Crystallinity Tunes Permeability of Polymer Nanocapsules

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ABSTRACT: Permeability is the key property of nanocapsules because it dictates the release rate of encapsulated payloads. Herein, we engineer the crystallinity of polymers confined in the shell of nanocapsules. Nanocapsules with crystalline shells are formed from polyurea and polyphosphoester. The thermal properties, such as crystallization temperature and degree of crystallinity, are different from the bulk. The degree of crystallinity is used to control the shell permeability and, therefore, the release of encapsulated payloads, such as fluorescent dyes, typically used as model components for biomedical applications.

INTRODUCTION

Nanocapsules (i.e., core–shell nanoparticles with a liquid core) are of outmost importance in the development of drug-delivery nanocarriers.1–3 Nanocapsules with an aqueous core are particularly interesting for therapy and diagnostics, as well as for the combination of therapy and diagnostics named theranostics,4,5 because they allow for the encapsulation of drugs, peptides, proteins,6–8 enzymes,9 nucleotides10,11 or contrast agents for medical imaging.12–15 The shell of nanocapsules is playing a key role in such applications because it protects the payload and dictates the permeability and, therefore, the release of the payload to the biological environment.16 In the case of nanocapsules with contrast agents for magnetic resonance imaging (MRI), the shell is even more important because it is also dictating the rate at which water molecules or protons are exchanged between the core and the biological milieu. In a previous work, we demonstrated that precise tuning of the chemistry of the nanocapsule polymer shell could yield a better performance for contrast agents expressed, in this case, by an increase in their relaxivity.17–19

Nanocapsule shells are basically curved nanosheets, sandwiched between a liquid core and the liquid continuous phase, creating a confined environment for polymer chains. It is now well-known that polymer chains in a confined environment exhibit properties that differ from their bulk properties,18,19 such as enhanced mobility20 and crystallization kinetics,21 nucleation mechanism,22 and crystal orientation.23 For example, although in the bulk the majority of polymers crystallize via a mechanism known as heterogeneous nucleation, poly(ethylene oxide) confined in ~100 nm droplets crystallizes in loosely layered lamellae via homogeneous nucleation.24 In addition, recent studies of polymer crystallization within nanometer size pores demonstrated that by confining polymers to small isolated volumes, one can nearly completely suppress heterogeneous nucleation in favor of homogeneous nucleation. In a simple view, this finding implies that heterogeneities are impurities extrinsic to the polymer that are effectively excluded in isolated nanometer size volumes.25 The degree of crystallinity of different polymers confined in nanoparticles (e.g., poly(l-lactide), syndiotactic or isotactic polystyrene) was found to decrease by decreasing the nanoparticle size.26 Furthermore, the permeability of polyurea microparticles was also found to depend on the degree of crystallinity of the polymer shell.27

The expectation born from these studies is that the physical properties of the polymer shell forming the nanocapsule must be significantly different from the bulk. This is particularly interesting because orientation and arrangement of polymer chains play a key role in the permeability of polymer materials. Torino et al. controlled the degree of crystallinity and shell thickness of poly(l-lactide) nanocapsules with sizes lower than 500 nm produced by thermally induced phase separation.28

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These physical properties induced a change in the hydrophilic drug entrapment, corresponding to the encapsulation efficiency, which was, however, below 25%. The authors hypothesized that the reduction in conformational entropy due to confinement induced more interactions between the polymer chains and the nanodroplet surface. The release rate was also found to be dependent on degree of crystallinity and shell thickness, both factors being not decoupled in the experiments proposed by the authors.

On the other hand, the miniemulsion process is a suitable method to fabricate nanocapsules with hydrophilic core and high encapsulation efficiency.27 It has been notably used for encapsulating contrast agents for magnetic resonance imaging (MRI).17,30 Wang et al. prepared nanosized poly(l-lactic acid) with homopolymers,32 copolymers,33 and triblock copoly-mer adduction in inverse miniemulsion 29 and (ii) using the reduction in conformational entropy due to con

Release of Cy5 from the Nanocapsules. The aqueous nanocapsule dispersion was filtered over Kim weave tissues to remove agglomerates formed during the transfer from cyclohexane into water. To calculate the loss after filtration, the solid content of the filtrated sample was determined and compared to the theoretical solid content. The aqueous nanocapsule dispersion (4 g) was filled into a dialysis membrane (MWCO 14,000, regenerated cellulose, Carl Roth) and dialyzed against water (246 g). At certain time intervals aliquots were withdrawn from the dialysate, and the Cy5 concentration was assessed by fluorescence spectroscopy.

Synthesis of PPE Nanocapsules. PhPPE (30 mg) was dissolved in chloroform (2 g), and PDMS (100 mg) was added to the solution. The organic phase was added to SDS solution (5 g, 0.3 wt % SDS in water) during sonication in an ultrasonic bath. Afterward, the mixture was stirred at 900 rpm for 24 h at room temperature in a glass vial with an open lid to slowly evaporate the cyclohexane.

Analytical Tools. The hydrodynamic radius and size distribution of the nanocapsule dispersions were determined by dynamic light scattering (DLS) performed with a PSS Nicomp Particle Sizer 380 at a scattering angle of 90°. For DLS measurements, the nanocapsule dispersions were diluted with cyclohexane or water. Scanning electron microscopy (SEM) images were recorded using a LEO (Zeiss) 1530 Gemini field emission microscope at an extractor voltage of 0.2 kV. Transmission electron microscopy (TEM) images were measured on a JEOL JEM-1400 electron microscope operating at an acceleration voltage of 120 kV. The samples for TEM and STEM were diluted to a solid content of about 0.01 wt % and drop-casted onto a silicon wafer or a carbon-coated copper grid, respectively. The shell thickness was assessed from TEM images and averaged over 100 measurements. The solid content was assessed gravimetrically by weighing 100 μL of sample before and after freeze-drying. Thermogravimetric analysis (TGA) was carried out using a Mettler Toledo ThermoSTAR TGA. The experiments were run in a nitrogen atmosphere heating from 25 to 800 °C with a heating rate of 10 °C/min. Differential scanning calorimetry (DSC) was performed using a Mettler Toledo DSC 3 calorimeter. The sample was filled in a 100 μL aluminum crucible and subjected to heating, cooling, and again heating cycles in a N2 atmosphere (30 mL/min) with a rate of 10 °C/min. DSC of the PhPPE nanocapsules was carried out in dispersion to keep the nanocapsule confinement intact after melting. The enthalpy of melting was evaluated as the area under the endothermal signal of the first
heating curve. Integration was performed with automatic baseline correction using the software STAR e 14.00 provided by Mettler Toledo. X-ray diffraction (XRD) analysis was performed using a Philips PW 1820 diffractometer with monochromatic Cu Kα radiation ($\lambda = 1.54$ Å) at 30 kV (5 s, $\Delta \theta = 0.02^\circ$). The degree of crystallinity was evaluated as the ratio of the integrated intensity of the crystalline reflections to the total area under the XRD pattern. Prior to integration the XRD patterns were corrected for background scattering. The size of the crystallites $L$ was calculated using the Scherrer equation (eq 1).

$$L = \frac{K\lambda}{b_{1/2} \cos \theta}$$  \hspace{1cm} (1)

where $K$ is a shape factor ($K = 0.9$), $\lambda$ the wavelength of Cu Kα radiation ($\lambda = 1.54$ Å), $b_{1/2}$ the full width at half-maximum of the reflection, and $\theta$ the scattering angle.

The concentration of Cy5 was assessed by fluorescence intensity measurements performed with a Tecan Infinite M1000 plate reader. The fluorescence intensity was recorded at an excitation wavelength of $\lambda_{ex} = 646$ nm, and an emission wavelength of $\lambda_{em} = 662$ nm, and was averaged over three measurements and divided by the solid content of the sample.

Dielectric spectroscopy measurements were performed with a Novocontrol Alpha frequency analyzer as a function of temperature. Dielectric spectroscopy measurements were recorded at different temperatures in the range from 223 to 433 K in steps of 5 K for frequencies in the range from $10^{-2}$ to $10^7$ Hz. The nanocapsules dispersion was dried by solvent evaporation prior to dielectric spectroscopy measurements. The complex dielectric permittivity $\varepsilon^*(T, \omega)$ was obtained as a function of frequency $\omega$ and temperature $T$, i.e., $\varepsilon^*(T, \omega)$. The analysis of the $T$-dependent experiments was made by using the empirical equation of Havriliak and Negami (HN) (eq 2).

$$\varepsilon^*(\omega, T) = \varepsilon_\infty(T) + \frac{\Delta\varepsilon(T)}{1 + (i\omega\tau_{HN}(T))^{mn}} + \frac{\sigma_0(T)}{i\omega\varepsilon_0}$$  \hspace{1cm} (2)

where $\varepsilon_\infty(T)$ is the high-frequency permittivity, $\tau_{HN}(T)$ is the characteristic relaxation time in this equation, $\Delta\varepsilon(T) = \varepsilon_0 - \varepsilon_\infty(T)$ is the relaxation strength, $m$ and $n$ (with limits $0 < m, n \leq 1$) describe respectively the symmetrical and asymmetrical broadening of the distribution of relaxation times, $\sigma_0$ is the dc conductivity, and $\varepsilon_0$ is the permittivity of free space. From $\tau_{HN}$ the relaxation time at maximum loss, $\tau_{\text{max}}$, is obtained analytically following eq 3.

Figure 1. Synthesis of nanocapsules, SEM and TEM images: (a) Nanocapsules with an aqueous core in an inverse miniemulsion. The water droplets, formed by emulsification and stabilized by a surfactant, contain a diamine and the cargo (aI). Upon addition of diisocyanate (aII), the polymerization is initialized at the water/oil interface to form a polymer shell surrounding the aqueous core. Following polymerization, nanocapsules can be transferred into water (aIII). (b) Nanocapsules with a hydrophobic core in a direct miniemulsion. The presynthesized polymer is dissolved in a chloroform–PDMS mixture and emulsified in water (bI). The hydrophobic droplets are stabilized by a surfactant. Upon evaporation of chloroform (bII) the polymer becomes insoluble, and nanocapsules with an oily core are formed (bIII).
real and imaginary parts of representation (emulsification of the molecule that is permeating are hindered in fusion because the solubility and diffusion of the molecule that is permeating are hindered in crystalline domains. Therefore, engineering crystalline domains in nanocapsules shells can increase barrier properties. In this work, we have synthesized semicrystalline nanocapsules with an adjustable degree of crystallinity. The latter was varied either by controlling the shell thickness at a constant nanocapsule size or by introducing side groups in the chemical structure of the polymer to change the crystallinity. Two types of polymers were studied: an aliphatic polyurea formed in situ during the nanocapsule synthesis (Figure 1a) and a pre-synthesized polyphosphoester that was subsequently emulsified (Figure 1b). These nanocapsules have hydrophilic/hydrophobic cores to enable encapsulation of water/oil-soluble substances, respectively.

In inverse miniemulsions, water droplets are dispersed in oil and nanocapsules having a hydrophobic core will form. The aqueous phase containing a diamine is dispersed in a cyclohexane phase containing a surfactant to stabilize the water droplets. Following emulsification, a diisocyanate dissolved in an apolar solvent is added. The polymerization reaction takes place at the droplet surface to form nanocapsules. The reaction takes place very fast, and a polyurea surrounding aqueous droplets is obtained. The droplets and the nanocapsules are stabilized by a surfactant. After polymerization, the polyurea nanocapsules can be transferred into water. Nanocapsules displayed a diameter of 300–500 nm (Table S1, Supporting Information). Scanning electron microscopy (SEM) micrographs show nanocapsules, which are collapsed upon sample preparation (i.e., drop casting followed by drying) and under the SEM vacuum conditions. Transmission electron microscopy (TEM) micrographs confirm the hollow structure of the nanocapsules (Figure 1a).

By direct miniemulsion (i.e., oil-in-water miniemulsion), nanocapsules with a hydrophobic core are obtained. We selected a polyphosphoester as a nanocapsule shell material because of its semicrystalline nature and its low melting temperature of about 50 °C, which make DSC measurements in aqueous dispersions possible. The core of nanocapsules was formed by poly(dimethyl)siloxane, a polymer that is initially miscible with the polymer solution but immiscible with water. For preparing semicrystalline nanocapsules, the polyphosphoester is dissolved in chloroform, mixed with poly(dimethyl)siloxane, and emulsified in water. Upon evaporation of chloroform, an internal phase separation occurs because the polymer is insoluble in the core, yielding oil-filled polyphosphoester nanocapsules dispersed in water with a hydrodynamic diameter of 190 nm and a PDI of 0.11. SEM images show collapsed nanocapsules, and TEM images identify core–shell structures (Figure 1b).

**Crystallinity of Nanocapsules.** Nanocapsules based on semicrystalline polymers are rarely reported. The polymeric nanocapsule shell is sandwiched between a liquid core and the liquid continuous phase, generating therefore a confinement for crystal growth. Crystalline lamellae are planar, but inside the nanocapsule shell they can only grow in a curved manner.

\[
\tau_{\text{max}} = \frac{\tau_{\text{IN}}}{\sin^{-1n}(\frac{\varepsilon m}{2(1+n)}) \sin^{1\alpha} (\frac{\varepsilon m}{2(1+n)})}
\]

(3)

In addition to the measured \( \epsilon^* \) spectra, the derivative of \( \epsilon^* \) (de/d ln \( \omega \) \( \sim - (2/\pi) \epsilon^* \)) was used in the analysis of the dynamic behavior. The characteristic time of ion mobility is obtained from the crossing of the real and imaginary parts of \( \epsilon^* \) or, equivalently, of the modulus \( M^* \) representation (\( \epsilon^* = 1/M^* \)).

**RESULTS AND DISCUSSION**

**Preparation of the Nanocapsules.** To tailor encapsulation and release behavior of nanocarriers, the nature of nanocapsule shell is of utmost importance. Crystalline domains are known to hinder diffusion because the solubility and diffusion of the molecule that is permeating are hindered in crystalline domains. Therefore, engineering crystalline domains in nanocapsule shells can increase barrier properties. In this work, we have synthesized semicrystalline nanocapsules with an adjustable degree of crystallinity. The latter was varied either by controlling the shell thickness at a constant nanocapsule size or by introducing side groups in the chemical structure of the polymer to change the crystallinity. Two types of polymers were studied: an aliphatic polyurea formed in situ during the nanocapsule synthesis (Figure 1a) and a pre-synthesized polyphosphoester that was subsequently emulsified (Figure 1b). These nanocapsules have hydrophilic/hydrophobic cores to enable encapsulation of water/oil-soluble substances, respectively.

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Hence, the growth of the crystalline domains and the overall degree of crystallinity are limited by the nanocapsule shell thickness as well as by the curvature of nanocapsules. In the present case, the shell thickness was adjusted by the total amount of polymer given by the amount of monomers used during the nanocapsule synthesis. This facilitates a comparison under a fixed nanocapsule size (Table S1). The increase in shell thickness is visible in TEM images (Figure S1). The re-arrangement of crystallinity. The relative intensity of the reflection at 2θ = 32° for polyurea nanocapsules (Figure 2a) exhibit prominent reflections in the region 15° < 2θ < 27°, a typical region for polyurea.38 The reflections indicate the semicrystalline character of the nanocapsules. XRD patterns showed an increasing degree in crystallinity (from 75% to 88% relative to the bulk) with increasing shell thickness (Figure 2b). As expected, nanocapsules were less crystalline than the bulk polyurea prepared by precipitation polymerization. In the XR patterns of the nanocapsule samples a reflection at 2θ = 32° is observed, which can be attributed to the NaCl present in the nanocapsules. The area under the reflection caused by NaCl was therefore not included in the calculation of the degree of crystallinity. The relative intensity of the reflection at 2θ = 32° correlates to the ratio of polymer to NaCl. The degree of crystallinity was further analyzed by DSC. In the first heating curve, a melting transition was found for all samples (Figure 2c). To ensure that the nanocapsules confinement was still intact and not destroyed by melting processes only the first heating curve of the DSC measurements was taken into account. With increasing shell thickness, an increase in melting enthalpy was found (Figure 2d), indicating that the nanocapsules were more crystalline.

A shift of about 30 °C to lower temperatures for the nanocapsules as compared to the bulk material was observed for the crystallization temperature during the DSC cooling cycle (Figure S2). The shift in crystallization temperature can be explained either by the occurrence of a different crystalline phase or by confinement effects. The latter results to higher undercooling derived from the small confining volume of nanocapsule shells. Moreover, as shown in Figure 2c, the DSC thermogram of the bulk and relative thick sample contained two transitions, which is different from the thinner nanocapsules that display only one transition. Indeed, in the bulk, the broad and bimodal melting peaks reflect melting of crystals of variable thicknesses. Under confinement, and especially for the nanocapsule with smaller shell thickness, there is first a reduction in melting temperature and, second, a single melting peak. Both observations suggest the melting of a more uniform crystal of reduced thickness as compared to the bulk. These findings are consistent with finite size effects as described by the Gibb–Thomson equation.

Dielectric spectroscopy (DS) measurements were carried out on the pure bulk polyurea, the surfactant polyisobutylene succinimide pentamine, and the nanocapsules to investigate their molecular dynamics. In contrast to X-ray scattering, which emphasizes the order within crystalline segments, DS is probing the segmental dynamics for those segments located in amorphous parts. Since all crystallizable polymers are semicrystalline in nature, X-ray scattering and DS provide complementary information on the structure and molecular dynamics, respectively. Figure S3 presents representative dielectric loss curves of the surfactant, the bulk polymer, and the nanocapsules at the same temperature. The curves indicate higher losses for the more polar surfactant. In addition, the segmental dynamics within the amorphous parts of the bulk material are effectively plasticized by the surfactant, as indicated by the shift of the relaxation times at maximum loss to lower temperatures (Figure S4).

**Release of Cargo from Semicrystalline Nanocapsules.** Release experiments were performed by encapsulating a fluorescent dye in the polyurea nanocapsules. The Cy5 molecule was selected because it is a dye presenting a good quantum yield and that is commonly used in biology. The only difference between the nanocapsules with Cy5 and the aforementioned nanocapsules was the presence or absence of Cy5. To evaluate the impact of polymer crystallinity on the diffusion of encapsulated payloads through the nanocapsules shell membrane, nanocapsules with comparable size and shell thickness should be formed. Accordingly, nanocapsules differing only in the diamine were synthesized. Side chain branches act as defects and are known to reduce crystallinity. The methyl group in methylpropane-1,3-diamine (MPDA) disturbs the packing and results in a polyurea (PUA) with a lower degree of crystallinity as compared to polyurea synthesized with 1,4-diaminobutane (DAB). DSC and XRD measurements (Figure S5) demonstrated that both types of nanocapsules were semicrystalline. The degree of crystallinity of MPDA-PUA nanocapsules was calculated to be roughly 60% of the degree of crystallinity from corresponding nanocapsules made of DAB-PUA. No significant difference in the shell thickness was observed (the shell thickness was 16 ± 3 and 16 ± 4 nm for DAB-PUA and MPDA-PUA, respectively). Subsequently, the release of encapsulated Cy5 from nanocapsules was measured during dialysis (Figure 3). Evidently, the MPDA-PUA-based nanocapsules showed a faster release of Cy5 than DAB-PUA-based nanocapsules. After 72 h, roughly twice of the amount of Cy5 was released from MPDA-PUA as compared to DAB-PUA capsules. This confirms that crystalline domains in the nanocapsule shell may act as barriers that hinder Cy5 diffusion. However, it is important to notice that properties such as specific volume and molecular weight are different for the two types of polyurea. This may also influence the release behavior of the payloads from the nanocapsules.

**Semicrystalline Polyphosphoester Nanocapsules.** To show that the crystallinity of the nanocapsules is not limited to the process and to the nature of polyurea nanocapsules, we prepared nanocapsules from a presynthesized semicrystalline polymer (i.e., polymer not formed in a dispersed medium) in
direct miniemulsion. In this case, polymer crystallization is confined between the core formed by polydimethylsiloxane (PDMS) and the outer interface of nanocapsules, which are dispersed in water. Firstly, an organic solution of PDMS and polyphosphoester is prepared and emulsified in an aqueous solution of surfactant. Small droplets are obtained after ultrasonication. The dispersion is then subjected to the evaporation of the organic solvent so that PDMS and the polyphosphoester remain in the dispersed state. Because both polymers are immiscible, an internal phase separation occurs, leading to the formation of core–shell nanoparticles. PDMS is more hydrophobic than the polyphosphoester and therefore the PDMS is in the core of the nanoparticles.

XRD patterns of the nanocapsules and the corresponding bulk material were recorded (Figure 4a). Both exhibit a reflection at 2θ = 21°, corresponding to a lattice spacing of 4.1 Å, which can be assigned to the polyethylene unit cell.38 At 2θ = 12° a halo for PDMS40 is observed. For the phenoxypolyphosphoester, two crystalline phases were reported: a 2-dimensional orthorhombic unit cell with lattice parameters a = 7.4 Å and b = 5.0 Å and a pseudohexagonal unit cell with lattice parameters a = 8.2 Å and b = 4.7 Å.41 The XRD pattern of the nanocapsules displayed broader reflections than the bulk material. Following the Scherrer equation (eq 1), the thickness of the crystals L was calculated from the full width at half-maximum of the reflections. L was found to be 5 nm for the reflections of the nanocapsules at 2θ = 21°. This observation indicates that smaller crystallites are present in the nanocapsule shell as in the bulk material (L = 8 nm).

DSC thermograms of nanocapsules were recorded in the dispersed state to ensure that confinement is kept intact upon melting. The latter was confirmed by DLS, SEM, and TEM measurements made after the thermal treatment experienced during DSC. As for the polyurea nanocapsules also the DSC cooling curves of PPE nanocapsules (Figure 4b) displayed a shift of 10 °C in crystallization temperature as compared to the bulk material. This shift was not observed for nanoparticles made of PPE (Figure S6).

**CONCLUSIONS**

It is shown that the permeability of the nanocapsule shell and therefore the release of small molecules depend not only on the thickness of the polymer shell but also strongly on the degree of crystallinity of the semicrystalline polymer. The degree of crystallinity can be further tuned by the molecular structure of the polymer. Increasing degree of crystallinity in the shell acts as a barrier and effectively hinders molecular diffusion from the capsules. This opens the way to construct nanocapsules with a tunable permeability for defined release kinetics.

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**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.7b00667.

SEM and TEM images of polyurea nanocapsules with different shell thicknesses, DLS results and thermograms, XRD patterns, and dielectric spectroscopy results (PDF)

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**Notes**

The authors declare no competing financial interest.

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**ABBREVIATIONS**

Cy5, sulfo-cyanine-5-carboxylic acid; DAB, 1,4-diaminobutane; HMDI, hexamethylene-1,6-diisocyanate; MPDA, 2-methyl-1,3-propylenediamine; PPE, polyphosphoester; PUA, polyurea; TDI, toluene-2,4-diisocyanate; THF, tetrahydrofuran.

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