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Hollow nanoparticles *via* stepwise complexation and selective decomplexation of poly(ethylene imine)†

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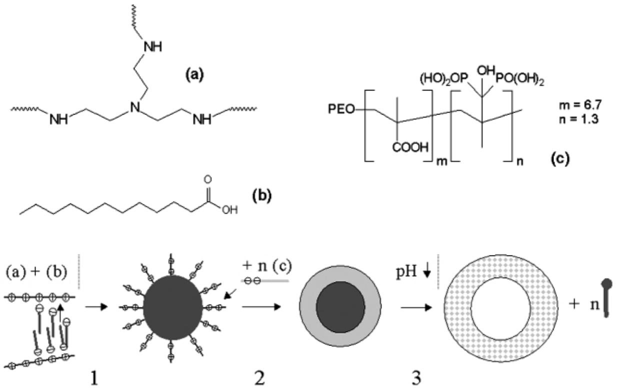
The preparation of hollow nanoparticles with amino groups on the inner side *via* the stepwise complexation and selective decomplexation of poly(ethylene imine) is presented.

The complexation of polyelectrolytes with oppositely charged surfactants[1,2] as well as with oppositely charged poly- or oligo-electrolytes[3,4] has been extensively studied. These investigations were carried out because of the similarities in biological systems *e.g.* the stabilization of cell membranes by peptide association[5] or DNA–histone complexes,[6] and to imitate such natural processes. By applying a stepwise complexation of two different counterions to poly(ethylene imine) and then a selective decomplexation of one of these complexes, we are able to generate hollow nanoparticles with an interior that is filled with amino groups. These particles have potential as nanoreactors with internal binding sites or, for pharmaceutical application, as detoxification devices (heavy metals) or drug carriers for controlled release.

The complexation of charged surfactants to oppositely charged polyelectrolytes in particular is driven by the combination of electrostatic and hydrophobic interactions. This typically leads to water-insoluble, charge-neutralized aggregates.[7] If the amount of polyelectrolyte exceeds the amount of added surfactant, the result in most cases is colloidal particles consisting of a stabilizing shell of uncomplexed polyelectrolyte chains and a core of domains with surfactant-complexed polyelectrolyte.[8] The components used and the proposed particle formation mechanism are summarized in Scheme 1.



Scheme 1 Compounds used and steps of particle formation. **Chemical compounds** (**a**) branched poly(ethylene imine) (PEI; M_W = 25000 g mol^{-1}, *ca.* 580 monomer units); (**b**) dodecanoic acid; (**c**) poly(ethylene oxide)-*block*-poly(methacrylic acid) with phosphonized carboxylic acid groups, PEO-*b*-PMAA-$(PO_3H_2)_2$.[9] The nonionic (PEO) block contains 68 and the ionic block 8 monomer units. The ratio of neat to phosphonized carboxylic acid groups is 6.7 to 1.3. **Particle formation** (**1**) complexation of (a) and (b) (charge-ratio 2 positive (a) to 1 negative (b)); (**2**) adsorption of (c) to the surface of pristine particles; (**3**) selective decomplexation of the complex derived in step (1).

In the first step of this investigation we prepared nanoparticles from a poly(ethylene imine) (PEI)–dodecanoate complex with a stoichiometry of 2 positive charges (PEI) to 1 negative charge (dodecanoate). The particles display a positively charged shell of free, uncomplexed PEI on the surface (see Scheme 1 step 1). The preparation is described in detail elsewhere.[8]

The obtained pristine complex particles display an average hydrodynamic diameter of 150 ± 25 nm and a zeta potential of 52 ± 9 mV. Fig. 1, left image, shows the pristine PEI–dodecanoate complex particles. The cores consisting of a PEI–dodecanoate complex appear dark due to the ionic character of the complex. The shells from uncomplexed PEI chains appear diffuse, forming a gel-like matrix in which the cores are embedded. The average size of the cores is 100 ± 20 nm.

In a second step the shells of the above described particles were neutralized by the adsorption of a double-hydrophilic block copolymer with an acidic PMAA-$(PO_3H_2)_2$-block (negatively charged in aqueous solution at $pH > pK_a$ (−1) and a noncharged PEO-block (PEO-*b*-PMAA-$(PO_3H_2)_2$[9]). The adsorption of the negative block onto the positively charged shell leads to the formation of a condensed shell of a polyelectrolyte–polyelectrolyte complex (Scheme 1 step 2). Neutralized particles exhibiting a zero zeta potential show the same hydrodynamic diameter of 150 nm. Interactions of oppositely charged polyelectrolyte species are frequently used for film formation on planar or colloidal surfaces.[10] Caruso *et al.* showed that porous thin films on planar substrates can be obtained by salt-induced structural changes of multilayers of weak oppositely charged polyelectrolytes.[11] Also pH-induced structural changes of polyelectrolyte multilayers have been reported.[12] Here we use the change of the pH for the dissolution of the PEI–dodecanoate complex within the cores which is accompanied by the generation of 10.5 nm pores in the shells of the nanoparticles.

A solution of the double-hydrophilic block-copolymer (PEO-*b*-PMAA-$(PO_3H_2)_2$) was added stepwise to the dispersion of the nanoparticles in the second preparation step for its adsorption onto the complex particle surfaces until the measured zeta

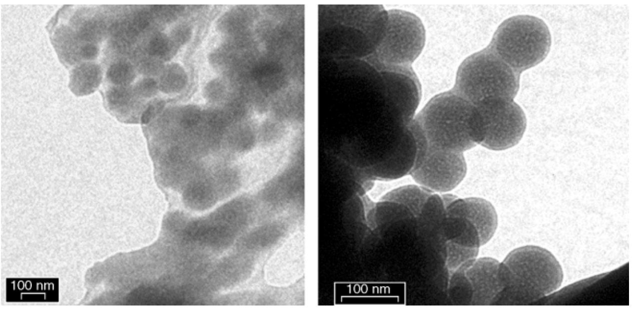


Fig. 1 PEI–dodecanoate complex particles before (left image) and after (right image) adsorption of the PEO-*b*-PMAA-$(PO_3H_2)_2$ block copolymer. The contrast of the cores is due to its ionic character. The scale bars are 100 nm.

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† Electronic supplementary information (ESI) available: synthesis and physico-chemical data for PEO-*b*-PMAA-$(PO_3H_2)_2$, (polymer C). See http://www.rsc.org/suppdata/cc/b1/b110786k/

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potential of the particles reached 0 mV. All complexable PEI-charges[13] were complexed at this point, either with dodecanoic acid or with PEO-*b*-PMAA-$(PO_3H_2)_2$. The size of the particles, as determined by dynamic light scattering, did not change during the titration. The charged shell of the unmodified particles is approximately of the same size as the modified uncharged shell. Fig. 1, right image, shows the particles after adsorption of the PEO-*b*-PMAA-$(PO_3H_2)_2$ where the zeta potential was determined to be 0 mV. The shells appear condensed but the core sizes are unchanged at about 100 nm. The PEI is now complexed with two different counterions; a PEI–dodecanoate complex in the cores of the particles which is surrounded by a shell of PEI–PEO-*b*-PMAA-$(PO_3H_2)_2$ complex. The stability of the ionic bonds is dependent on the charges of the components.[14,15] If the pH is decreased below the pK_a value of the acidic compounds (dodecanoic acid $pK_a \approx 4.9$,[16] phosphonate-groups of PEO-*b*-PMAA-$(PO_3H_2)_2$ $pK_{a1} \approx -1$,[17] methacrylic acid-groups of PEO-*b*-PMAA-$(PO_3H_2)_2$ $pK_a \approx 5.5$[18]) then they are protonated, thus losing their charges for binding to the PEI chains.

In the third and last step of preparation, the PEI–dodecanoic acid complex—located in the core of the particles—was selectively dissolved (see Scheme 1, step 3). This was induced by lowering the pH below the pK_a-value of the dodecanoic acid.[8]

As we adjusted the pH to a value of 2.5 only the dodecanoate–PEI complex and the weak carboxylic acid (methacrylic acid groups)–PEI complex are destroyed, whereas the phosphonate–PEI complex is left unchanged. After 1 h of stirring at pH 2.5 and rt we obtained the flocculation of dodecanoic acid. The acid was identified by differential scanning calorimetry measurements and by comparing melt transition and melt enthalpy with the pure compound. The flocculate was filtrated and the remaining dispersion was dried on carbon grids and investigated by transmission electron microscopy (TEM). Two typical images are shown in Fig. 2.

Fig. 2a presents an overview at low magnification revealing that the complexes are still displaying discrete particles with an average diameter of 400 nm resembling pancake-like morphologies. The diameter is considerably larger than found for the particles after step 2.

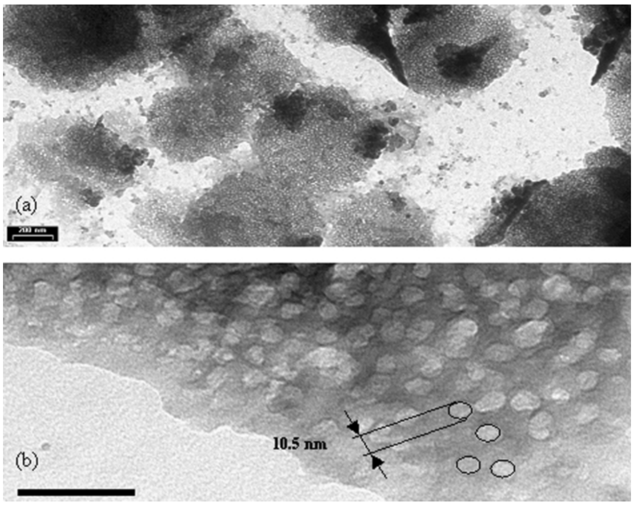

Fig. 2 TEM image of hollow particles of the PEI–(dodecanoate)–PEO-*b*-PMAA-$(PO_3H_2)_2$ complex as obtained after adjusting the solution to pH 2.5 and filtration of the flocculated dodecanoic acid. The scale bar is 200 nm. Fig. 2b shows an image of an expanded shell (dark) which is perforated by pores of uniform size (bright). The scale bar is 60 nm.

We explain the increased diameter of the particles as a consequence of high osmotic pressure in the cores after decomplexation of the PEI–dodecanoic acid complex and the generation of pores in the shells. In addition the repulsion forces of the now free, highly charged PEI chains in the interior are likely to play a role in inflating the shell. The driving force for displacing the dodecanoic acid is its protonation and the breaking of the electrostatic interactions. However the reason for the diffusion of the acid to form a precipitate outside the particles is not clear.

The TEM investigation also showed that the particles have porous shells (see Fig. 2b). The pores appear uniform with a pore diameter of 10.5 nm ± 1.5 nm.

In a separate investigation we substituted the dodecanoic acid with octadecanoic acid in step 1 of the particle formation process. This did not change the pore diameter. For comparison, a pure complex of PEI and PEO-*b*-PMAA-$(PO_3H_2)_2$ did not form particles. The combination of pH- and surfactant-induced structural changes seem to be essential for the formation of the hollow particles with the nanoporous shells just described. The exact mechanism and factors determining the pore size is however not clear.

If we consider that selective dissolution of the PEI–dodecanoate complex removed the dodecanoic acid from the cores, uncomplexed, charged PEI-chains on the inner side of the porous shells are left. This interior, enriched with amino groups, is capable of further interactions. Especially the binding of heavy metals such as cadmium[19] to the PEI could provide an efficient detoxification/cleaning device, *e.g.* for use in the human body.

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