Supporting Information

Charged microcapsules for controlled release of hydrophobic actives

Part III: Effect of polyelectrolyte brush- and multilayers on sustained release

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Materials and Methods

Release measurements

The release was measured in 1 wt% Brij 35 solutions in which the saturation concentration of Disperse Red 13 was 86 ppm. Normally, sodium dodecyl sulphate (SDS) is the common choice of when it comes to increasing the solvency of a hydrophobic active for release measurements. However, SDS is an anionic surfactant and the resulting charged SDS-micelles may affect the PEM on the surface of the microspheres. Therefore, the non-ionic surfactant Brij 35 was chosen as solubility augmenting release-additive.

The concentration of microspheres in the suspension was diluted so that the total Disperse Red 13 concentration would correspond to 7.4 ppm. Immediately after dilution, samples were taken and the suspension was filtrated with PTFE syringe filters 0.2 µm (Millipore, Solna, SE).

The saturation concentration in water was very low and could not be determined by UV-vis measurements (<<0.1 ppm). This implies that the washing step using water as solvent during the polyelectrolyte multilayers assembly will not result in any significant release of Disperse Red 13 from the microspheres. The calibration curve for concentration determination is presented in Figure S1.

![Figure S1. Calibration curve of Disperse Red 13 in 1 wt% Brij 35.](image-url)
AFM

The atomic force microscope (AFM) measurements were performed at YKI (Stockholm, Sweden) using a PeakForce TUNA™ AFM (Bruker, Karlsruhe, Germany) equipped with a triangular silicon nitride probe (ScanAsyst-Air, Bruker, Karlsruhe, Germany). The measurements were performed in peak force tapping mode in order to obtained, in addition to the topography, the Young’s modulus using the Derjaguin–Muller–Toporov (DMT) model, the adhesion force and the maximum deformation.
Results

Light Microscopy

Table S1. Summary of the log-normal distribution determination of microsphere radius

<table>
<thead>
<tr>
<th>Dispersants</th>
<th>Size distribution</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>c [wt%]</td>
<td>$\mu$ [μm]</td>
</tr>
<tr>
<td>Conventional dispersants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMAA</td>
<td>0.4</td>
<td>3.9</td>
</tr>
<tr>
<td>PVA</td>
<td>0.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Block copolymer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600-6-4600</td>
<td>0.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Figure S2. Light microscope image of microspheres prepared with 600-6-4600. The microspheres obtain the characteristic red colour of Disperse Red 13.
Microelectrophoresis

In Fig. 3 in the article, the electrophoretic mobility is presented rather than the $\zeta$-potential derived using the Smoluchowski equation (Equation 4 in the article). The plane of shear (at which the $\zeta$-potential is defined) is not well defined for particles with adsorbed polymer layers. This is the reason why the surface charge is represented by the electrophoretic mobility in Fig. 3 in the article. However, regarding polyelectrolyte LbL adsorption on colloidal particles, the $\zeta$-potential is still the most common representation of the charge inversion. Therefore, the derived $\zeta$-potential is presented in Figure S3.

![Graph](image)

**Figure S3.** LbL adsorption of PDADMAC and PMANa on a 600-b-4600 based PMMA surface. $\delta$ is the thickness of the adsorbed film as measured using QCM-D (right y-axis, ●, ---), $n$ is the number of layers that build up the film (x-axis) and the $\zeta$-potential (left y-axis, ■, --) is measured using microelectrophoresis on the corresponding colloidal system. The plot has been normalized so that for the adsorbed 600-b-4600 brush layer $n=0$ and $\delta=0$. The hypothetical layer $n=-1$ corresponds to the bare PMMA surface, which is uncharged, and $\Delta\delta=\delta_{n=-1} - \delta_{n=0}$ is the thickness of the block copolymer brush layer.
Figure S4. Pure gold surface of a QCM-D crystal displaying the topography (A), the Young’s modulus (B), the adhesion force (C) and maximum deformation (D).

The pure gold surface of the QCM-D crystals was rather rough (see Figure S4) and appeared to consist of ~100 nm sized gold flakes. It is clear that the spin-coating of the surface with a PMMA solution resulted in a significant smoothing of the surface (see Figure S5). The homogenous surface had a surface roughness of less then 1 nm.
Figure S5. QCM-D crystal coated with a PMMA layer displaying the topography (A), the Young’s modulus (B), the adhesion force (C) and maximum deformation (D).

The functionalization of the PMMA surface with the block copolymer 600-b-4600 rendered the surface more heterogeneous (see Figure S6) with a larger surface roughness, yet still with a significantly lower surface roughness as compared with the pure gold surface. Moreover, the block copolymer brush surface was softer as compared with the PMMA surface (see Figure S6B and Figure S5B). In addition, the adhesion force between the cantilever and the block copolymer surface was higher as compared with the PMMA surface. The heterogeneity was most apparent in the adhesion image where areas of higher adhesion surrounded areas of lower adhesion, comparable with the adhesion for pure PMMA. We propose that the darker areas (lower adhesion) correspond to PMMA and the brighter areas (higher adhesion) correspond to the polyelectrolyte block.
Figure S6. QCM-D crystal coated with a PMMA layer and subsequently functionalized by the block copolymer 600-b-4600 displaying the topography (A), the Young’s modulus (B), the adhesion force (C) and maximum deformation (D).
**QCM-D measurements**

Adsorptions isotherms of the dispersants on model PMMA surfaces (see Figures S7-S8) reveal that PVA adsorbs in much higher amounts compared with PMAA and 600-b-4600. The preparation of surfaces and solutions and details of the measurements have been described in detail elsewhere\(^1,2\).

The adsorption of the dispersants displayed in Fig. 2 in the article were fitted according to a Langmuir adsorption isotherm (see Equation S1), where \(\Gamma\) is the adsorbed amount, \(\Gamma_{\text{max}}\) the *maximum adsorbed amount or binding site density*, \(K\) the *equilibrium or affinity constant* and \(c\) the bulk concentration. The product \(\Gamma_{\text{max}}K\) is sometimes called the *binding capacity*. The obtained parameters are presented in Table S2.

\[
\Gamma = \Gamma_{\text{max}} \frac{Kc}{1 + Kc}
\]

**S1**

<table>
<thead>
<tr>
<th>Dispersant</th>
<th>QCM-D</th>
<th>(K_{\text{max}}) [ng/cm(^2)]</th>
<th>(K) [wt%(^{-1})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA</td>
<td>1664</td>
<td>517.9</td>
<td></td>
</tr>
<tr>
<td>PMAA</td>
<td>402.0</td>
<td>33.78</td>
<td></td>
</tr>
<tr>
<td>600-b-4600</td>
<td>266.1</td>
<td>6039</td>
<td></td>
</tr>
</tbody>
</table>

Table S2. Parameters from adsorption isotherms obtained with QCM-D measurements.

The QCM-D measurements provide information concerning both the adsorbed amount of solute (polymeric dispersant in our case) and the amount of “bound water”\(^3\). The amount of bound water gives, for the adsorbed polymer, consequently information on the degree of swelling and the chain segment conformation. The adsorbed polymer is usually described as consisting of trains, loops and tails\(^4\). A polymer swelled with water will have a high fraction of tails whereas a collapsed polymer layer will consist predominantly of trains\(^4\). These different situations are reflected in the QCM-D signals\(^3,5\). A collapsed layer consisting of small amounts of water will have a very low dissipation\(^5\). In addition, the shift of the different
harmonics will coincide. In contrast, if the adsorbed layer contains a significant portion of water and therefore possesses significant viscoelastic properties, the different harmonics will be separated. The higher the harmonics, the shorter the decay depth of the acoustic wave. Higher harmonics are therefore probing layers closer to the surface. In addition, the dissipation will be large due to the loss of mechanical energy via viscous forces. Therefore, the adsorbed mass as estimated using the Sauerbrey equation (see Equation 5 in the article) is underestimated and viscoelastic models (Voight or Maxwell elements) should be applied.

Regarding the PVA adsorption in Figure S7, both the frequency shift and the dissipation are very large and the harmonics are well separated, even for the adsorption at the lowest concentration. This indicates that PVA adsorbs as a thick layer, heavily swelled with water. It is also apparent that a large fraction is irreversibly adsorbed after rinsing.

The PMAA adsorption in Figure S8 is very different as compared with the PVA adsorption in Figure S7. The amount adsorbed polymer is much smaller as indicated by the frequency shift. In addition, the dissipation and the spreading of the harmonics is very small, which indicate that the PMAA layer initially is very collapsed up to the highest concentration of 1 wt%. The peculiar behaviour during the rinsing step needs a clarification. Since PMAA is a weak acid, the pH of the bulk is low for the adsorption at higher concentrations. However, the pH of the

Figure S7. Adsorption isotherm of PVA on a PMMA surface. The legends D and F indicate the dissipation and the frequency of the third (3), fifth (5) and seventh harmonics (7).

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rinsing medium is neutral. This results in an initial swelling of the adsorbed layer followed by desorption. This has been investigated by us in detail elsewhere².

![Graph showing adsorption of PMAA on a PMMA surface](image)

**Figure S8.** Adsorption of PMAA on a PMMA surface. The legends D and F indicate the dissipation and the frequency of the third (3), fifth (5), seventh (7) and ninth (9) harmonics.

The adsorption of the block copolymer 600-\(b\)-4600 in Figure S9 is high already at very low concentrations. Here, the separation of lower harmonics is much more pronounced as compared with the separation of the higher harmonics. It is likely that this reflects that the adsorbing polymer is indeed a block copolymer where the segments closer to the PMMA surface consists of densely packed PMMA blocks whereas the polyelectrolyte blocks, which are more swelled by water, extends into the solution. This situation is also reflected in the separation of the harmonics of the dissipation. Rinsing of the surface results in less desorption as compared with the corresponding PMAA system and a large portion appear to be more irreversibly adsorbed.
Figure S9. Adsorption of 600-b-4600 on a PMMA surface. The legends D and F indicate the dissipation and the frequency of the third (3), fifth (5), seventh (7), ninth (9), eleventh (11) and thirteenth (13) harmonics.

**LbL adsorption**

It is clear from Figure S10 that the LBL adsorption of the PDADMAC/PMANa pair resulted in a consecutive adsorption of polyelectrolyte multilayers on a PMMA surface functionalized with embedded block copolymer (600-b-4600). The dissipation and the separation of the harmonics were high during the adsorption stage of both PDADMAC and PMANa indicating a large fraction of loosely bound polyelectrolyte and a high content of tails. However, as the surface was rinsed, the dissipation and the separation of the harmonics became very small which indicated a significant compaction of the polyelectrolyte multilayer, indicating that these consisted predominantly of trains. It is important to note that the rinsing medium was 1M NaCl Milli-Q solution. The high salt concentration used should result in a swelling of the PEM due to the screening of the electrostatic attraction. This further accentuates the efficient charge matching and dense packing of the PEM. This has been studied and reported in more detail by us elsewhere. 

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Figure S10. Adsorption of PDADMAC and PMANa on PMMA embedded block copolymer 600-b-4600 surface. The legends D and F indicate the dissipation and the frequency of the third (3), fifth (5) and seventh harmonics (7).

In order to account for the initial, surface induced, stronger adsorption, the thickness, $\delta$, from Figure S10 and Fig. 3 in the article was fitted with a second grade hyperbolic growth (see Equation S2). $A$ represents the saturation limit for the strong adsorption, $B$ is a theoretical value describing at which layer number half the saturation limit is achieved and $C$ is the growth per layer at higher layer numbers. Note that $B$ is a continuous variable and purely theoretical whereas $n$ (number of layers) is a discrete variable.

$$\delta = A \frac{n}{B + n} + C n$$  \hspace{1cm} (S2)

After the first or the second adsorption cycle, for which the underlying surface played a decisive role, the layer growth was linear ($C=0.32$ for the 600-b-4600 based system).
Release measurements

Table S3. Diffusion coefficient and fraction of burst released amount obtained from the fitted model (Equation 6 in the article).

<table>
<thead>
<tr>
<th></th>
<th>PMAA 600-b-4600</th>
<th>bare</th>
<th>0.5 bilayer</th>
<th>1.0 bilayer</th>
<th>1.5 bilayer</th>
<th>2.0 bilayer</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D \times 10^{22}$ [m$^2$s$^{-1}$]</td>
<td>261</td>
<td>17.7</td>
<td>3.34</td>
<td>1.83</td>
<td>2.36</td>
<td>1.68</td>
</tr>
<tr>
<td>Burst rate [s$^{-1}$] $\times 10^3$</td>
<td>15.9</td>
<td>14.3</td>
<td>0.213</td>
<td>0.260</td>
<td>0.204</td>
<td>0.087</td>
</tr>
<tr>
<td>Burst fraction [%]</td>
<td>27.3</td>
<td>2.31</td>
<td>3.07</td>
<td>2.34</td>
<td>2.37</td>
<td>2.28</td>
</tr>
</tbody>
</table>

![Graph](image)

Figure S11. Release measurements from PMAA based microspheres at acidic (red) and neutral (blue) conditions.

Diffusive release

The release data (Fig. 4 in the article) were evaluated by applying a fitting function that includes both burst release and diffusive release (Equation 7 in the article). The diffusive part is modelled as diffusion out from homogeneous spherical particles, i.e. both the PMMA sphere and the dispersant layer are taken into consideration as one piece of material. An effective diffusion constant is thus calculated and reflects the diffusion in the entire microparticle. From a modelling point of view, a core-shell geometry (PMMA as core and dispersant layer as shell) would be a more appropriate selection compared to a homogeneous
sphere. However, such a model requires knowledge of (i) the initial distribution of the active substance in the core and the shell and (ii) the partition coefficient between these domains. We therefore find the model of homogeneous spherical particles as a simplified but justified choice. The specific effect of the dispersant layer on the release is further evaluated by Equation S3 and Equation 8 (Section 3.2.2. in the article) and explained in detail below.

The following derivation of the effective diffusion coefficient or total permeability (Equation S3 and Equation 8 in the article) from the microsphere is based on a number of simplifications. These include the reduction to planar geometry (which however is appropriate for sufficiently thin sections at the surface of the microsphere), perfect sink conditions and a linearization of the concentration gradient in the barrier \( \partial c(\delta)/\partial \delta \approx \Delta c_i/\delta_i \) where \( \Delta c_i \) and \( \delta_i \) is the concentration difference and the thickness of the \( i \)th barrier and \( c_0 \) is the concentration of Disperse Red 13 in the centre of the microsphere. We are only using this expression to qualitatively describe the behaviour of the permeability as a function dispersant layer/PEM thickness. No attempts should be made to try to quantify the results.

We can assume that the dispersant/PEM thickness is much smaller than the PMMA barrier thickness \( \delta_m \ll \delta_p \), around 2-3 orders of magnitude since \( \delta_p \approx \delta_{TOT} \), where \( \delta_{TOT} \) should be on the order of the microsphere radius.

\[
J = \frac{c_0}{r_{TOT}} = \frac{c_i D_{eff}}{\delta_{TOT}} = \frac{c_i}{r_m + r_m} = \frac{c_i}{D_p K_{pp} + D_m K_{mp}} \\
K_{pp} = 1 \\
D_{eff} = \frac{\delta_{TOT}}{D_p + \frac{\delta_m}{D_m K_{mp}}} = \frac{A}{B + \frac{\delta_m}{P_m}}
\]

The function \( D_{eff}(\delta_m) \) in Equation S3 has a few properties that need some clarification and which are visualized in Figure S12. According to Equation 3, the permeability \( (D_{eff}) \) will be dominated by the diffusion through the PMMA matrix and \( r_m \) can be omitted for very low values of \( \delta_m \), i.e. the PMMA phase will be the rate determining barrier. As \( \delta_m \) approaches a critical thickness \( \delta_m^* \), \( r_m = r_p \) and the total permeability will be strongly dependent on the properties of both barriers (see Figure S12). The exact value of \( \delta_m^* \) depends on the magnitude of \( P_m \) in relation to \( P_p \). As \( \delta_m \) increase beyond \( \delta_m^* \), the reduction of the permeability \( D_{eff} \) will become less pronounced and \( D_{eff} \approx D_m K_m \delta_m/\delta_{TOT} \). Naturally, the effective diffusion constant
will approach the asymptotic value $D_{\text{eff}}(\delta_m \to \infty) = D_m K_m$ for very large $\delta_m$ since $\delta_{\text{TOT}}(\delta_m \to \infty) = (\delta_p + \delta_m) \approx \delta_m$.

\[
D_{\text{eff}} = P_{\text{TOT}}
\]

**Figure S12.** Schematic graph of the effective diffusion constant or permeability as a function of $\delta_m$ according to Equation S3. Here, $P_p$ and $\delta_p$ is set to 1 which renders $r_p = 1$. $P_m$ is set to 0.01 and $\delta_{\text{TOT}} = \delta_p + \delta_m$.

In Fig. 6 in the article, $D_{\text{eff}}(\delta_m)$ was plotted such that $\delta_m = 0$ corresponds to the effective diffusion coefficient of the bare and untreated block copolymer surface. However, it might be reasonable to speculate that $D_{\text{eff}}(\delta_m = 0)$ should rather correspond to the diffusion coefficient obtained from the PMAA based microspheres for a number of reasons. The PEM functionalized microspheres do not have an intact polyelectrolyte brush since this dispersant layer collapses during the PEM assembly. Moreover, $D_{\text{eff}}$ for the PMAA based microspheres is most likely representative of the actual diffusion in the PMMA matrix. If the thickness of the collapsed polyelectrolyte brush is omitted (which is most likely very low given the low molecular weight of the PMANa block), the plot of $D_{\text{eff}}(\delta_m)$ in Figure S13 would correspond to the effect of a charged PEM barrier on top of a solid PMMA matrix. However, it is interesting to note that the fits of $D_{\text{eff}}(\delta_m)$ in Figure S13 and Fig. 6 in the article result in almost equivalent values of $P_m$. The *effective thickness* of the block copolymer polyelectrolyte brush layer would according to the fit in Figure S13 correspond to 0.15 nm (compare with the actual brush thickness of 3.8 nm).
Figure S13. The modelled effective diffusion coefficient obtained from Equation S3 as a function of the PEM thickness obtained from QCM-D measurements. The data has been fitted with a hyperbolic function $A/(B+\delta_m/C)$. Here, $D_{\text{eff}}(\delta_m=0)$ is the obtained diffusion coefficient for the PMAA based surface. The thickness of the collapsed block copolymer brush has been omitted.

References