze-dried PLA NPs before and after the thermal treatment display characteristic peaks of PLA (Figure SI6). No major differences were observed for these peaks between the spectra of the various materials. The breadth of the band in the 600–725 cm\(^{-1}\) range (associated with the alkyl-ketone chains out-of-plane bending vibration) and the absence of a band at 920 cm\(^{-1}\) have been associated to disorder in the material and are thus an indication of the amorphous nature of our PLA.51,53

**Nanoparticle-Stabilized W/O/W Emulsion.** Surfactant-free micron-sized W/O/W systems stabilized by biodegradable lactide-based polymeric nanoparticles are attractive for biomedical, food, and pharma applications. Here, surfactant-free PLA and PLGA NPs were chosen as Pickering stabilizer colloidal interfacial layers for double emulsions. Thermally treated PLA NPs were chosen for the inner shell due to their hydrophobic character that effectively emulsifies W/O emulsions (Figure 6A). PLGA NPs were chosen for the outer shell due to their hydrophilic character and their ability to emulsify and stabilize O/W emulsions (Figure 7A). We prepared water-in-oil emulsions that consisted of an inner water phase comprising 25% maltodextrin and 0.02 wt % fluorescent dye (calcein). Calcein was used as a model drug molecule. The oil phase consisted of 5 wt % PLA NPs previously freeze-dried and thermally treated (Figures 5 and SI6). These nanoparticles were resuspended in cyclohexane at constant agitation during 15 min. To get the W/O emulsion, 25% of the inner water phase was added to the oil phase. The mix was then emulsified using Ultra Turrax (Figure 6A).

Remarkably, single W/O emulsions were only properly stabilized by thermally treated PLA nanoparticles. For comparison, Figure 6B shows the unsuccessful stabilization of a W/O emulsion using freeze-dried PLA NPs that did not undergo a thermal treatment afterward. We explain this by the fact that the latter NPs are poorly wetted by water and are very strongly wetted by cyclohexane (see Figure 5C,E). This means that at the water—cyclohexane interface, these particles reside almost completely in the cyclohexane phase, which means that...
the free energy of adhesion is low. It has been shown before that particles with a large contact angle at the water–oil interface are poor emulsifiers.

In Figure 6A, the size distribution of water droplets ranges between 10 and 15 μm, and the W/O emulsion is stable enough to be emulsified in the final continuous water phase containing PLGA NPs (Figure 7A). Notably, the resulting double emulsion rendered stable W/O/W droplets with a size between 50 and 100 μm that did not show coalescence or notable leakage of the encapsulated calcein (Figure 7B,C).

The produced double emulsions were freeze-dried to remove the oil and water phases to obtain antibubbles. SEM was used to observe the structure of the freeze-dried product (Figure 8). Figure 8A shows the result of freeze-drying of the double emulsion stabilized by PLA and PLGA NPs. It can be seen that freeze-drying converted the aqueous maltodextrin solutions into porous maltodextrin matrices. These porous structures of maltodextrin surround the spherical structures that were previously filled with oil and that are now filled with air.

Figure 5. (A–D) Contact angle measurements of water drops and (E, F) cyclohexane drops on PLA NPs supported on a carbon tape: (A) water on the carbon tape alone; (B) water on PLA NPs without freeze-drying; (C) water on freeze-dried PLA NPs; (D) water on freeze-dried and thermally treated (14 days at 30 °C) PLA NPs; (E) cyclohexane on freeze-dried PLA NPs; and (F) cyclohexane on freeze-dried and thermally treated (14 days at 30 °C) PLA NPs. Calculation of the contact angle was done following the Young–Laplace equation.

Figure 6. Optical micrographs of (A) W/O emulsion stabilized using freeze-dried and thermally treated PLA NPs and (B) W/O emulsion stabilized using PLA NPs without the thermal treatment after the freeze-drying step. Bars represent 100 μm.
Likewise, the inner W/O emulsion is now converted into cores inside these air bubbles. The SEM picture also shows the organization of NPs after freeze-drying at the interfaces of the freeze-dried W/O inner emulsion (Figure 8B). PLA NPs merged into a network at the inner interface, probably as a result of stress on the particles during freezing and drying, e.g.,

Figure 7. W/O/W double emulsion stabilized by Pickering stabilization using freeze-dried and thermally treated PLA and PLGA NP interfacial layers. (A) Optical micrographs and (B, C) optical fluorescent micrographs: (A) with no filters, (B) to observe the entire W/O/W structure and using a green filter, and (C) to show the lack of linking of the encapsulated calcein. Scale bars represent 100 μm.

Figure 8. (A) SEM micrograph of the W/O/W emulsion stabilized by 5 wt % PLA and 2 wt % PLGA NPs after freeze-drying and (B) close-up of the cores stabilized by freeze-dried and thermally treated PLA NP networks.

Figure 9. (A) Optical and (B) fluorescent micrographs of antibubbles stabilized by Pickering stabilization using freeze-dried and thermally treated PLA NPs and PLGA NPs.

Figure 10. (A) Optical micrograph of antibubbles stabilized by Pickering stabilization using freeze-dried and thermally treated PLA NPs (core interface) and PLGA NPs (outer core interface) at room temperature. (B) Same system after destabilization at 37 °C for 2 min as an example of a triggered release mechanism (video available in the SI). Scale bars represent 50 μm.
because of expansion of water crystals growing upon freezing. The size distribution of the bubbles and cores in Figure 8 is comparable to the size distribution of water droplets and oil droplets of the double emulsion before freeze-drying (Figure 7), suggesting that the structure of the double emulsion is preserved in the freeze-drying step.

**Formation of Antibubbles and Triggered Release.**

The freeze-dried W/O/W emulsion was reconstituted in water containing 25% maltodextrin (pH = 7) to form antibubbles. Right after the reconstitution, pictures of the resulting antibubbles were taken with the optical and fluorescent microscope (Figures 9 and S15).

The antibubbles showed good stability. Over the course of a day, no obvious changes were detected in the amount and appearance of the antibubbles, and no major coalescence of the cores was observed. In the literature, stabilized water droplets in air using PLA particles, the so-called liquid marbles, were reported. This is in line with our finding that PLA particles can stabilize the water droplets inside the antibubbles, which can be considered as micron-sized liquid marbles entrapped inside a bubble. After reconstitution and rehydration, the cores become liquid due to the uptake of water vapor through the gaseous layer of the antibubbles. Finally, the ability of the antibubbles to allow controlled release of the encapsulated species was investigated. As a first attempt to trigger release, we increased the temperature of the antibubble suspension to 37 °C, which led to a fast (in the course of several minutes) bursting of the antibubbles. One such “popping” event can be visualized by comparing the left and right images in Figure 10. The temperature of 37 °C is close to the T_g of NPs in contact with water. We hypothesize that this temperature leads to the disentanglement and diffusion of the polymer chains, which in turn causes NPs to merge in such a way that the shell that stabilizes the antibubbles is weakened and more prone to lose its integrity. In line with our hypothesis, Robin et al. found that lactide-based polymer particles become easily deformable and sticky and lose their ability to stabilize emulsion droplets when heated to just above their glass transition temperature.

**CONCLUSIONS**

The surfactant-free formulation of different double emulsions stabilized by lactate-based nanoparticles was tested. PLA NPs could successfully stabilize W/O emulsions, but only after freeze-drying and thermal treatment of the NPs, which led to a favorable contact angle that effectively stabilized the water−oil interface. PLGA NPs could successfully stabilize O/W emulsions and both particles when combined allowed the formation of stable W/O/W emulsions. Using these W/O/W emulsions as a template for the production of antibubbles led to the formation of stable Pickering-stabilized antibubbles. We have thus shown that a range of emulsified structures suitable for encapsulation and delivery purposes can be stabilized solely through the use of lactate-based polymer nanoparticles without the need to use surfactants. This makes these emulsified structures uniquely suitable for applications in which low toxicity and biodegradability is required, such as pharmaceutical, cosmetic, biomedical, and agricultural applications. The destabilization of antibubbles upon an increase in temperature allowed observing a possible mechanism for delivery through bursting of the antibubbles. This result is promising for application in the field of encapsulation technology.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.langmuir.1c02320.

Schematic representation of the nanoparticle preparation by the antisolvent technique (SI1); 1H NMR spectrum of PLA and PLGA NP suspension after the removal of acetone (SI2); size distribution of PLGA (a) and PLGA (b) nanoparticles in water after rotary evaporation of acetone (SI3); DCS thermal analysis of PLA NPs after freeze-drying and thermal treatment at 30 °C for 2 min as an example of a triggered release mechanism. Scale bar represents 100 μm (SI5); FTIR spectra of PLGA NPs before and after thermal treatment (SI6); (A) PLA NPs coated on the carbon tape and (B) SEM micrograph from the carbon tape covered by PLA NPs showed in panel (A) (SI7); DSC characterization of PLGA NPs (Table S1); SEM micrograph of PLGA NPs (SI8); and contact angle measurement of PLGA NPs film (SI9) (PDF).

Optical video of antibubbles stabilized by Pickering stabilization (shown in Figure 10) subjected to destabilization at 37 °C for 2 min as an example of a triggered release mechanism. Scale bar represent 50 μm (AVI).

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