Degradation versus self-assembly of block copolymer micelles

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The stability of micelles self-assembled from block copolymers can be altered by the degradation of the blocks. Slow degradation shifts the equilibrium size distribution of block copolymer micelles and change their properties. Quasi-equilibrium scaling theory shows that the degradation of hydrophobic blocks in the core of micelles destabilize the micelles reducing their size, while the degradation of hydrophilic blocks forming coronas of micelles favors larger micelles and may, at certain conditions, induce the formation of micelles from individual chains.

I. INTRODUCTION

Physicochemical properties of block copolymers often determine their function in many useful applications ranging from biotechnology and drug delivery to painting and oil extraction. The possibility to control essential properties of block copolymers capable to adapt the behavior to changes in the environment is thus a challenging task. One of the main properties of amphiphilic diblock copolymers in solution is their ability to self-assemble in micelles composed of a hydrophobic core surrounded by a hydrophilic corona. Such compact finite size aggregates can encapsulate hydrophobic agents in their cores. In particular, this loading capacity of block copolymers can be used for selective transport of hydrophobic nanoparticles and lipophilic active molecules to specific targets and through the cell membrane.

However, the use of block copolymer micelles for targeted drug delivery implies also the necessity to control the release of the transported particles from the cores of micelles, for example by external stimuli. In turn, the release process is closely related to thermodynamic stability of micelles. Micelles assembled from block copolymers can be relatively stable and thus limits their use for biomedical applications.

Degradable polymers provide for additional degree of freedom allowing to control the longevity and stability of block copolymer micelles. Degradation of the polymer backbone may change significantly the thermodynamics of block copolymer self-assembly and thus stability of the micelles. Tuning the rate of degradation would allow for modulation of the thermodynamic stability of micelles in large extent. In addition, tumor tissues have tendency to selectively accumulate polymers. This effect is known as the enhanced permeation and retention (EPR) and is attributed to larger size of the pores in blood vessels of tumor tissues. Polymers can interact with the cell membranes and reticuloendothelial system (RES), what can potentially increase their cytotoxicity. From this perspective, the degradation of polymers up to metabolites may solve biocompatibility issues and excessive accumulation in tissues.

Usually biomedical applications require long-circulating delivery vectors with constant release for days. This implies that polymer degradation in such systems is much slower than the time required to reach the thermodynamic equilibrium. Kinetics of micelle formation from monomers can be rather fast. Characteristic times of exchange of oligomers between micelles and the bulk and the relaxation do not exceed millisecond, while for longer block copolymers, the characteristic time is of order of minutes. Thus, in such systems the self-assembly in micelles is a quasi-equilibrium process with a fixed length distribution of the blocks, that changes with time. Micelles of degradable block copolymers can assemble and reassemble changing their internal structure and shape thus changing the loading capacity of the cores. The balance between steric repulsion of hydrophilic blocks in the coronas of micelles and interaction of hydrophobic blocks forming part of the cores defines the finite size of micelles. Degradation of hydrophilic blocks would then lead to destabilization of micelles leading to fusion and formation of larger cores. In turn, degradation of hydrophobic blocks in the cores may induce splitting the cores of micelles.

Using a scaling theory we study the interplay between the degradation of one of the blocks of block copolymers and equilibrium self-assembly and re-assembly of block copolymers into micelles in case of both corona and core degradation. We present a scaling theory of block-copolymer self-assembly into micelles, and discuss the degradation kinetics of the polymer blocks. However, we note that scaling theories have limitations, (i) Scaling theories in principle only apply to (infinitely) long chains. (ii) the theory does not include kinetics; (iii) it does not include morphological changes. We assume two types of degradation mechanisms, (i) random chain scission mechanism, which implies stochastic process of a polymer chain division at random posi-
tion. This mechanism causes a gradual decrease in the number average molecular weight. Such random division of a chain is usually observed in hydrolytic degradation of polyesters\cite{31,32} or certain polyamides\cite{33,34}. (ii) End-evaporation mechanism\cite{35,36}, when the monomers are gradually detached from the ends of the polymer chain. This mechanism is typical for enzymatic degradation. The degradation of the blocks shifts the critical micellar concentration (CMC) and changes the size distributions and the average sizes of the micelles (Figure 1). The degradation of the chains can induce or suppress the self-assembly process.

II. SELF-ASSEMBLY

Diblock copolymers composed of soluble and insoluble blocks can spontaneously self-assemble into micelles.\cite{1} The micellization is the entropy driven process, the entropy of mixture of individual chains in the solution is balanced by the tendency of insoluble blocks to reduce contacts with the solvent in the cores of micelles. Thus, the stability of the micelles is defined by the energy of insoluble blocks forming compact cores and the steric repulsion of soluble blocks in the coronas of micelles.\cite{28,29} Characteristic equilibration time of block copolymers depends exponentially on the length of the insoluble block\cite{16,17}. In the cases of long insoluble blocks and high interfacial tensions,\cite{31} the relaxation time may be hours, and thus non-equilibrium kinetics should be considered. However, we focus on situations when the hydrophobic block is relatively short or the interfacial tension is low. In this case the relaxation time is small (milliseconds)\cite{15} and thus the kinetics of self-assembly is much faster than the degradation. If the degradation process is slow enough to allow for the equilibrium assembly of block copolymers into micelles, the scaling model of equilibrium self-assembly can be applied. We assume that only one block, either insoluble or soluble, is degradable, so that the total number of block copolymers does not change with time. In addition, we consider spherical micelles, while morphological transitions are not considered. We denote $c_p$ the number density of aggregates comprising of $p$ copolymers, where $p$ is the aggregation number. The total free energy per unit volume of the solution of copolymers at a given time is

$$\frac{F}{kT} = \sum_{p=1}^{\infty} c_p \ln\left(\frac{c_p e^{p \Lambda^3}}{kT}\right) + \int_0^{\infty} c(n) \ln\left(\frac{c(n) e^{\Lambda^3}}{kT}\right) \, dn$$

(1)

where the first term is the entropy and $F_p$ is the free energy of a micelle comprising $p$ copolymers, $\Lambda$ is the de Broglie wavelength. $p = 1$ corresponds to individual block copolymers contributions, while the entropy of free fragments is taken into account in the last term. Degradation of blocks provokes the detachment of fragments of different lengths floating in the solution and the last term takes into account the entropy of fragments where $c(n)$ is their length distribution function. The total number of monomers in the self-assembly and the degradation process is conserved. This is reflected in the conservation of mass condition,

$$\sum_{p=1}^{\infty} p c_p = \varphi$$

(2)

where $\varphi$ is the total copolymer concentration. Since we consider the degradation of one block, the total number of copolymers in the solution is not changed with time and the degradation does not affect this condition. Minimization of the free energy (1) subject to the constraint (2) gives the quasi-equilibrium distribution of the copolymers in the micelles,\cite{38}

$$c_p = c_1^p \Lambda^{3(p-1)} \exp\left(-\frac{F_p - pF_1}{kT}\right)$$

(3)
This expression describes the distribution of micelles of degradable copolymers at each time.

Explicit form of the free energy $F_p$ is defined by the molecular structure of copolymers forming a micelle and is the sum of the corona and the core contributions,

$$F_p = F^\text{corona}_p + F^\text{core}_p$$

The free energy of individual chains, $p = 1$, is also described by this expression, where the corona term transforms in the entropy contribution of a linear chain and the insoluble block gives the corresponding core contribution. The exact expressions of $F^\text{corona}_p$ and $F^\text{core}_p$ depend on degradation mechanism and are functions of time.

In the following, we denote the chain length of the soluble block as $N$ and the chain length of the insoluble block as $N_c$. We assume sufficiently long soluble chains, $N \gg 1$, and the monomers of both blocks being of the same size $a$.

III. DEGRADATION KINETICS

We consider random chain scission and end evaporation mechanisms and degradation of soluble and insoluble blocks.

A. 1) Random chain scission

Random scission mechanism implies homogeneous distribution of splitting points along the chain. At a given time a chain is divided into random parts. Thus, the distribution of fragments of different lengths $P(n, t)$ is given by

$$\frac{1}{\kappa} \frac{\partial P(n, t)}{\partial t} = -n P(n, t) + \int_n^{\infty} dy P(y, t)$$

The negative term refers to the loss of chains of length $n$, and the positive term describes the gain of chains of length $n$ due to the degradation of longer chains (with lengths more than $n$) at a given time $t$. The coefficient $\kappa$ takes into account the fraction of chains that degrade simultaneously at each time, practically defining the timescale. Initial distribution of chains at $t = 0$ is assumed to be monodisperse. This equation is solved numerically by considering the integral in the right hand side $Q(n, t) = \int_n^{\infty} dy P(y, t)$ a numerical function. This function is calculated for a given time as a function of $n$ and then the equation (5) is solved numerically. Typical length distribution functions are shown in Figure 2 left column. Initial homogeneous distribution gradually disperses and shifts to small $n$.

1. a) Core degradation

Insoluble blocks tend to avoid contacts with water and favor assembly into the core of the micelle. The degradation of insoluble blocks makes block copolymers more soluble and this would shift the equilibrium towards smaller micelles. Assuming that the core of a micelle is a dense and homogeneous sphere formed by $p$ copolymers, the free energy of the core is given by

$$F^\text{core}_p = kT(36\pi)^{1/3}a N_c^{2/3} p^{2/3} + \frac{3\pi^2 p^2}{80N_c^4}$$

where $a$ is the surface tension of a sphere of radius $R_c = (3/(4\pi)pN_c)^{1/3}$ and the second term describes the elastic contributions arising from the stretching of insoluble blocks in the core. The “effective” surface tension of the core $\sigma$ describes implicitly the fact that the insoluble chains tend to avoid contact with the solvent by forming a dense core. The lengths of the insoluble blocks $N_c$ depend on time and for each time $t$ the length distribution is given by equation of random scission degradation (5).

Steric repulsion in the corona of the micelles, formed by soluble blocks, penalizes the formation of large micelles. Since the soluble block does not degrade, the corona of micelles is composed of chains of equal length $N$. The partition function of a monodisperse star $Z_p$ yields in the form

$$Z_p \propto N^{\gamma_p - 1}$$

where $N$ is the length of the arm, $\gamma_p$ are the universal critical exponents of the star polymers. The numerical values of $\gamma_p$ are known exactly for a wide range of $p$ and in the range $0 < p < 200$ can be interpolated by the power law expression $\gamma_p = 1 - 0.0893(p - 1.5)^{1.08}$. With this, the free energy of polydispers corona is given by

$$F^\text{corona}_p = -kT\ln Z_p = -kT(\gamma_p - 1)\ln N$$

Eqs. (6) and (8) define the free energy of micelles of $p$ copolymers and the free energy of individual chains for $p = 1$. It allows to calculate the size distribution of micelles as a function of time (3). The results are presented in Figure 3b. The degradation of the core starts when the micelles are formed (concentration above CMC). The micelles gradually decrease in size and disassemble. The degradation rate $\kappa$ is related to the time step in the degradation equation (6). The chosen value $\kappa = 0.0003$ is low enough to insure gradual changes in the size of the micelles. If the rate is higher, the micelles would disappear faster. In a real experimental situation this parameter connects the time step with real time, e.g. $\kappa = 0.0003$ signify that only three of ten thousand chains dissociate at one time step. In experiments this parameter may vary in a wide range.
2. b) Corona degradation

Situation is different when the soluble blocks can degrade while the insoluble blocks are stable. The cores of the micelles are formed by insoluble blocks and the core contribution has the same form as in previous case, eq. (6), but \( N_c \) remains constant. In turn, soluble blocks forming corona now can degrade with time and the corona contribution changes. Coronas of micelles are formed by polydisperse arms with the length distribution \( P(n, t) \) given by (5). The partition function of a polydisperse star \( Z_p \) yields in the form

\[
Z_p \propto n_1^{\gamma_p-\gamma_p-1} n_2^{\gamma_p-\gamma_p-2} \cdots n_{p-1}^{\gamma_p-\gamma_p-1} n_p^{\gamma_p-1} \tag{9}
\]

where \( n_1 < n_2 < \ldots < n_{p-1} < n_p \) are the lengths of the corresponding arms, sorted in ascending order. This partition function leads to the corresponding expression of the free energy of the corona,

\[
F_p^{\text{corona}} = -kT \left[ (\gamma_p - \gamma_{p-1}) \ln n_1 + (\gamma_{p-1} - \gamma_{p-2}) \ln n_2 + \ldots + (\gamma_1 - 1) \ln n_p \right] \tag{10}
\]

This expression defines, together with eq. (6), the free energy of the micelles and individual chains in the solution. In fact, the scaling expression of the corona contribution of a micelle with one arm, \( F_p^{\text{corona}} = -kT(\gamma_1 - 1) \ln N \) corresponds exactly to the scaling expression of a soluble chain in a solution.

The resulting size distribution of micelles (3) is shown in Figure 3b) and c) for different times. The effect of corona degradation is opposite to the case of core degradation. Figure 3b) shows the corona degradation kinetics for the same initial conditions as in Figure 3a) when the micelles are formed for conditions above CMC. Degradation of corona induces self-assembly of micelles from initially homogeneous solution of individual chains. Individual chains associate into micelles and the distribution of micelles grows. Consequent degradation leads to
the shrinkage of the corona, thus larger micelles become more stable and small micelles unstable. The size distribution of the micelles becomes broader with time due to increased polydispersity. Further degradation of hydrophilic blocks would lead to the growth of micelles, morphological changes of the micelle shape and consequent bulk phase separation.

Another important effect of corona degradation is the possibility to induce self-assembly of micelles from the solution below CMC (Figure 3c). The degradation induces formation of micelles from initially homogeneous solution first for small aggregation numbers. Consequent degradation increases the number of micelles, the polydispersity and the average size. Thus, the degradation influence the CMC, which is time dependent, Figure 4. It decreases with time in case of corona degradation (red curve) and increases with time in case of core degradation (blue curve).

The effect of degradation on micellization process can be summarized in the plot showing the position of the maximum of the size distribution, $p_{\text{max}}$. Parameters are the same as in Figure 3.

FIG. 3. Time evolution of the normalized size distribution $p_{c_p}$. a) core degradation above CMC, $\sigma = 0.81$, $\kappa = 0.0003$ b) corona degradation above CMC, $\sigma = 0.81$, $\kappa = 0.01$ c) corona degradation below CMC, $\sigma = 0.75$, $\kappa = 0.01$. The initial lengths of the blocks are: $N = 200$, $N_c = 20$, copolymer concentration $c_1 = 10^{-6}$.

FIG. 4. Time dependence of the critical micelle concentration (CMC). Parameters are the same as in Figure 3a) and b).

FIG. 5. Time evolution of the aggregation number of the maximum of the size distribution, $p_{\text{max}}$. Parameters are the same as in 3.

The effect of degradation on micellization process can be summarized in the plot showing the position of the maximum $p_{\text{max}}$ of the size distribution $c_p$, Figure 5. In case of core degradation (blue line) the maximum of the
distribution moves to small numbers (see Figure 3a) until the micelles disappear completely (dashed line), while in case of corona degradation (red curve) the size of the micelles increases (see Figure 3b) until the morphology changes or phase separation occur. If the degradation starts below CMC, the self-assembly into micelles starts at a given time which depends on the rate of degradation $\kappa$.

B. 2) End evaporation

Random division of a chain is not the only degradation mechanism of polymer chains. Degradation in certain chemical reactions and enzymatic degradation may lead to gradual decrease of the chains from the ends (chain-end-activated degradation). The process of loosing the monomers from the end is described by the following process, $P(n, t+1) - P(n, t) = \kappa (P(n+1, t) - P(n, t))$ which can be written in the integral form similar to (5) as

$$\frac{1}{\kappa} \frac{\partial P(n, t)}{\partial t} = -P(n, t) + \int_{n}^{\infty} \delta(y-n-1)dyP(y, t) \quad (11)$$

where $\delta$ is the Dirac function. Using this equation instead of (5), one can obtain the time dependence of the free energy of micelles for core and corona degradation. Figure 2 right column presents the kinetics end evaporation degradation. The starting and the final chain length distributions are very close for both types of degradation. That is why the micelle distributions shown for core degradation in Figure 6 also coincide. The difference is only seen for intermediate times. However, end evaporation degradation is much slower than random scission, thus the rates of degradation differ in this example 100 times.

In conclusion, scaling theory of quasi-equilibrium micellization coupled with the degradation of the blocks demonstrates that the degradation of hydrophilic blocks can induce self-assembly of copolymers into micelles and increase the size of the micelles, while the degradation of the hydrophobic blocks destabilize the micelles, reduce the equilibrium size of the micelles and can lead to complete disassociation of the micelles. It is valid for random scission mechanism assumed for degradation mechanics as well as for enzymatic (chain-end) scission mechanism. These findings may suggest the ways of controlled self-assembly and destabilization of micelles by degradation of the blocks. Our model do not account for morphological transitions and we plan to study them in future with a more detailed microscopic theory.

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[1] Hamley, I. Block Copolymers in Solution: Fundamentals and Applications; John Wiley & Sons: New York, 2005.
[2] Riess, G.; Hurtrez, G.; Bahadur, P. Block Copolymers, 2nd ed.; Wiley: New York, 1985; Vol. 2.
[3] Alexandridis, P.; Holzwarth, J. F.; Hatton, T. A. Macromolecules 1994, 27, 2414–2425.
[4] Adams, M. L.; Lavasanifar, A.; Kwon, G. S. J. Pharm. Sci. 2003, 92, 1343–1355.
[5] Torchilin, V. P. Pharm. Res. 2007, 24, 1–16.
[6] Savic, R.; Luo, L.; Eisenberg, A.; Mayninger, D. Science 2003, 300, 615–618.
[7] Hussein, G. A.; Pitt, W. G.; Christensen, D. A.; Dickinson, D. J. J. Control. Release 2009, 138, 45–48.
[8] Torchilin, V. Eur. J. Pharm. and Biopharm. 2009, 71, 431–444.
[9] Scott, Degradable Polymers, Principles and Applications; Kluwer Acad.Pub.: Dordrecht, 2002.
[10] Matsumura, Y.; Maeda, H. Cancer Research 1986, 46, 6387–6392.
[11] Pack, D. W.; Hoffman, A. S.; Pun, S.; Stayton, P. S. Nature Reviews: Drug discovery 2005, 4, 581–593.
[12] Lynch, A. L.; Chen, R.; Dominowski, P. J.; Shalaev, E. Y.; Yancey Jr., R. J.; Slater, N. K. H. Biomaterials 2010, 31, 6096–6103.
[13] Bastioli, C. Handbook of biodegradable polymers; Rapra Technology: Shawbury, UK, 2005.
[14] Moghimi, S. M.; Hunter, A. C.; Murray, J. C. *Pharmacol. Rev.* 2001, 53, 283–318.
[15] Kaatze, U. *J. Phys. Chem. B* 2011, 115, 10470–10477.
[16] Lund, R.; Willner, L.; Stellbrink, J.; Lindner, P.; Richter, D. *Phys. Rev. Lett.* 2006, 96, 068302.
[17] Lund, R.; Willner, L.; Pipich, V.; Grillo, I.; Lindner, P.; Colmenero, J.; Richter, D. *Macromolecules* 2011, 44, 6145–6154.
[18] Geng, Y.; Discher, D. E. *J. Am. Chem. Soc.* 2005, 127, 12780–12781.
[19] Hu, Y.; Jiang, Z.; Chen, R.; Wu, W.; Jiang, X. *Biomacromolecules* 2010, 11, 481–488.
[20] Frazza, E. J.; Schmitt, E. E. *J. Biomed. Mater. Res.* 1971, 5, 43–58.
[21] Mahmud, A.; Xiong, X.-B.; Lavasanifar, A. *Eur. J. Pharm. and Biopharm.* 2008, 69, 923–934.
[22] E. Pierri, K. A. 2005.
[23] Sun, H.; Guo, B.; Cheng, R.; Meng, F.; Liu, H.; Zhong, Z. *Biomaterials* 2009, 30, 6358–6366.
[24] Agrawal, S. K.; Sanabria-DeLong, N.; Coburn, J. M.; Tew, G. N.; Bhatia, S. R. *J. Control. Release* 2006, 112, 64–71.
[25] Wang, Y.-C.; Tang, L.-Y.; Sun, T.-M.; Li, C.-H.; Xiong, M.-H.; Wang, J. *Biomacromolecules* 2008, 9, 388–395.
[26] Lee, J.; Cho, E. C.; Cho, K. *J. Control. Release* 2004, 94, 323–335.
[27] Li, S.; Anjard, S.; Rashkov, I.; Vert, M. *Polymer* 1998, 39, 5421–5430.
[28] Sens, P.; Marques, C. M.; Joanny, J.-F. *Macromolecules* 1996, 29, 4880–4890.
[29] Baulin, V. A.; Lee, N.-K.; Johner, A.; Marques, C. M. *Macromolecules* 2006, 39, 871–876.
[30] Ben-Naim, E.; Krapivsky, P. *Physica D* 1997, 107, 156–160.
[31] Li, S. *J Biomed Mater Res.* 1999, 48, 342–353.
[32] Brown, D. W.; Lowry, R. E.; Smith, L. E. *Macromolecules* 1982, 15, 453–458.
[33] Garcia-Martin, M. G.; Hernandez, E. B.; Perez, R. R.; Galbis, J. A. *Polym. Degradation and Stability* 2008, 93, 1370–1375.
[34] Ruiz-Donaire, P.; Bou, J. J.; Munoz-Guerra, S.; Rodriguez-Galan, A. *J. Appl. Polym. Sci.* 1995, 58, 41–54.
[35] Marques, C. M.; Turner, M. S.; Cates, M. E. *J. Chem. Phys.* 1993, 99(9), 7260–7266.
[36] Dubbeldam, J. L. A.; van der Schoot, P. *J. Chem. Phys.* 2005, 123, 144912.
[37] Zinn, T.; Willner, L.; Lund, R.; Pipichc, V.; Richter, D. *Soft Matter* 2012, 8, 623–626.
[38] Baulin, V. A.; Johner, A.; Avalos, J. B. *J. Chem. Phys.* 2010, 133, 174905.
[39] Zhulina, E. B.; Adam, M.; LaRue, I.; Sheiko, S. S.; Rubinstein, M. *Macromolecules* 2005, 38, 5330–5351.
[40] Johner, A.; Joanny, J. F.; Diez-Orrite, S.; Bonet-Avalos, J. *Europhys. Lett.* 2001, 56, 549–555.
[41] Baulin, V. A.; Johner, A.; Marques, C. M. *Macromolecules* 2005, 38, 1434–1441.
[42] Duplantier, B. *J. Stat. Phys.* 1989, 54, 581–680.
[43] Hsu, H.-P.; Nadler, W.; Grassberger, P. *Macromolecules* 2004, 37, 4658–4663.
[44] Pogodin, S.; Baulin, V. A. *Soft Matter* 2010, 6, 2216–2226.