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Poly(ethylene oxide)-*b*-poly(ethylene imine) Dodecanoate Complexes: Lamellar-*within*-lamellar Morphologies and Nanoparticles

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ABSTRACT: The complexes formed between poly(ethylene oxide)-*b*-poly(ethylene imine)s and dodecanoic acid were studied in the solid state and as nanoparticles. The poly(ethylene imine) blocks had different architectures, cyclic, linear, and branched, while the poly(ethylene oxide) blocks were held constant. Self-organized lamellar-*within*-lamellar structures were obtained with two different length scales, which are, for example, 15 and 3 nm. Small-angle X-ray scattering methods were used to quantify the morphological differences between noncomplexed and complexed diblock copolymers. Core−shell nanoparticles were prepared from the complexes in aqueous solution with sizes around 200 nm. Their cores are formed by poly(ethylene imine) dodecanoate while their shells consist of poly(ethylene oxide). It was found that the shapes of the nanoparticles depend on the PEI block. They are, for example, prolate if the PEI is linear and spherical if the PEI is branched. The nanoparticles are block ionomer complexes and supposed to be potentially useful as drug carrier systems.

Introduction

Polymer−surfactant complexes formed between polyelectrolytes and oppositely charged ionic surfactants are a subject of intense investigation.[1−3] The salt bonds between the ionic units of the polyelectrolytes and the surfactant headgroups together with the hydrophobic interactions of the surfactant aliphatic tails stabilize the liquid crystalline-like structures of the polyelectrolyte−surfactant complexes. A novel family of polymer−surfactant complexes which is formed by block copolymers containing ionic and nonionic water-soluble segments (double-hydrophilic block copolymers, block ionomers) and surfactants of opposite charge has been reported by Kabanov et al.[4,5] Earlier studies on polycation/DNA complexes[6] as gene delivery systems also include PEI−DNA complexes.[7] Moreover, PEO−PEI block copolymers have been used in formulations for delivery of oligonucleotides[8] and as drug carriers for retinoic acid.[9] Recently, we have demonstrated that poly(ethylene oxide)-*b*-poly(L-lysine) can be used for the immobilization of retinoic acid.[10] An overview of the synthesis, the applications, and the complexation behavior of double-hydrophilic block copolymers has been given by Cölfen.[11] In the block copolymer complexes, the surfactant molecules are bound to the oppositely charged units of the polyelectrolyte segment as is the case in regular polymer surfactant complexes formed by homopolymers.[12] However, the solubility behavior of the block copolymer complexes is different because of the nonionic segment. In particular, the soluble complexes of poly(ethylene oxide)-*b*-poly(methacrylate) (PEO-*b*-PMA) and various single-tail cationic surfactants are described.[4,5] It has been shown that the complexes formed by PEO-*b*-PMA anions arrange into small vesicles with a wall formed by the surfactant-neutralized polyelectrolyte surrounded by the hydrophilic PEO shell.[4] Such vesicles are stable and encapsulate hydrophilic molecules in the internal aqueous volume. The complexes formed between the cationic graft copolymer of poly(ethylene oxide) and poly(ethylene imine) and alkyl sulfate surfactant has been studied by Kabanov et al.[13] They reported that, in contrast to the complexes of PEI homopolymer, which phase separate, the PEO-*g*raft-PEI complexes are water-soluble over the whole range of compositions of the mixture, including the electroneutral stoichiometric complexes. These species represent micelle-like aggregates with a hydrophobic core from the polyelectrolyte−surfactant complex and a hydrophilic corona from the ethylene oxide chains. Kunitake et al. were able to prepare surfaces made of a PEI-surfactant complex which show an excellent blood compatibility.[14] PEI−DNA complexes as gene vectors with an excellent safety profile[15] are interesting examples of the efforts in food, cosmetic and pharmaceutical research which are being made in order to develop new applications for PEI. In an earlier study, we reported on the complexes of PEI homopolymers and retinoic acid, which can serve as a possible new colloidal drug formulation.[16] It was further shown that PEI forms lamellar structured complexes in bulk materials with perfluorinated *n*-alkyl[17] and *n*-alkylated carboxylic acids.[18] The counterpart of PEI, *n*-dodecanoic acid, is a typical medium chain fatty acid with an amphiphilic character, which has been widely investigated for its colloidal purposes and considered for pharmaceutical applications.[19] Its complexes with PEI homopolymers were developed for core−shell nanoparticles that act as carriers for water-insoluble compounds such as the coenzyme Q10 and the hormone triiodothyronine.[20]

In this work, we report on the formation of hierarchically ordered liquid crystalline-like structures and

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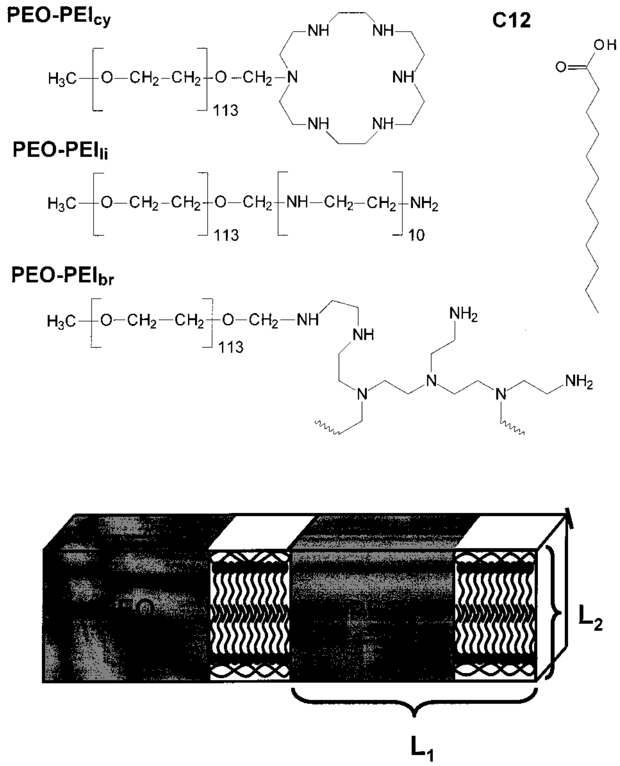

Figure 1. Chemical structure of the poly(ethylene oxide)-*b*-poly(ethylene imine)s. The poly(ethylene oxide) blocks (PEO) of the polymers are identical. They are linear and contain about 113 monomer units. By contrast, the poly(ethylene imine) blocks differ in their structures. It is cyclic in PEO−PEI$_{cy}$, linear in PEO−PEI$_{li}$, and branched in PEO−PEI$_{br}$. Dodecanoic acid (C12) is used for the complexation of the polymers resulting in PEO−PEI$_{cy}$−C12, PEO−PEI$_{li}$−C12 and PEO−PEI$_{br}$−C12. The lower figure shows the proposed lamellar-*within*-lamellar structure model for the complexes PEO−PEI$_{li}$−C12 and PEO−PEI$_{br}$−C12. A larger long period is formed by the polymer (L_1) and a shorter by the complex (L_2).

nanoparticles of the complexes formed between poly(ethylene oxide)-*b*-poly(ethylene imine)s and dodecanoic acid (C12). The poly(ethylene oxide) blocks (PEO) of the polymers were taken to be constant while the poly(ethylene imine) (PEI) blocks differ in their structures. They were cyclic, linear or branched. Their complexation with C12 resulted in the block copolymer complexes PEO−PEI$_{cy}$−C12, PEO−PEI$_{li}$−C12 and PEO−PEI$_{br}$−C12, respectively. The molecular structures of the compounds are shown in Figure 1.

Experimental Section

Materials. The synthesis and the characterization of the poly(ethylene oxide)-*b*-poly(ethylene imine)s were carried out and described in detail by Sedlak, Cölfen, and Antonietti.[11,21−23] They used a PEO monomethyl ether (M_w = 5000 g mol^{-1}), which was transferred into PEO methyl glycidether by reaction with sodium hydride. This reactive epoxide was coupled to poly(ethylene imine) of different structures yielding PEO-*b*-PEI with cyclic, linear and branched PEI blocks as shown in Figure 1. The purification of the polymers was carried out by ultrafiltration techniques. ^{1}H NMR spectroscopy ($CDCl_3$) was used to determine the stoichiometry of the block copolymers at $\delta = 2.68$ ppm (broad multiplet, CH_2-CH_2-N) and $\delta = 3.58$ ppm (broad multiplet, CH_2-CH_2-O). Analytical ultracentrifugation showed that about 96% of the PEG-*b*-PEI$_{br}$ copolymer was the AB block and only 4% the ABA copolymer.[22] The presence of block copolymer structures was shown by GPC measurements. It was, however, not possible to determine the polydispersity of the samples as it has been discussed in detail by Cölfen.[22] The number of PEI monomer units was 6 (PEO−PEI$_{cy}$), 10 (PEO−PEI$_{li}$), and 16 (PEO−PEI$_{br}$). The dodecanoic acid and ethanol (HPLC grade) were supplied by Aldrich and used as received.

Complex Preparation. Amounts of 100.0 mg each of PEO-*b*-PEI, which corresponds to 1.14×10^{-4} mol amino functions of PEO-*b*-PEI$_{cy}$, 1.95×10^{-4} mol amino functions of PEO-*b*-PEI$_{li}$, and 2.8×10^{-4} mol amino functions of PEO-*b*-PEI$_{br}$, were dissolved in 10 mL of hot ethanol. Then the block copolymer solutions were added to 0.5 equiv of dodecanoic acid, which were prepared as 1% (w/v) solutions in hot ethanol. The transparent solutions were stirred for a further 30 min and then cast at 50 °C into films of the complexes as described earlier[12] and dried for a period of 12 h in a vacuum oven at 40 °C and 10^{-3} mbar. Macroscopically oriented samples of the complexes were prepared by pressing the samples between Teflon sheets at room temperature into pellets.

Nanoparticle Formation. The 20 mg samples of the PEO−PEI−C12 complexes were each added to 20 mL of water, stirred at 35 °C for 2 h, then treated for 10 s with ultrasound, and finally purified by a 0.8 μm filter supplied by Nalgene Co.

Methods. The FTIR spectra were recorded on a Nicolet Impact 400 spectrometer. The differential scanning calorimetry measurements were performed on a Netzsch DSC 200. The samples were examined at a scanning rate of 10 K min^{-1} by applying two heating scans and one cooling scan. The maxima of the exothermic peaks in the second heating cycles were used to determine the melt transitions of the PEI−C12 complexes. Wide-angle X-ray scattering (WAXS) measurements were carried out with a Nonius PDS120 powder diffractometer by transmission geometry. A FR590 generator was used as the source for Cu Kα radiation, monochromatization of the primary beam was achieved by means of a curved Ge crystal, and the scattered radiation was measured with a Nonius CPS120 position sensitive detector. The resolution of this detector in 2θ was 0.018°. Small-angle X-ray scattering (SAXS) measurements were carried out with an X-ray vacuum camera with pinhole collimation (Anton Paar, model A-8054) equipped with image plates (type BAS III, Fuji). The image plates were read with a MAC Science Dip-Scanner (type IPR-420) and IP reader (type DIPR-420). The SAXS measurements were carried out at a temperature of 20 ± 2 °C. Dynamic light scattering measurements were carried out with a submicron particle sizer, model 370 (Nicomp). The scanning force microscopy was performed with a Nano Scope IIIa microscope (Digital Instruments, Santa Barbara, CA), operating in tapping mode. The instrument was equipped with a 10×10 μm E-scanner and commercial silicon tips (model TESP, the force constant was 50 N/m, the resonance frequency was 300 kHz and the tip radius was smaller than 20 nm). The samples were prepared by letting droplets of diluted aqueous solutions (0.01% w/w) dry on a freshly cleaved muscovite mica surfaces at room temperature. Transmission electron microscopy (TEM) was performed on a DSM 940 A (Carl Zeiss, Jena, Germany) microscope operating at 200 kV. Grids were prepared by depositing a droplet of the dispersion onto a carbon-coated copper grid and removing excess water with a paper tip.

Results and Discussion

The complexation of the PEO−PEIs with C12 was monitored by IR-spectroscopy. A ratio of amino functions to carboxylic acid functions was taken 2:1 in order to ensure that each carboxylic acid group will be attached to an amino group. It can be seen in Figure 2 that a strong carboxylic acid vibration band at 1690 cm^{-1} is present in the FTIR spectrum of C12 (curve a) while it is absent in the spectrum of PEO−PEI$_{li}$−C12 (curve b). In the latter the band of the carboxylate is found at 1550 cm^{-1}. From this we conclude that, within the experimental error, all of the carboxylic acid functions of C12 form acid−base pairs with the amino functions of PEI blocks in the complexes.

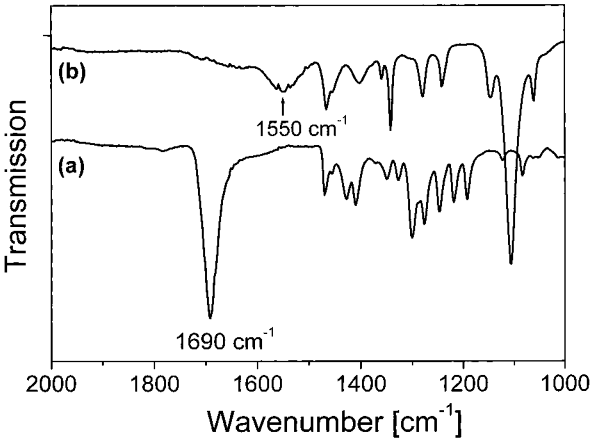

Figure 2. FTIR spectrum of C12 (curve a) and that of complex PEO−PEI$_{\text{br}}$−C12 (curve b). The stoichiometry of PEI to C12 is 2:1. In the complex of C12 an intense carboxylic acid band at 1690 cm^{-1} is found resulting from the C=O stretch vibration. This band is absent in the spectrum of PEI−C12 indicating a complete complexation of the dodecanoic acid.

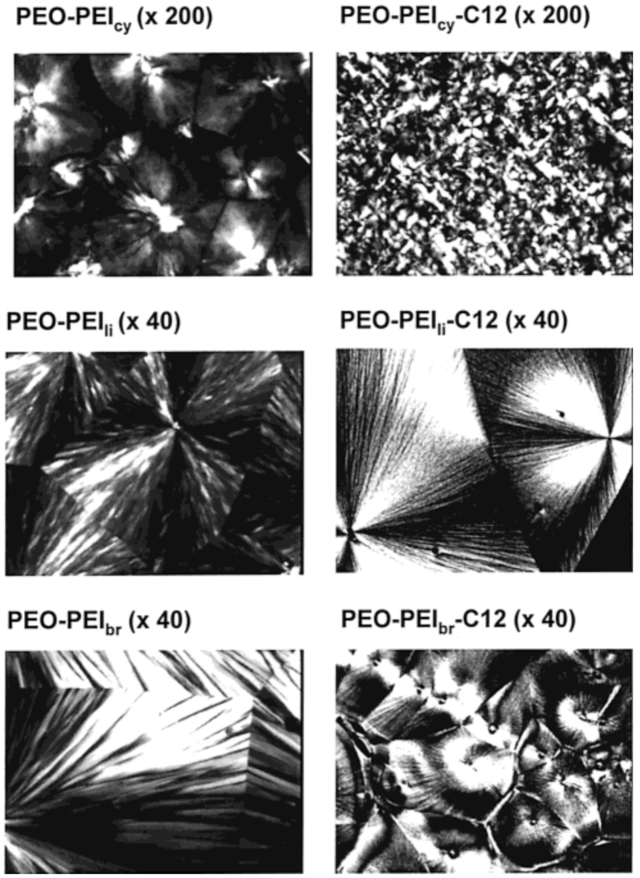
PEO-PEI$_{\text{cy}}$ (x 200)
PEO-PEI$_{\text{cy}}$-C12 (x 200)
PEO-PEI$_{\text{li}}$ (x 40)
PEO-PEI$_{\text{li}}$-C12 (x 40)
PEO-PEI$_{\text{br}}$ (x 40)
PEO-PEI$_{\text{br}}$-C12 (x 40)

Figure 3. Polarization micrographs of the PEO−PEI block copolymers and their complexes with dodecanoic acid as films. The magnifications are given in brackets.

Crystallinity. Recently we have shown by small-angle X-ray scattering measurements that a PEI−C12 homopolymer complex forms a smectic A-like mesophase with a repeat unit of 2.90 nm at room temperature.[18] Films of PEI−C12 are optically anisotropic, as was found during examination between crossed polarizers. Typical fan-shaped textures confirmed the smectic A-like structure proposed on the basis of small-angle X-ray scattering measurements.[18,20] Films of the block copolymer complexes PEO−PEI$_{\text{cy}}$−C12, PEO−PEI$_{\text{li}}$−C12, and PEO−PEI$_{\text{br}}$−C12 are also optically anisotropic. But in contrast to the fan-shape textures of the PEI−C12 homopolymer complexes their polarization microscopy pictures display the textures of spheroids, which are typical for crystalline compounds. It can be seen in Figure 3 that the diameters of the crystallites are relatively large. The sizes of the crystallites are about 10^2 μm (PEO−PEI$_{\text{cy}}$), 10^1 μm (PEO−PEI$_{\text{cy}}$−C12), 2×10^3 μm (PEO−PEI$_{\text{li}}$), 2×10^3 μm (PEO−PEI$_{\text{li}}$−C12), 2×10^3 μm (PEO−PEI$_{\text{br}}$) and 5×10^2 μm (PEO−PEI$_{\text{br}}$−C12). Obviously, the crystal sizes are reduced due to complexation in the case of PEO−PEI$_{\text{cy}}$−C12 and PEO−PEI$_{\text{br}}$−C12, but not for PEO−PEI$_{\text{li}}$−C12. The melt transitions of the crystallites as determined by differential scanning calorimetry are in the range 50−52 °C; this is independent of whether the PEO−PEIs are complexed or not. Homopolymers of poly(ethylene oxide) are known to form lamellar crystals with melt transitions that depend significantly on their molecular weights. As an example, the melting points of poly(ethylene oxide)s with narrow molecular weight distributions are 48, 58, and 64 °C for molecular weights of 1500, 3000, and 6000 g/mol, respectively.[24] Therefore, we assign the transitions in the copolymers and in their complexes to the melting of the crystalline poly(ethylene oxide) segments. Compared to a poly(ethylene oxide) homopolymer with a molecular weight of 5000 g/mol, its copolymerization with a poly(ethylene imine) block lowers the melting transition of poly(ethylene oxide) by about 5 °C. The lowering of the melt transition temperature for the complexes is the same as it is for the noncomplexed polymers. We compared the measured enthalpies of the melt transitions with the perfect heat of fusion of PEO (203 J/g)[25] in order to estimate the degree of the bulk crystallinity. Taking into account the different amount of PEO in the compounds we found the crystallinity of the PEO chains to be in the range 60−80%. This is something lower than that of neat PEO, whose crystallinity is in the range 70−80%.[25] The effect of the copolymerization with PEI is similar to the effect of blending PEO with PMMA,[25] while the complexation has no further significant influence on the melt transition of the PEO. Probably the complexed moieties do not significantly disturb the formation of the extended chain conformation and the integral number of folded chain conformations, which are typical for the crystalline form of PEO.[26] The conclusion that crystalline PEO segments are the origin of the endothermic transitions was confirmed by wide-angle X-ray experiments. It can be seen in Figure 4 (middle and upper curves) that the noncomplexed and the complexed polymers show the intense reflections of the PEO at scattering vectors of s = 2.18 and 2.65 nm^{-1}. But no crystalline reflections of the dodecanoic acid, for example at s = 2.44 nm^{-1} (Figure 4, lower curve), were found in the scattering curve of the complexes. Therefore, it can be concluded that, at room temperature, only the PEO segments are crystalline in the solid state of the complexes but the alkyl tails of the dodecanoate moieties are amorphous. They crystallize, similarly to PEI−C12 homopolymer complexes, partially at temperatures lower than about 0 °C.

Supramolecular Solid-State Structures. Small-angle X-ray scattering techniques were used to investigate the structure of the PEO−PEIs and their complexes with C12 on length scales in the range 1−50 nm. Small-angle diagrams are shown in Figures 5−7. A number of broad, equidistant reflections can be seen in the small-angle scattering diagram of PEO−PEI$_{\text{cy}}$ (Fig-

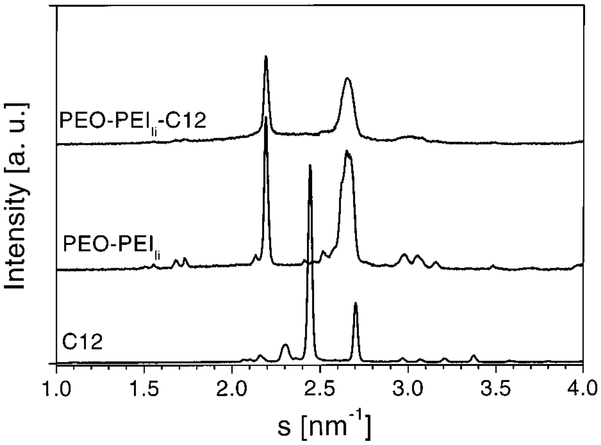

Figure 4. Wide-angle X-ray scattering curves of dodecanoic acid (C12), the noncomplexed poly(ethylene oxide)-*b*-poly(ethylenimine) (PEO−PEI$_{li}$−C12), which has a linear PEI block, and of the complex PEO−PEI$_{li}$−C12.

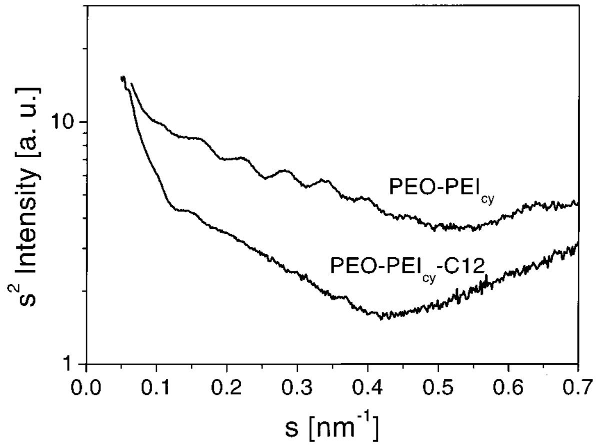

Figure 5. Small-angle X-ray scattering of samples with cyclic PEI blocks: PEO−PEI$_{cy}$ and PEI−PEI$_{cy}$−C12. The intensity is multiplied by the square of the scattering vector.

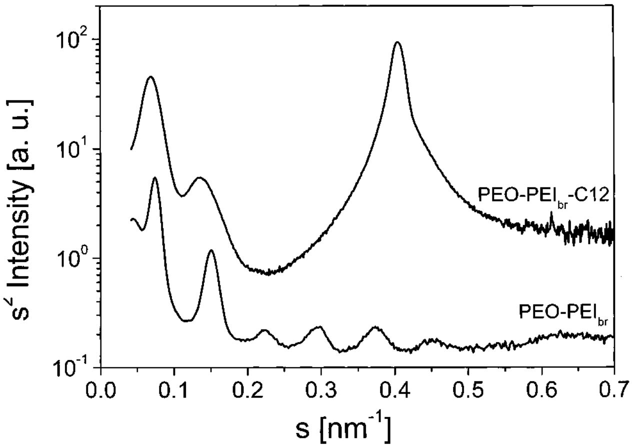

Figure 6. Small-angle X-ray scattering of samples with branched PEI blocks: PEO−PEI$_{br}$ and of PEI−PEI$_{br}$−C12. The intensity is multiplied by the square of the scattering vector.

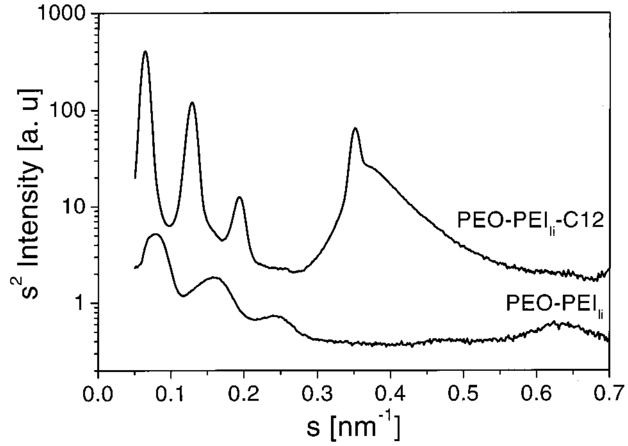

Figure 7. Small-angle X-ray scattering of samples with linear PEI blocks: PEO−PEI$_{li}$ and PEI−PEI$_{li}$−C12. The intensity is multiplied by the square of the scattering vector.

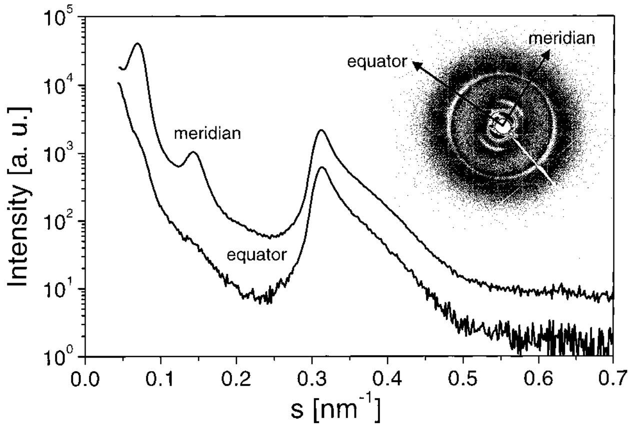

Figure 8. Two-dimensional small-angle X-ray scattering of an oriented sample of PEO−PEI$_{li}$−C12 (insert) and linear sections of the scattering intensity along the meridian and the equator. The direction of the X-ray beam was normal to the pellet surface.

ure 5, upper curve). This can be interpreted as resulting from a lamellar structure with a repeat unit in the range 12−15 nm. In contrast to PEO−PEI$_{cy}$, no reflections are present in that of PEO−PEI$_{cy}$−C12 (Figure 5, lower curve). Obviously the supramolecular lattice of PEO−PEI$_{cy}$ is destroyed by its complexation with C12. The situation is different for the two other complexes. In the small-angle scattering diagram of PEO−PEI$_{br}$ (Figure 6, lower curve) six equidistant reflections are found which can be interpreted as resulting from a lamellar structure with a long period of L = 13.3 nm. L is composed of lamellae with the thicknesses d_1 and d_2 in a way that $L = d_1 + d_2$. Assuming an idealized lamellar two-phase system with sharp interfaces and using a standard evaluation procedure[27] we calculated d_1 = 10. 5 nm and d_2 = 2.8 nm for PEO−PEI$_{br}$. d_1 can be attributed to lamellae that consist of PEO, and d_2, to lamellae that consist of PEI$_{br}$. The scattering pattern of the polymer changes after its complexation. It can be seen in Figure 6 (upper curve) that three reflections are present in the diagram of PEO−PEI$_{br}$−C12. We attribute the first and second reflection to the (100) and (200) reflection of a lamellar block copolymer spacing of L = 14.3 nm. d_1, the thickness of the PEO block, was calculated to be about 10.5 nm as found for the noncomplexed polymer whereas d_2 is about 3.8 nm, which can be attributed to lamellae consisting of the PEI$_{br}$−C12 complex. We tentatively assign the reflection, which corresponds to a Bragg spacing of 2.5 nm, to a short lamellar repeat unit formed by the PEI$_{br}$−C12 complex, which is itself within the large block copolymer lamellae. A sketch of the proposed structure is given in Figure 1. Similarly, so-called, lamellar-*within*-lamellar structures were reported by ten Brinke et al. and investigated in detail for a system of poly(styrene)-*b*-poly(4-vinylpyri-

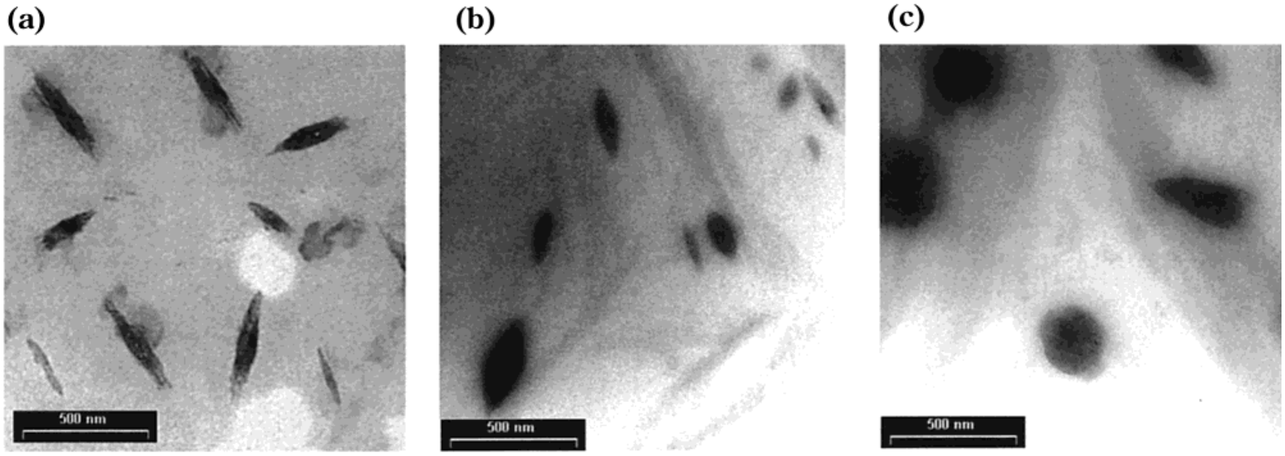

Figure 9. Typical transmission electron microscopy pictures of dried dispersions on a copper grid: (a) PEO−PEI$_{cy}$−C12; (b) PEO−PEI$_{li}$−C12; (c) PEO−PEI$_{br}$−C12.

Table 1. Structure Parameters of the Poly(ethylene oxide)-*b*-poly(ethylene imine)s and Their Complexes with Dodecanoic Acid As Calculated from Small-Angle Scattering Data

compound	L_1 (nm)	d_1 (nm)	d_2 (nm)	L_2 (nm)	type of structure
PEO−PEI$_{cy}$	12−15				lamellar
PEO−PEI$_{cy}$−C12					amorphous
PEO−PEI$_{li}$	12.5	10.8	1.7		lamellar
PEO−PEI$_{li}$−C12	15.5	11.8	3.7	2.9	lamellar-*within*-lamellar
PEO−PEI$_{br}$	13.3	10.5	2.8		lamellar
PEO−PEI$_{br}$−C12	14.3	10.5	3.8	2.5	lamellar-*within*-lamellar

dine) and pentadecylphenol with and without the addition of methanesulfonic acid.[28−31]

From the width of the first-order reflection of the block copolymer structure, it can be concluded that the correlation length of PEO−PEI$_{br}$ (125 nm) is larger than that of PEO−PEI$_{br}$−C12 (50 nm). Consequently, the long-range order of the block copolymer long period is reduced, in this case, due to complexation. The reverse condition was found for the corresponding scattering curves of PEO−PEI$_{li}$ and PEO−PEI$_{li}$−C12 (Figure 7, upper and lower curves, respectively). Here the correlation length of the complex (320 nm) is larger than that of the noncomplexed polymer (35 nm). Three equidistant reflections are present in the scattering curve of PEO−PEI$_{li}$, which are indicative for a lamellar system with a long period of $L = 12.5$ nm. Again we regard d_1 as being due to the PEO block (10.8 nm) and d_2 to the PEI block (1.7 nm). After complexation four sharp reflections were found in the scattering curve of PEO−PEI$_{li}$−C12, which were again tentatively assigned to a lamellar-*within*-lamellar structure. The larger lamellar structure has a long period of $L_1 = 15.5$ nm while the shorter lamellar structure has a long period of $L_2 = 2.9$ nm. L_1 was calculated to be composed of $d_1 = 11.8$ nm (PEO block) and $d_2 = 3.7$ nm (PEI−C12). The shorter long period that results from the PEI−C12 moieties is identical to that of the long period found for the PEI−C12 homopolymer (2.9 nm).[18] This is a further indication for the proposed structure model as shown in Figure 1. Macroscopically oriented samples of PEO−PEI$_{li}$−C12 were prepared in order to verify the lamellar-*within*-lamellar structure model. An example of the two-dimensional scattering diagram of such a sample of PEO−PEI$_{li}$−C12 can be seen in Figure 8 (inset). Furthermore, a meridional section and an equatorial section through the scattering curve are displayed in Figure 8. The direction of the scattering beam was normal to the pellet surface. Obviously the (100) and (200) block copolymer reflections are located around the meridian, while the center of the (010) reflection resulting form the PEI$_{li}$−C12 domains is located around the equator. The integral widths of the reflections are 50 (100), 57 (200), and 90° (010). These findings are in agreement with the proposed structure model of a lamellar-*within*-lamellar structure for the complex PEO−PEI$_{li}$−C12. The results from the small-angle scattering can be summarized in the following way: the two complexes PEO−PEI$_{li}$−C12 and PEO−PEO$_{br}$−C12 probably have a lamellar-*within*-lamellar structure and PEO−PEI$_{cy}$−C12 displays no periodic mesomorphic ordered structure. All the noncomplexed block copolymers display a simple lamellar mesophase structure. The structure parameters are summarized in Table 1. For more information, for example, on order−order and order−disorder transitions, it is necessary to measure the X-ray scattering as a function of the temperature, as it has been shown by ten Brinke et al.[28] We tried to dope the complexes with test drugs such as Q10 and triiodothyronine in analogy to the PEI−C12 homopolymer complexes described earlier.[20] It was found that both test drugs are incorporated in the structures of the complexes without crystallization. The loading capacities are of the order of 20% (Q10) and 15% (triiodothyronine) with respect to the amount of PEI−C12.

Core—Shell Micelles. Block copolymers containing a PEO block as a water-soluble segment and a second, water-insoluble block are known to be suitable for the formation of core−shell micelles whose cores can be loaded with hydrophilic drugs.[32] As an extension of this hydrophilic−hydrophobic concept, we have shown recently that double hydrophilic poly(ethylene oxide)-*b*-poly(L-lysine) can be converted into hydrophilic−hydrophobic ones by their complexation with retinoic acid, which resulted in micellar solutions of the complexes.[10] Therefore, we expected similar behavior in the PEO−PEI−C12 complexes. In fact, the complexes in the solid state dissolve easily in water to form micellar solutions, which was confirmed by dynamic light scattering. It was

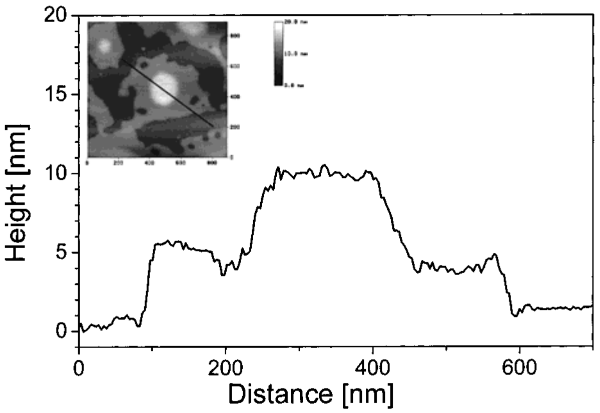

Figure 10. AFM image with a height profile of a PEO−PEI$_{br}$−C12 micelle dried on mica (insert) and a cross section of that micelle along the displayed line.

found that the mean micelle diameters depend on the PEI block. They were 190 nm (PEO−PEI$_{cy}$−C12), 140 nm (PEO−PEI$_{li}$−C12), and 280 nm (PEO−PEI$_{br}$−C12). The standard deviations of the micelle sizes were about 20%. The dispersions were tested to be stable at room temperature for a period of at least 30 days by using dynamic light scattering.

Measurements of the ζ potentials revealed that the micelles are electrically neutral. Obviously steric stabilization effects by the PEO blocks control the stability of the micelles. This is in contrast to core−shell micelles of PEI−C12 homopolymer complexes, which are highly positively charged, and show electrochemical stabilization.[20] Electron microscopy was carried out in order to determine differences in the shape of the micelles. An overview is given in Figure 9. It can be seen there that the micelles differ significantly in their shapes. PEO−PEI$_{cy}$−C12 micelles are strongly elongated, (Figure 9a), the micelles of PEO−PEI$_{li}$−C12 are slightly elongated (prolate, Figure 9b), and those of PEO−PEI$_{br}$−C12 are spherical (Figure 9c). We assume that the contrast of the particles in the electron microscopy pictures results from the cores of the micelles which are formed by PEI−C12, while the PEO blocks spread on the copper grid, which produce a nonuniform gray background. AFM measurements confirmed the assumption of a core−shell morphology of the micelles. An example is shown in Figure 10. It displays a height profile of a PEO−PEI$_{li}$−C12 micelle dried on mica which resembles a fried egg (insert) and further a cross section of the micelle along the displayed line. It can be seen that the core of the micelle rises about 12 nm above the mica substrate. Its diameter is about 150 nm. The cores are surrounded by a corona of PEO which rises about 5 nm above the mica. The reasons for the different shapes of the particles are not yet clear. Probably geometrical constraints due to the packing of the amphiphiles into the structures are significant in this respect. However, detailed investigations of such complexes with a number of molecular weights as well as structure simulations are necessary in order to justify this argument. In analogy to stealth liposomes,[33,34] it can be expected that the nanoparticles, which belong to the class of block ionomer complexes, exhibit prolonged circulation half-lives and dose-independent pharmacokinetics. Their lipophilic cores are able to carry drugs, while their shells, which consist of biocompatible PEO, guarantee their solubility.

Conclusions

We have demonstrated that poly(ethylene oxide)-*b*-poly(ethylene imine)s with a cyclic, linear as well as a branched poly(ethylene imine) block form lamellar structures. It was found that the complexation results in lamellar-*within*-lamellar structures in the case of the complexes with linear and branched poly(ethylene imine) blocks. The larger long period is formed by the block copolymer itself and the smaller long period is formed by the complexed blocks (cf. Figure 1). All the complexes form core−shell micelles in aqueous solution. Their cores are formed by poly(ethylene imine) dodecanoate each surrounded by a corona of poly(ethylene oxide).

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References and Notes

(1) Goddard, E. D. *Colloid Surf.* **1986**, *19*, 255.
(2) Wegner, G.; Ober, C. *Adv. Mater.* **1997**, *9*, 17.
(3) Antonietti, M.; Thünemann, A. *Curr. Opin. Colloid Interface Sci.* **1996**, *1*, 667−671.
(4) Kabanov, A. V.; Bronich, T. K.; Kabanov, V. A.; Yu, K.; Eisenberg, A. S *J. Am. Chem. Soc.* **1998**, *120*, 9941−9942.
(5) Bronich, T. K.; Kabanov, A. V.; Kabanov, V. A.; Yu, K.; Eisenberg, A. *Macromolecules* **1997**, *30*, 3519−3525.
(6) Kabanov, A. V.; Kabanov, V. A. *Bioconjugate Chem.* **1995**, *6*, 7−20.
(7) Boussif, O.; Lezoualch, F.; Zanta, M. A.; Mergny, M. D.; Scherman, D.; Demeneix, B.; Behr, J.-P. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 7297−7301.
(8) Vinogradov, S. V.; Bronich, T. K.; Kabanov, A. V. *Bioconjugate Chem.* **1998**, *9*, 805−812.
(9) Bronich, T. K.; Nehls, A.; Eisenberg, A.; Kabanov, V. A.; Kabanov, A. V. *Colloids Surf. B: Biointerfaces* **1999**, *16*, 243−251.
(10) Thünemann, A. F.; Beyermann, J.; Kukula, H. *Macromolecules* **2000**, *33*, 5906−5911.
(11) Cölfen, H. *Macromol. Rapid Commun.* **2001**, *22*, 219−252.
(12) Antonietti, M.; Conrad, J.; Thünemann, A *Macromolecules* **1994**, *27*, 6007−6011.
(13) Bronich, T. K.; Cherry, T.; Vinogradov, S. V.; Eisenberg, A.; Kabanov, V. A.; Kabanov, A. V. *Langmuir* **1998**, *14*, 6101−6106.
(14) Uchida, M.; Kunitake, T.; Kajiyama, T. *New Polym. Mater.* **1994**, *4*, 199−211.
(15) Nguyen, H. K.; Lemieux, P.; Vinogradov, S. V.; Gebhart, C. L.; Guerin, N.; Paradis, G.; Bronich, T. K.; Alakhov, V. Y.; Kabanov, A. V. *Gene Ther.* **2000**, *7*, 126−138.
(16) Thünemann, A. F.; Beyermann, J. *Macromolecules* **2000**, *33*, 6878−6885.
(17) Thünemann, A. F. *Langmuir* **2000**, *16*, 824−828.
(18) Thünemann, A. F.; General, S. *Langmuir* **2000**, *16*, 9634−9638.
(19) Ogiso, T.; Koike, K.; Iwaki, M.; Tanino, T.; Tanabe, G.; Muraoka, O. *Biol. Pharm. Bull.* **2000**, *23*, 844−849.
(20) Thünemann, A. F.; General, S. *J. Controlled Release* **2001**, *75*, 237−247.
(21) Sedlak, M.; Antonietti, M.; Cölfen, H. *Macromol. Chem. Phys.* **1998**, *199*, 247.
(22) Sedlak, M.; Cölfen, H. *Macromol. Chem. Phys.* **2001**, *202*, 587−597.

(23) Qi, L.; Cölfen, H.; Antonietti, M. *Nano Lett.* **2001**, *1*, 61−65.

(24) Point, J. J. *Macromolecules* **1997**, *30*, 1375−1384.

(25) Talibuddin, S.; Wu, L.; Runt, J.; Lin, J. S. *Macromolecules* **1996**, *29*, 9, 7527−7535.

(26) Dosiere, M. *Macromol. Symp.* **1997**, *114*, 51−62.

(27) Thünemann, A. F.; Janietz, S.; Anlauf, S.; Wedel, A. *J. Mater. Chem.* **2000**, *10*, 2652−2656.

(28) Ruokolainen, J.; Mäkinen, R.; Torkkeli, M.; Mäkelä, T.; Serimaa, R.; ten Brinke, G.; Ikkala, O. *Science* **1998**, *280*, 557−560.

(29) Ruokolainen, J.; Saariaho, M.; Ikkala, O.; ten Brinke, G.; Thomas, E. L.; Torkkeli, M.; Serimaa, R. *Macromolecules* **1999**, *32*, 1152−1158.

(30) Ikkala, O.; Ruokolainen, J.; Torkkeli, M.; Tanner, J.; Serimaa, R.; ten Brinke, G. *Colloid Surf. A: Physicochem. Eng. Asp.* **1999**, *147*, 241−248.

(31) Mäkinen, R.; Ruokolainen, J.; Ikkala, O.; de Moel, K.; ten Brinke, G.; de Odorico, W.; Stamm, M. *Macromolecules* **2000**, *33*, 3441−3446.

(32) Allen, C.; Maysinger, D.; Eisenberg, A. *Colloids Surf. B: Biointerfaces* **1999**, *16*, 3−27.

(33) Marjan, J. M. J.; Allen, T. M. *Biotechnol. Adv.* **1996**, *14*, 151−175.

(34) Allen, T. M.; Hansen, C. B.; Demenezes, D. E. L. *Adv. Drug Delivery Rev.* **1995**, *16*, 267−284.

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