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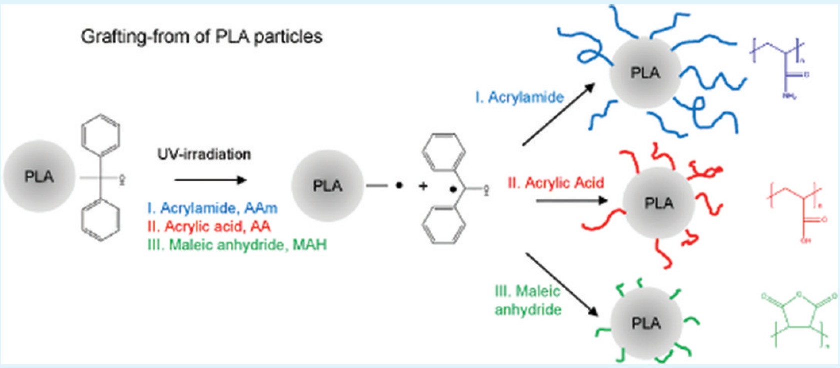
Nondestructive Covalent “Grafting-from” of Poly(lactide) Particles of Different Geometries

Robertus Wahyu N. Nugroho, Karin Odelius, Anders Höglund, and Ann-Christine Albertsson*

Department of Fibre and Polymer Technology, KTH Royal Institute of Technology, SE-10044, Stockholm, Sweden

Supporting Information



ABSTRACT: A nondestructive “grafting-from” method has been developed using poly(lactide) (PLA) particles of different shapes as substrates and three hydrophilic monomers as grafts. Irregularly shaped particles and spheres of PLA were covalently surface functionalized using a versatile method of photoinduced free radical polymerization. The preservation of the molecular weight of the PLA particle bulk and the retention of the original particle shape confirmed the negligible effect of the grafting method. The changes in surface composition were determined by FTIR for both spherical and irregular particles and by XPS for the irregular particles showing the versatility of the method. Changes in the surface morphology of the PLA spherical particles were observed using microscopy techniques showing a full surface coverage of one of the grafted monomers. The method is applicable to a wide set of grafting monomers and provides a permanent alteration of the surface chemistry of the PLA particles creating hydrophilic PLA surfaces in addition to creating sites for further modification and drug delivery in the biomedical fields.

KEYWORDS: *surface grafting, PLA, hydrophilic, particles, geometry*

■ INTRODUCTION

Particles for use in biomedical applications require a controlled 3D-structure and a controlled chemical composition of the particle surface.[1] Hence, there is a need to be able to create particles with attributes such as a predetermined narrow particle size range, anisotropic properties, a well-defined surface microstructure, topography, and shape factor, i.e., symmetricity, while simultaneously retaining or creating an appropriate particle surface composition. Spherical particles are created through techniques such as oil-in-water emulsion, precipitation, solvent evaporation, and mini-emulsion polymerization.[2,3] More complex particle shapes have been demonstrated using progressive techniques such as electrospraying,[4] particle replication in nonwetting templates,[5] and recently by the manipulation of spherical particles.[6] These techniques create particles of different geometries, and their shape can directly influence the performance in an intended application. Knowing the shape factor is therefore necessary to determine the primary role of the particles in a wide range of applications.[7−9]

In surface modification, in contrast to bulk modification, only the surface of the object should be physically or chemically modified. Physical modification entails the physical adsorption of a polymer onto the substrate surface, whereas in chemical modification grafted chains are covalently attached to the substrate surface. Numerous chemical modification techniques have been established including wet-chemical reactions, ozone treatment, UV-treatment and photografting, plasma treatment, high-energy irradiation, and vapor-phase grafting.[10−12] Vapor-phase grafting employs a solvent-free system that under reduced pressure creates a vapor of monomer and initiator that upon UV-irradiation polymerizes from the substrate surface. This procedure has been proven viable for biostable and biodegradable substrates and for simpler and more complex structures, creating covalently attached grafted chains without degrading the substrate.[13−16] Unfortunately, many of these methods are not easily translated from polymer films to polymer particles with different geometries if complete surface coverage of new functionality is desired. Thus, there are today few viable routes for the covalent attachment of functional moieties on particle surfaces. One method that has been proven

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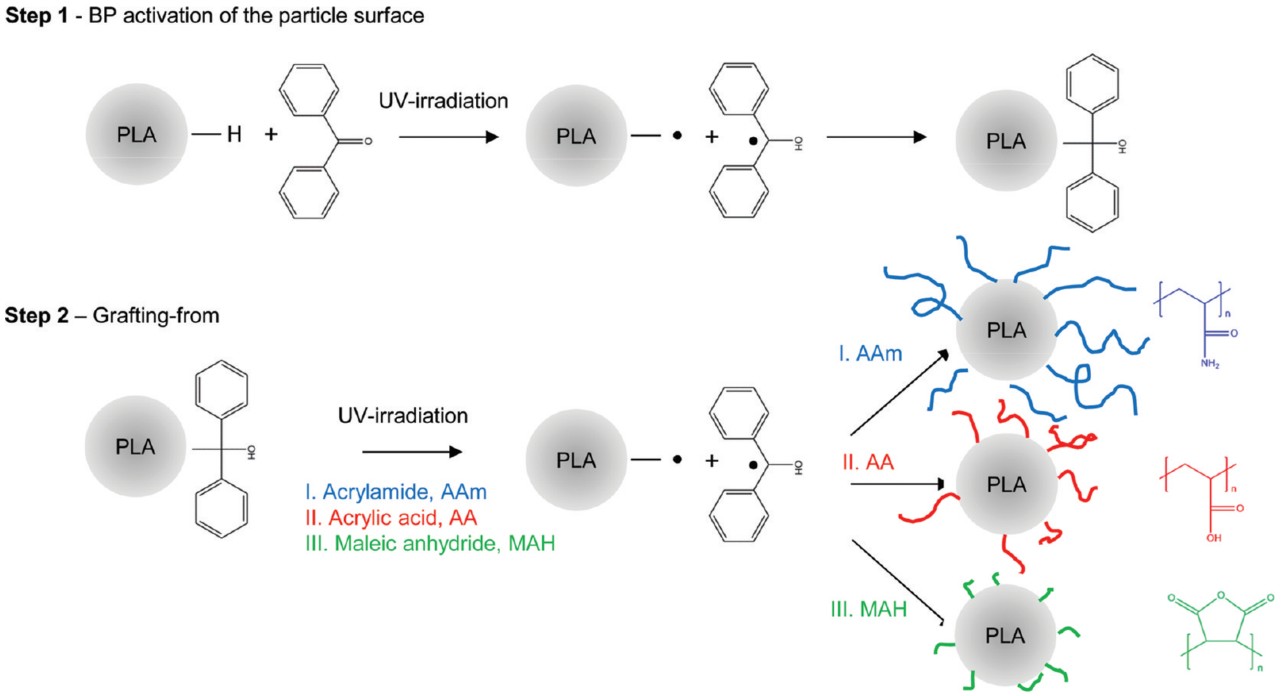
Scheme 1. Two-Step “Grafting-from” Technique to Produce Spherical Particles Indicated with Acrylamide, Acrylic Acid, and Maleic Anhydride



to work in the case of particles is the use of wet-chemical reactions where chemical compounds in solution react with the surface of the objects. For biodegradable polymers such as polylactide, this is normally performed through aminolysis,[17] hydrogen peroxide treatment,[18,19] and alkaline or acidic hydrolysis.[20,21] An increase in the wettability and surface roughness are benefits commonly seen, but there are also some limitations, including nonspecificity giving a range of functional groups, a lack of reproducibility, and sometimes accelerated degradation rates of the modified substrates. Another method that can be used with particles is UV-treatment and photografting. The UV treatment of films has been extensively studied[22−25] mainly because it is easily performed under mild reaction conditions and because in the presence of a photoinitiator, such as benzophenone and hydrogen peroxide, the UV-radiation selectively influences the sample surface.[23] However, less attention has been paid to the surface modification of particles and, perhaps more importantly, to the introduction of covalent functionalization without deterioration in the properties of the substrate.

Our main objective in the present work was to design a nondestructive surface “grafting-from” technique that can be applied to sensitive biodegradable polymers particles. The technique should be valid for simple to complex geometries and allow the substrates to maintain their original shape without degradation of the substrate particle. In addition, it should be applicable to a wide range of grafting monomers and should provide permanent alteration of the surface chemistry of the substrate creating not only hydrophilic poly(lactide) (PLA) surfaces but also sites for further modification. The surface grafted particles can be used in biomedical applications where secondary interactions are important such as drug delivery.

■ EXPERIMENTAL SECTION

Materials. Poly(lactide) (PLA) was obtained from Nature Works Co. Ltd. USA (5200D) and used as received. Benzophenone (BP) (99%, SigmaAldrich), acrylamide (AAm) (98.5%, Acros), and maleic anhydride (MAH) (>99%, Fluka) were used as received. Acrylic acid (AA) (90%, Alfa Aesar) was purified by vacuum distillation at 40 °C prior to use. Dichloromethane (DCM) (>99%, Fisher Scientific), ethanol (96% v/v, VWR), and polysorbate 80 (commonly known as Tween 80) (Fluka) were used as received.

Particle Fabrication. *Oil-in-Water Emulsion.* PLA spherical particles were fabricated by an oil-in-water emulsion technique (O/W). PLA (0.2 g) was dissolved in 100 mL of DCM (organic phase), and 10 mL of this organic phase was thereafter poured into an aqueous solution containing 0.05% w/v of Tween 80. The two immiscible phases were continuously stirred at room temperature overnight until the organic solvent had evaporated, and PLA spherical particles with diameters in the range of 10−60 μm were then recovered from the aqueous phase. The spheres were filtered, rinsed with deionized water to remove surfactant, and finally dried overnight.

Cryogenic Milling. Ten grams of PLA pellets was frozen in a cylindrical thermos filled with liquid nitrogen in order to minimize overheating during the grinding process. The grinding process was conducted using a ZM 200 Retsch mill, equipped with a stainless steel bath to collect the irregular particles, and adjusted at a fixed rotational velocity of 12 000 rpm. PLA irregular particles (for SEM images see Figure S1 in the Supporting Information) with Feret’s diameter in the range of 600−1200 μm were thereafter recovered from their bath. The mill was run for a maximum of 1 min in order to avoid thermal degradation during the process.

“Grafting-from” Approach. *Photoactivation.* The PLA particles were activated by soaking them in 5% w/v BP in ethanol in a Pyrex glass tube. The particle-containing solution was then placed on a stirring plate and UV-irradiated for 20 min with a UV lamp (Ohsram Ultra Vitalux, 300 W) having a wavelength range of 280−320 nm and an output intensity of 38 mW/cm^2. After activation, the particles were centrifuged using a Hettich Universal 30 F at a fixed speed of 5000 rpm for 3 min to remove all ungrafted initiator. The particles were rinsed with ethanol several times, placed in a closed Petri dish, dried overnight, and finally characterized by FTIR spectroscopy. Control particles without BP were also prepared using the same procedures.

Photoinduced Polymerization from the Activated Particles. The BP-activated particles were placed in Pyrex glass tubes using ethanol as solvent and 20% w/v acrylamide (AAm), 20% v/v acrylic acid (AA), or

20% w/v maleic anhydride (MAH). The particle-containing solutions were exposed to UV-radiation for periods of 15 min, 30 min, 45 min, 1 h, and 1.5 h. The surface-grafted particles were thereafter centrifuged at a fixed speed of 5000 rpm for 3 min to eliminate any free polymer chains, washed with ethanol, dried overnight, and characterized by FTIR spectroscopy. Control particles without added monomer were also prepared using the same procedure.

Characterization. *Size Exclusion Chromatography (SEC).* The molecular weights of the pristine, control, activated, and grafted particles were determined using a Waters 717 plus autosampler and a Waters model 510 apparatus equipped with two PLgel 10 μm mixed B columns, 300 × 7.5 mm (Polymer Laboratories, U.K). Chloroform was used as eluent at a flow rate of 0.1 mL/min. The instrument was calibrated with polystyrene standards with narrow molecular weight distributions in the range from 580 to 400 000 g/mol.

Fourier Transform Infrared (FTIR) Spectroscopy. The success of the surface grafting technique was verified using FTIR. Spectra were recorded in the range of 4000−600 cm^{-1} on a Spectrum 2000 Perkin-Elmer spectrometer equipped with an attenuated total reflectance (ATR) accessory (Golden Gate) that makes measurements to a depth of approximately 1 μm on the sample surface. All FTIR spectra were obtained as means of 5 samples and 16 individual scans at 4 cm^{-1} resolution.

X-ray Photoelectron Spectroscopy (XPS). The success of the surface grafting on the PLA irregular particles was verified using XPS. The XPS measurements were run on a Phi Electronics Quantum 2000, using a monochromatic Al X-ray source (hυ = 1486.86 eV). For X-ray surface analysis, a 45° angle monochromatic Al Kα X-ray source operating at 21.1 W and a pass energy of 58.7 eV was used.

Scanning Electron Microscope (SEM). The PLA spherical particles produced by O/W emulsion were examined using a Hitachi S-4800 scanning electron microscope (SEM) at an accelerating voltage of 0.7 kV. The particles were mounted on adhesive carbon black and sputter-coated with a 10 nm gold/palladium layer.

Atomic Force Microscopy (AFM). The PLA spherical particles were topographically characterized using a nanoscope IIIa multimode AFM (Digital Instruments, Santa Barbara, CA) via 5346 EV scanner. A silicon-etched probe tip (NSC14/noAl, Mikromasch, Estonia), with a normal spring constant (k) of 5 N/m and a resonant frequency (f_o) of 110−220 kHz, was used to scan the image in the tapping mode. The surface of the emulsified PLA particles was scanned in the range of 1−2 Hz. The very slow scan rate was chosen to avoid sample deformation. The maximum sample size (512 × 512 pixels) was selected.

Table 1. Number-Average Molecular Weights and Polydispersity Indices of the PLA Particles before, during, and after Surface Grafting

sample	M_n[b]	PDI[b]
PLA pellet	166 000 ± 3800	1.46 ± 0.00
cryogenic milled PLA particles	145 000 ± 200	1.62 ± 0.01
emulsified PLA particles	146 000 ± 10 300	1.62 ± 0.05
irregular PLA particles with BP[a]	144 000 ± 3300	1.64 ± 0.02
spherical PLA particles with BP[a]	142 000 ± 13 000	1.66 ± 0.17
BP activated irregular particles and UV irradiated for 1.5 h	158 000 ± 3600	1.54 ± 0.02
BP activated spherical particles and UV irradiated for 1.5 h	131 000 ± 5423	1.72 ± 0.14
MAH grafted PLA irregular particles for 1.5 h	126 000 ± 3600	1.46 ± 0.02
MAH grafted PLA spherical particles for 1.5 h[c]		

[a] The PLA particles were activated in ethanol for 20 min. [b] Determined using SEC. [c] Immiscible in chloroform.

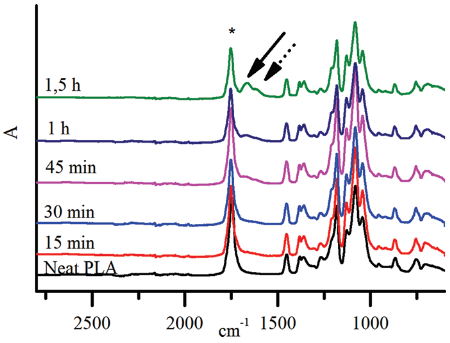


Figure 1. ATR-FTIR spectra of pristine PLA particles and acrylamide-grafted PLA particles at different times. The amide I band is indicated by a solid arrow, and the amide II band is indicated by a dotted arrow. The asterisk (∗) shows the absorption peak of —C═O stretching.

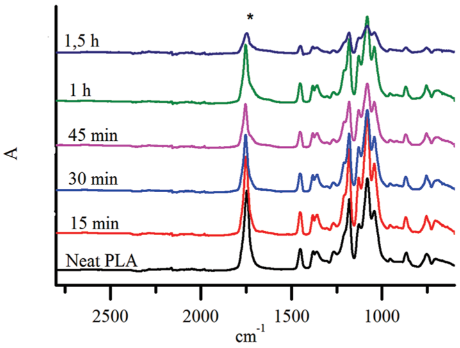


Figure 2. ATR-FTIR spectra of pristine PLA particles and acrylic acid-grafted PLA particles at different times. The asterisk (∗) shows the absorption peak of —C═O stretching.

RESULTS AND DISCUSSION

We here demonstrate a surface "grafting-from" method of PLA particles having two different shapes with three different monomers: acrylamide (AAm), acrylic acid (AA), and maleic anhydride (MAH). The "grafting-from" approach is a two-step process where the PLA particle surfaces are first activated with benzophenone, BP, one of the three chosen monomers is then "grafted-from" the surface of the PLA particles through a photoinduced free-radical polymerization method. A schematic view of the two-step "grafting-from" technique onto spherical particles is shown in Scheme 1.[23] PLA pellets were used to create particles with two different geometries; irregularly shaped particles made by cryogenic milling and spherical particles from an oil/water emulsion. Due to their higher yield and more complex structure, the grinded particles were used to develop the surface-grafting method and the nondestructive character was thereafter confirmed using the spherical particles. Alterations in surface chemistry, morphology, and topography were characterized to verify that the "grafting-from" technique is an applicable nondestructive method and that the three-dimensional shape of the particles was retained after modification. Control experiments with acrylamide in the absence of benzophenone under UV irradiation source for 1.5 h were performed to verify that the grafted layers were not a result of physisorbed monomer.

Nondestructive Nature of the "Grafting-From" Technique. It is well-known that the surface modification of biodegradable polymers tends to cause polymer degradation by chain scission, unzipping, or cross-linking reactions. High-energy techniques such as electron-beam[26,27] and gamma-ray irradiation,[28] and in many cases also UV-irradiation,[29] are detrimental to biodegradable aliphatic polyesters such as

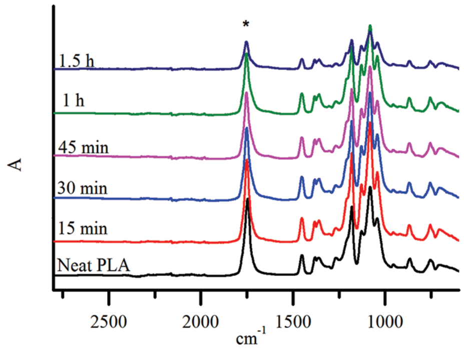


Figure 3. ATR-FTIR spectra of pristine PLA particles and maleic anhydride-grafted PLA particles at different times. The asterisk (∗) shows the absorption peak of —C═O stretching.

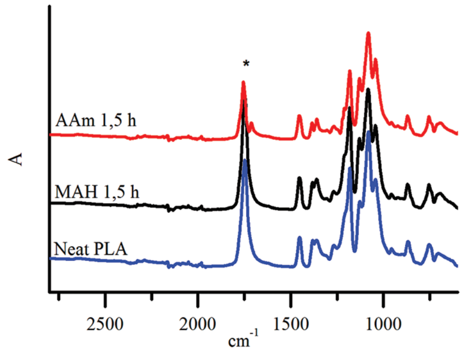


Figure 4. ATR-FTIR spectra of pristine PLA and spherical PLA particles grafted with acrylic amide and maleic anhydride, respectively. The asterisk (∗) shows the absorption peak of —C═O stretching.

Table 2. Elemental Composition of Pristine and Grafted PLA Particles as Determined by XPS

sample	C 1s atomic %	O 1s atomic %	N 1s atomic %
PLA[a]	60.0	40.0	
AAm[a]	60.0	20.0	20.0
MAH[a]	57.1	42.9	
AA[a]	60.0	40.0	
irregular PLA particles	63.9	36.1	
PLA-AAm	61.5	36.3	2.1
PLA-MAH	61.4	38.6	
PLA-AA	61.1	38.9	

[a] Theoretical elemental composition.

poly(lactide). However, it has been shown that the reduction in molecular weight due to UV-irradiation is reduced if the PLA sample is placed in a pyrex tube that prevents wavelengths shorter than 300 nm from reaching the sample.[25,29] To confirm the nondestructive nature of our approach, the molecular weights of the PLA particles before and after surface activation and grafting were determined, Table 1. The molecular weights of the PLA particles were not significantly affected either during the activation or during the surface modification initiated by UV-irradiation. Unfortunately, the molecular weights of the particles after "grafting-from" of the three different monomers could only be determined for MAH due to the limited solubility of the grafted chains in common SEC solvents. The molecular weight of the MAH-grafted PLA particles was slightly lower than that of the pristine PLA particles. An increase or decrease in molecular weight is commonly seen in co- and graft-polymers when the two polymers have different hydrodynamic volumes in the SEC solvent and an artificial change in the molecular weight can be measured. Depending on the graft thickness, the molecular weights of films have in certain cases previously been measured by SEC.[15,25] A low grafting yield results in a thin grafted film that is soluble, whereas a high grafting yield results in thicker grafted films that are insoluble. The same reasoning can be applied to particles that have a much higher surface area-to-volume than that of the films and explain the insolubility of the grafted particles with a low graft thickness.

Since the benzophenone initiator is a hydrogen abstractor, it could lead to cross-linking reactions between PLA chains in the particles or between the growing chains resulting in gel formation. This was, however, no major side reaction in our system since the PLA particles activated by BP showed no change in molecular weight. In addition, the BP-activated chains that were subsequently UV-irradiated for 1.5 h showed only a very a slight increase in molecular weight and a small decrease in PDI, indicating that a small fraction of the formed radicals had combined, Table 1. Further, the PAA-grafted PLA particles were soluble in 1,4-dioxane, a common solvent for the two polymers, which showed that the grafted chains had not formed networks.

Covalent Surface Modification. The surface chemistries of the PLA irregular particles after "grafting-from" were evaluated using FTIR and compared to that of the pristine PLA irregular particles, Figures 1, 2, and 3. As a control, PLA particles UV-irradiated for 1.5 h in ethanol were used and no change in the surface chemistry was observed. The PLA particles showed the expected FTIR spectra with a characteristic ester C═O band at 1745 $\mathrm{cm^{-1}}$ (asterisk). Upon AAm grafting, Figure 1, this band was shifted down and showed a marked change in area and height. With increasing grafting time, a shoulder formed near 1653 $\mathrm{cm^{-1}}$, which is consistent with the characteristic C═O band which primary amides typically portray in the 1670−1650 $\mathrm{cm^{-1}}$ region (amide I band). Primary amides also typically show a band around 1620 $\mathrm{cm^{-1}}$ (amide II band), observed here at 1615 $\mathrm{cm^{-1}}$,[15,25,30] confirming the successful grafting of the AAm onto the PLA. The C−N stretching bands that should appear in the 1440−1200 $\mathrm{cm^{-1}}$ region were difficult to identify because they overlap with bands originating from the PLA substrate.

For AA-grafted PLA, Figure 2, the C═O stretching bands originating from the carboxylic acid of PAA were seen as a shoulder on the C═O band originating from PLA at 1747 $\mathrm{cm^{-1}}$ and this shoulder was significantly wider[31] after UV-irradiation times exceeding 1 h. For the MAH-grafted PLA, Figure 3, the anhydride functionality should be visible as two C═O bands, separated by ~60 $\mathrm{cm^{-1}}$ in the 1840−1720 $\mathrm{cm^{-1}}$ region.[31] These bands were not however clearly identifiable. Instead, a broadening of the PLA C═O band was observed, which would be the case if the amount of MAH grafted onto the PLA were low. It has previously been shown that MAH is difficult to homopolymerize and it is most often found in copolymers.[32−34] MAH will thus form something similar to a monolayer on the substrate which would be difficult or impossible to observe with FTIR, since the depth of analysis of FTIR is approximately 1 μm. This means that a quite thick graft layer is required to prevent measurement of the bulk material as well. After prolonged grafting times, a pronounced shoulder appeared on the PLA C═O band of 1635 $\mathrm{cm^{-1}}$, but no band was visible at higher wavenumbers, implying that only a small

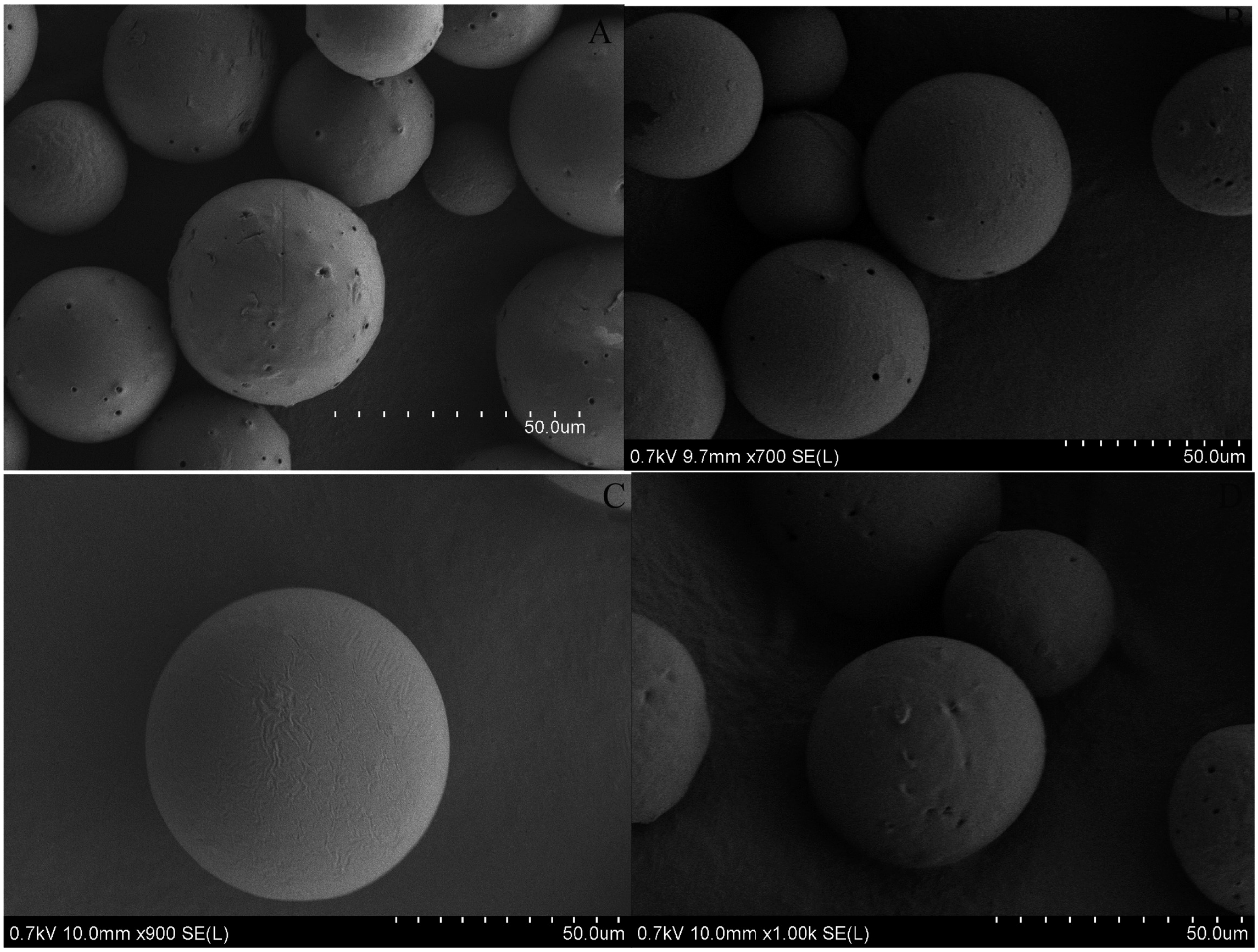


Figure 5. Scanning electron microscopy images of (A) pristine PLA spheres, (B) control PLA spheres UV-irradiated for 1.5 h without the presence of any monomer, (C) PLA spheres grafted with acrylamide for 1.5 h, and (D) PLA spheres grafted with maleic anhydride for 1.5 h.

amount of anhydride groups were present on the PLA particles. However, considering the probability of monolayer formation and the instability of anhydride functionalities toward water, this could be expected.

To assess the versatility of the surface grafting technique to different substrate shapes and two monomers, AAm and MAH were chosen as model monomers for grafting onto spherically shaped particles. The FTIR spectra of the grafted PLA particles after 1.5 h of grafting were similar to those found for the irregularly shaped particles. However, weaker absorption bands originating from the grafted AAm and MAH were observed, Figure 4. This effect is explained by the different shapes of the particles, where the spherical particles have a larger surface area than the irregular particles and hence need longer reaction times to reach the same grafting degree. This effect was even more pronounced after longer reaction times.

To confirm that the “grafting-from” technique resulted in the covalent attachment of grafts to the particle surface and not only adsorption of the polymers onto the particle surface, a postsurface grafting test was conducted. AAm-grafted particles were selected as test specimens since both the monomer and the polymer are soluble in water. Particles were soaked in water for 24 h; samples were regularly withdrawn, and the covalent attachment of AAm was assessed with FTIR. No change in the surface characteristics of the PLA-g-AAm was seen.

The surface compositions of the grafted films were also analyzed by XPS, permitting the elemental analysis of the outermost surface of the irregular particles, Table 2. The surface composition measured by XPS (as atomic % of the elements present, H excluded) of the AAm-grafted PLA particles revealed, as expected, that the AAm-grafted particles contained nitrogen, confirming the FTIR results. The amount of nitrogen was however lower than the theoretical value for pure PAAm. This could indicate that the substrate was not completely covered or more likely that the XPS penetrates deeper into the substrate than the thickness of the AAm layer and hence that the PLA bulk material of the substrate was included in the layer investigated by this analysis. For the AA- and MAH-grafted PLA particles, there was no significant difference between the theoretical composition of PLA and PMAH and PAA, making interpretation of the XPS results difficult. It can be seen that the oxygen amount was higher in the grafted samples than in the pristine PLA particles, indicating that a change in the surface composition had occurred. This is interpreted as confirming the successful surface grafting of AA and MAH onto the PLA particle surface. We can also conclude that carbon and oxygen were the only elements present on the surface and that the surface contained no nitrogen. The discrepancy between theoretical atomic composition of PLA (60% carbon and 40% oxygen) and measured atomic composition of PLA (63.9% carbon and 36.1% oxygen) is probably due to a combination of small amounts of impurities attached on the PLA surface and contamination of the XPS instrument.

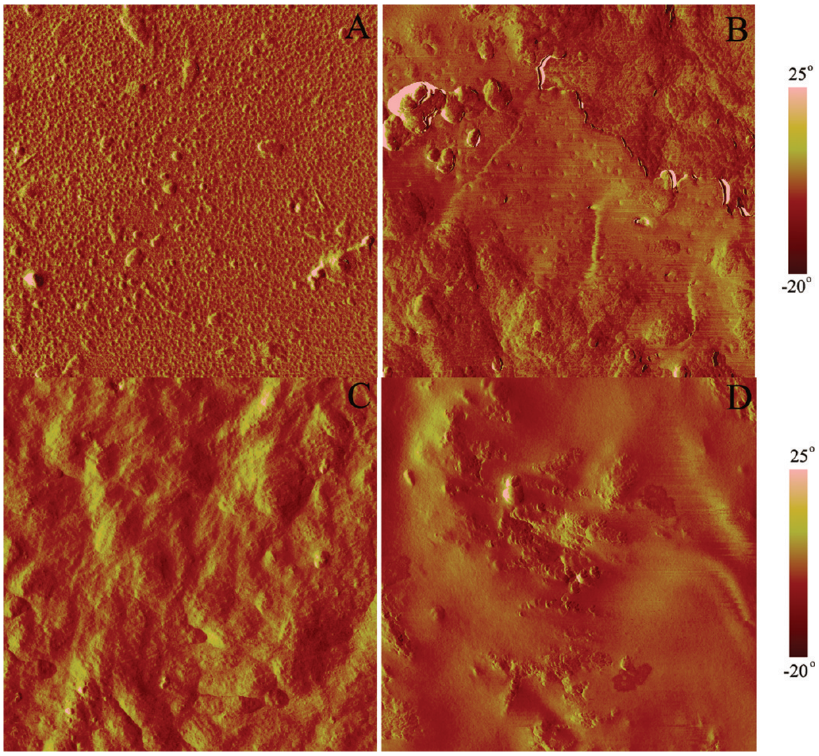


Figure 6. Atomic force microscopy phase images of the surfaces of (A) pristine PLA sphere, (B) PLA sphere UV-irradiated in ethanol only for 1.5 h, (C) acrylamide-grafted PLA sphere, and (D) maleic anhydride-grafted PLA spheres. All AFM pictures were scanned over an area of 5 μm × 5 μm.

Morphological and Topographical Changes of the Grafted PLA Particles. To elucidate the influence of the surface grafting technique on the morphology of the PLA spheres, SEM images were captured before and after surface grafting, Figure 5. The pristine PLA spheres had an average diameter of 36 ± 13 μm and in some cases showed a surface morphology with small pores formed during the fabrication process,[35] probably due to a very rapid evaporation of the organic solvent (DCM) and the air humidity, Figure 5. Although they were imperfect, the particles were chosen for surface morphology and topography measurements using the pores as indicators of complete or partial surface coverage. The control PLA spheres UV-irradiated for 1.5 h in ethanol without monomer showed that the ethanol does not harm the PLA particles since no change in the surface morphology was observed. A surface morphology similar to that of the pristine PLA spheres was observed for the MAH-grafted PLA, confirming the low degree of grafting indicated by FTIR. This again demonstrated the nondetrimental surface grafting approach. However, the surface morphology of the acrylamide-grafted spheres, with an average diameter of 63 ± 28 μm, was different from that of the pristine PLA spheres. A smooth surface and an increase in the diameter size were obtained, confirming the FTIR results and showing a complete but thin surface coverage. The diameters of the spheres were determined by ImageJ software measuring approximately 100 randomly chosen spheres.

Atomic force microscopy was used to evaluate the topographies of pristine PLA spheres, PLA spheres UV-irradiated in ethanol only for 1.5 h, and acrylamide-grafted and maleic anhydride-grafted PLA spheres, Figure 6. The pristine PLA spheres had a relatively smooth surface with a surface asperity of 5.33 nm, calculated as the root-mean-square (rms) roughness. UV-irradiation of the PLA spheres in ethanol gave a surface asperity with a rms roughness of 37.2 nm, showing the effect of ethanol on the surface topography of the spherical particles. The surface roughness of maleic anhydride-grafted PLA spheres was slightly greater at 42.8 nm, while the acrylamide-grafted PLA spheres had a rms roughness of 16.9 nm. This again indicates that a monolayer of maleic anhydride was grafted-from the PLA backbone but that the grafting layer of the polyacrylamide was thicker and smoother and covered the PLA surface evenly as shown by SEM and FTIR. The AFM phase images thus show that the monomer-carrier solvent influenced the rms roughness, even though there was no significant change in molecular weight before and after treatment.

■ CONCLUSIONS

A nondestructive surface "grafting-from" technique was developed and shown to be successful in covalently grafting three different monomers (acrylamide, acrylic acid, and maleic anhydride) onto particle substrates of different geometries. The molecular weight of the PLA particles did not change after the surface activation and grafting process, and the particles retained their 3D-shape, proving the nondestructivity of the method. Alterations in the surface chemistry of the two PLA substrates were confirmed by FTIR and XPS, for the irregular particles. Additionally, an increase in the diameter size of acrylamide-g-PLA spheres, as compared to pristine PLA spheres, has exhibited the success of the nondestructive "grafting-from" technique. The root-mean-square roughness determined by AFM decreased upon grafting of acrylamide compared to the PLA control and showed that the grafting layer was evenly distributed over the spherical particle surface. Maleic anhydride formed a monolayer of grafted monomer on the PLA sphere surface, as confirmed by FTIR, SEM, and AFM.

We emphasize that the designated "grafting-from" technique described here is nondestructive, achieves covalently attached grafts, is applicable to PLA particles of different geometries, and induces hydrophilicity to the PLA surface and a functionality that can be used for further coupling reactions and colloidal stability in the medical applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

SEM images of irregular PLA particles. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Author

*Tel. +46-8-790 82 74. Fax: +46-8-20 84 77. E-mail: aila@kth.se.

Notes

The authors declare no competing financial interest.

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