Wrinkling of an Enteric Coating Induced by Vapor-Deposited Stimuli-Responsive Hydrogel Thin Films

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ABSTRACT: In this contribution, we report on the thin-film synthesis of a thermosensitive polymer onto another polymer used as an enteric coating in drug applications. In particular, we deposit cross-linked poly(N-vinylcaprolactam) (pNVCL) thin films by initiated chemical vapor deposition (iCVD) onto spin-coated Eudragit (EUD) layers. Already upon iCVD synthesis, the layered structure starts to form wrinkles at a minimum iCVD thickness of 30 nm. By changing the EUD layer thickness and the amount of cross-linking used during iCVD, the morphology of the wrinkles is demonstrated to be readily tunable. Laterally, the double-layer structures vary in morphology from being ultrasmooth to exhibiting up to a 3.5 μm wrinkle wavelength. The surface roughness and, thus, the wrinkles’ height can be tailored from below 1 nm up to 100 nm. From the resulting wavelength of wrinkles, an estimation of the elastic modulus of pNVCL proves its tunability over a wide range of values thanks to the iCVD process. This study elucidates an uncomplicated way to tune the wrinkles’ morphology and, thus, the surface area of a system that can be employed in drug delivery applications. Hence, an enteric coating of EUD together with an iCVD-synthesized thermosensitive thin film is proposed as a promising composite encapsulation layer to outperform established systems in terms of tunability of the response to multiple external stimuli.

INTRODUCTION

Besides fundamental interest in wrinkling, wrinkled structures are used in applications, where an enhancement of the surface area yields superior device performance. In photovoltaics, a larger contact area in pn-junctions allows for accessing higher area yields superior device performance. Hence, an enteric coating of EUD together with an iCVD-synthesized thermosensitive thin film is proposed as a promising composite encapsulation layer to outperform established systems in terms of tunability of the response to multiple external stimuli.

chemical vapor deposition (CVD) technique; the results showed that wrinkling occurs even without prestraining the substrate and, thus, directly upon coating an amorphous drug.1 While the direction of the wrinkles is not adjustable, the wrinkles’ size (height and wavelength) were clearly dependent on the thickness of the encapsulated layer. Further, the nature of the solid state of the encapsulated drug layer directly influenced the capability of wrinkle formation; while crystalline drug layers prevented the formation of wrinkles, an amorphous state was observed to induce wrinkled structures. Also, the chemical composition of the CVD coating had an impact not only on the wrinkle formation12 but also on the stabilization of the amorphous state of the drug in general.13

Employing initiated chemical vapor deposition (iCVD) as a solvent-free process allows for the coating also of delicate substrates, which might even be liquid. The underlying mechanism is similar to free-radical polymerization processes,11 where an initiator (typically, a peroxide) is decomposed into radicals at a heated filament, which interact with a monomer so that polymer synthesis is initiated, propagated by further monomer units until terminated by another radical. With the possibility of employing a plethora of chemical structures of the monomer, vast amounts of distinct polymers can be synthesized and conformly deposited onto three-dimensional (3D)-nanostructured substrates. For appli-
ations, the synthesis of smart polymer thin films is particularly interesting. Numerous polymers responding to variations in humidity, pH, salt, or solutes present in a solution have been developed. Cross-linking of the polymeric structures, for instance, by copolymerizing di(ethylene glycol) divinyl ether (DEGDVE) together with the monomer exhibiting the desired functionalities, enables the variation of the polymers’ swelling behavior. Recently, another interesting polymer, namely, poly(N-vinylcaprolactam) (pNVCL), has been synthesized by iCVD allowing for further tunability of the polymeric thermoresponsiveness. Importantly, this polymer is biocompatible, making it a promising candidate also for other medical applications, where coating might assist some purpose, i.e., abrasion or cell adhesion.

In this contribution, we study the wrinkle formation upon iCVD synthesis of a thermoresponsive polymer thin film (i.e., p(NVCL-co-DEGDVE)) directly onto another polymer, being Eudragit E100 (EUD). EUD is typically employed as a drug coating itself, adopting solution-based techniques; it is soluble at low pH and only swells at larger pH, typically above 5, making it usable as an enteric coating. On addition of the thermoresponsive pNVCL-based thin film, the temperature response can be tuned in potential applications. On the one hand, a superior coating might be achieved by the tunability in the thermoresponsiveness of pNVCL and the enteric properties of EUD. On the other hand, the larger surface area due to wrinkling might be used to alter the release behavior of the resulting structures, when used for encapsulation purposes.

### EXPERIMENTAL METHODS

Single crystal silicon wafers (Siegert Wafers, Germany) with a native oxide layer were used as substrates. Substrates were prepared by cutting the wafers into 2 × 2 cm² pieces, sonicating them in EtOH and acetone baths, and, finally, drying under a nitrogen stream. An amino methacrylate copolymer with the tradename Eudragit E100 from Evonik (Germany) is a coating material typically used in pharmaceutical applications. The material was used as delivered. For the sample preparation, the material was dissolved in toluene (Sigma-Aldrich, Germany) at different concentrations. Using a standard spin coater employing a spin speed of 17 rpm for 60 s, this allowed to deposit homogeneous layers of EUD ranging in thickness between a couple of nm up to nearly 1 μm. The thickness of these layers was determined using a spectroscopic ellipsometer (M-2000S, J.A. Woollam). The measurements were performed in a wavelength range of 370–1000 nm at three angles (65°/70°/75°). The experimental data was fitted within the CompleteEASE software package by an optical model consisting of a Si semi-infinite layer on the bottom, a 1.6 nm thick native SiO₂ layer in the middle, and the EUD film on top. The substrate materials were modeled by the corresponding material files available within the software, and the EUD layer was modeled as a Cauchy function with an Urbach tail accounting for adsorption in the low-wavelength region.

Poly(N-vinylcaprolactam-co-di(ethylene glycol) divinyl ether) thin films were synthesized by initiated chemical vapor deposition. The depositions were run in a custom-built iCVD reactor described elsewhere. N-Vinylcaprolactam (NVCL, 98%; Sigma-Aldrich, Germany) is used as the monomer and di(ethylene glycol) divinyl ether (DEGDVE, 99%; Sigma-Aldrich, Germany) as the cross-linker. NVCL and DEGDVE are delivered to the reactor from their individual glass jars held at elevated temperatures: 78 and 70 °C, respectively. The monomer flow rate (NVCL) is set to 0.2 sccm; the DEGDVE flow rate is varied to employ different amounts of cross-linking. The corresponding ratios of vapor pressures of the monomer and initiator to their saturation vapor pressures (p_sat/p_sat) in the employed temperature and pressure conditions are considered for estimating the resulting compositions. All of the corresponding p_sat/p_sat values are below 0.2 and, thus, lie in a range, where a linear relation to the surface concentration of the chemical species has been reported. The applied flow rates yield polymer layers of p(NVCL-co-DEGDVE) with a nominal cross-linking of 20–85%, as evaluated from the ratio of employed p_sat/p_sat Values at a working pressure of 250 mTorr and a substrate temperature of 35 °C. A filament temperature of 200 °C was used for all presented depositions. To monitor the deposited thickness, in situ laser interferometry with a He–Ne laser (λ = 633 nm; Thorlabs) is performed through a removable quartz glass lid. All samples of the cross-linker series exhibit film thickness values of 100 ± 5 nm; moreover, a film thickness series with 45% of nominal cross-linking has been deposited with 10, 30, and 50 nm layer thicknesses.

Atomic force microscopy (AFM) measurements were performed using a FlexAFM (Nanosurf, Switzerland) equipped with a C3000 controller. The tapping mode measurements were performed using aTap300-Al from BudgetSensors (Bulgaria). Data processing and analysis were performed using the software package Gwyddion. For the extraction of the roughness, the implemented statistic evaluation was used, from which its uncertainty was also estimated. As the wrinkles are randomly oriented in a lateral dimension, a simple line-scan analysis cannot be performed. Therefore, we used a two-dimensional (2D) fast Fourier transform of the AFM height data. From this calculation, we evaluated the radial information by summing over distances from zero and fitting a Lorentzian function to it to extract the peak position that corresponds to the wrinkle wavelength. The uncertainty of fitting yields the uncertainty for the wavelength extracted.

### RESULTS AND DISCUSSION

**Spacer Thickness Dependence.** Eudragit (EUD) is readily soluble in various solvents up to high amounts. This makes it possible to use techniques like spin coating for the deposition of homogeneous thin films, e.g., on silicon wafer substrates. By applying different polymer concentrations, fully closed EUD thin films with thicknesses ranging from 20 to 800 nm, as determined by spectroscopic ellipsometry, were prepared. The resulting layers are amorphous and, if touched, sticky; the films are very smooth so that AFM analysis did not reveal any structural features.

On top of such an amorphous EUD layer, an additional polymer layer can be directly synthesized by iCVD. For a first set of samples, we deposited 100 nm p(NVCL-co-DEGDVE) with a cross-linker content of 35%. Thin EUD films (up to 40 nm) coated by the iCVD layer show a rather smooth and homogeneous morphology (see Figure 1, top left). Small spots of 5 nm in height exhibiting radii of about 100 nm are also observable but appear less frequent. In fact, these kinds of structures are only present when the EUD layers are thin. In a
recent study using iCVD-deposited poly(2-hydroxyethyl methacrylat) (pHEMA) as an encapsulation for drug layers, a very similar behavior has been observed, i.e., particle-like structures concomitantly being present with rather smooth areas.11 Using thicker EUD layers of 100 nm, the onset of wrinkle formation on the sample surface can be observed, while the mentioned spots are hardly noticeable anymore (see Figure 1, top right).

The evaluation of such surfaces can be performed in various ways. Here, the root-mean-square roughness $\sigma_{\text{rms}}$ and the lateral wavelength of the structures $\lambda$, both calculated directly from the AFM height data, are plotted in Figure 2. For statistical reasons, these data were determined from scans of larger size (up to $50 \times 50 \mu m^2$), while the data in Figure 1 elucidate more details on a smaller scale. For samples of a 100 nm EUD thickness or less, the small structures reflected in the roughness value remain comparably small; a root-mean-square roughness of $\sigma_{\text{rms}} \approx 2$ nm or below was identified. For these samples of low EUD thickness, the evaluation of the lateral wavelength from the AFM data was not unambiguously possible due to the low roughness and the random statistical nature of the surface structure.

At a 180 nm EUD thickness, the morphology appears to be different and the formation of pronounced wrinkles is observed. The evaluation of the surface roughness shows an increase to around $\sigma_{\text{rms}} = 6$ nm. For these samples, the evaluation of the wrinkle wavelength reveals more precise and regular information and an average lateral size of about 600 nm could be extracted. It can be noted that, to a certain extent, $\sigma_{\text{rms}}$, determined here by the software, represents the amplitude of the structures (i.e., a measure for the deviation up and down from an average height).

For samples prepared from even thicker EUD layers, the situation remains similar, with homogeneous wrinkles being present on the entire surface; the surface roughness and lateral size of the apparent structures increase proportionally to the film thickness of the EUD layer (see Figure 2). For an EUD layer of 800 nm, the roughness increases to a maximum value of 45 nm. On the same sample, a lateral structure with a wavelength of about 1.6 $\mu m$ developed. The shallowness of these structures, apparent when comparing the thickness of the layer of about 900 nm (EUD and iCVD) to the relatively low roughness of 45 nm, suggests that the character of the wrinkles is more two-dimensional rather than fully 3D down to the substrate surface.

**Cross-Linker Density.** Besides the spacer thickness dependence, the observed wrinkle formation has also been studied as a function of cross-linking of the $p$(NVCL-co-DEGDV) coating. By employing the iCVD technique for the synthesis of thin films, one can easily adjust the amount of cross-linking by changing the cross-linker flow rate during synthesis. This can have various effects on the film’s performance. For instance, a cross-linking agent prevents the thin film from delaminating from the substrate when in contact with water. $p$(NVCL-co-DEGDV) thin films deposited by iCVD were reported to be stable above 10% cross-linking.20 Further, cross-linking alters the swelling response of the hydrogel layer drastically when in contact with water or just specifically humid environments.17,20 In medical or drug applications, this enables the tunability of release profiles of a drug out from an iCVD encapsulation with the dissolution rate being adjustable by orders of magnitude.12 In the present contribution, we study the impact of the cross-linker amount used in iCVD synthesis on the film morphology, when deposited onto EUD films. In Figure 3, exemplary AFM images of samples with about 400 nm EUD spacers coated by 100 nm $p$(NVCL-co-DEGDV) thin films with varying cross-linker amounts are summarized.

For the sake of direct comparability, the average dark/brightness of the images in Figure 3 gives an indication on the roughness of the structures using the exact same height scale of 250 nm for all images. Upon inspection, the overall roughness
appears to increase with increasing the amount of cross-linking from 20% (top left) to 85% (bottom right). The low surface roughness (σrms = 4 nm) of the 20% cross-linked sample indicates a rather flat homogeneous surface. When a part of the image of the 20% cross-linked sample (top left) is adjusted in the height scale (see the inset), additional features appear, which are very similar to those observed when the onset of wrinkling is not entirely reached yet (cf. Figure 1). For the same EUD layer thickness of about 400 nm, a sample coated with a cross-linking density of 35% clearly shows the presence of wrinkles; a roughness of about 20 nm was found, which is around 5 times higher than the 20% cross-linked system was able to induce. At cross-linking contents of 60 and 85%, large wrinkles develop, with the roughness increasing to 30 and 36 nm, respectively. In general, a change in morphology is often observed in different stages of wrinkling. For instance, in the present contribution, the morphology of the wrinkles appears to be more round/hexagonal and very shallow for low amounts of cross-linking. When the cross-linker amount is increased, the situation changes toward more elongated wrinkles also exhibiting more pronounced height variations.

The surface roughness (σrms) as evaluated from the AFM data as a function of the spacer thickness (EUD coating) for various differently cross-linked p(NVCL-co-DEGDVE) systems can be found in Figure 4. For low EUD spacer thicknesses, a similar morphology is observed with increasing slopes for increasing cross-linker amounts. Using this second regime, extrapolation to zero surface roughness by linear regression fits shows that the onset of wrinkling is taking place at around 320 nm spacer thickness when the cross-linker is just 20%. Increasing the cross-linker amount, the onset shifts to 100 nm (at 35% cross-linker), 50 nm (at 60% cross-linker), and down to about 40 nm for the largest density of cross-linking (85%).

Again, the lateral wavelength of the wrinkles (λ) was determined from a 2D fast Fourier transform of the AFM data and plotted in Figure 5a for the differently cross-linked samples. Thin spacer layers and low amounts of cross-linking do not result in significant wrinkling and, thus, unambiguous wavelength determination. Hence, the relatively small roughness of the samples with 20% nominal cross-linking did not allow for a determination of the wrinkle wavelength. For all of the other investigated samples, λ steadily increases with increasing the spacer thicknesses.

In the literature, there are several great examples of how the size of such wrinkles can be explained. For our previous work, when the iCVD layer was deposited on an amorphous drug layer made from clotrimazole, we used a model assuming a stiff film on a compliant substrate of similar thickness. For the case of an incompressible substrate (i.e., here EUD), an analytical expression can be derived, which relates the wrinkle wavelengths (λ), the thicknesses (d), and the elastic moduli (E) of the components

$$\frac{\lambda}{2\pi d_{iCVD}} = \sqrt{\frac{d_{EUD}}{d_{iCVD}} \left( \frac{E_{iCVD}}{18 E_{EUD}} \right)^{1/6}}$$

![Figure 4. Root-mean-square surface roughness (σrms) as a function of the spacer thickness (EUD) for various samples coated with 100 nm p(NVCL-co-DEGDVE) thin films with varying amounts of cross-linking as given in the legend; the onset thickness of wrinkle formation as evaluated by the morphology of the films is indicated at the x-axis as dashes for the respectively cross-linked systems (matching colors).](https://example.com/figure4)

![Figure 5. (a) Wavelength λ as evaluated from the AFM height images of differently cross-linked (35, 60, and 85%) p(NVCL-co-DEGDVE) layers of 100 nm thickness (d_{iCVD}) deposited on EUD layers of different thickness (d_{EUD}); (b) plot for the evaluation of the ratio of iCVD to EUD elastic modulus for the differently cross-linked systems from linear fits of the plotted data (respective intercept with the y-axis, y_int).](https://example.com/figure5)
From a double-logarithmic plot of the normalized experimental data\(^1\) (i.e., \(\frac{\lambda}{d_{iCVD}}\) over \(d_{EUD}\)), the ratio of the elastic moduli of the iCVD layer \((E_{iCVD})\) and the EUD layer \((E_{EUD})\) was determined from the intercept of the linear fit of the respective data with slope 0.5 with the \(y\)-axis \((y_{int}\) see Figure 5b). The respective ratios are calculated by the following formula

\[
\frac{E_{iCVD}}{E_{EUD}} = 18 \times \left(\frac{10^{y_{int}}}{2\pi}\right)^6
\]

Performing the evaluation of the samples with 85% nominal cross-linking reveals that the elastic modulus of the iCVD layer is about 128 times larger than the one of the underlying EUD layers. In a previous contribution, we estimated the apparent elastic modulus of differently cross-linked \(p(NVCL-co-DEGDVE)\) thin films swollen in water to lay between 5 and 120 MPa, with \(E\) increasing with cross-linking.\(^2\) The elastic modulus in air is expected to be at least 1 order of magnitude higher and should, thus, be in a range as for most polymers (e.g., polystyrene about 3.8 GPa within films).\(^2\) The elastic modulus of EUD is unknown, but 128 times higher elasticity would suggest that the material is in a rubbery state with a rather low \(E\)-value. As the substrate temperature was held at 35 °C during iCVD synthesis and the EUD possesses a \(T_g\) of around 45 °C\(^2\) with a typical layer thickness dependence of the \(T_g\)\(^2\), this might support this estimation.

For the samples with 60 and 35% cross-linker amounts, the elastic modulus ratios were determined to be 18 and 5, respectively. The magnitude of the range of values appears to be consistent with the assumption that the amount of cross-linking is directly related to the elastic modulus. This assumption has been proven to be present in the swollen state of differently cross-linked \(p(NVCL-co-DEGDVE)\) thin films.\(^2\)

In general, for the wrinkling to take place, at least two slabs of materials with deviating properties need to be in contact. Strain in the system or differences in the mechanical properties can induce wrinkling. In the case of the investigated EUD–iCVD double layers, it can be assumed that the EUD is rather relaxed with minimum or even absent strain after the spin-coating process in its amorphous state. Upon iCVD synthesis, the monomers and the initiator radicals arrive at the substrate and adsorb at the EUD–air interface. Eventually, initiator radicals attack the vinyl bonds of the adsorbed species, which leads to polymerization of these monomer units. As the components are highly reactive, the synthesis is a rather fast process and just limited by the amount of material being present on the substrate in the applied conditions. As such, the time for adapting to low energetic steric sites is limited, causing the material to evolve in a strained state. With the strain exceeding the mechanical strength of the underlying EUD layer, wrinkling will be induced. The amount of wrinkling is then dependent on the amount of strain and the difference in the elastic moduli of the materials involved. High cross-linking of the iCVD polymer causes a higher rigidity, resulting in a reduced capability of adapting to steric limitations and, thus, more strain might be introduced by applying more cross-linked polymers. In a similar manner, having differences in the amount of cross-linking changes the chemical appearance, which, for instance, alters the surface energy of the deposited material. This is reflected in the (advancing) water contact angle changing from below 70° for 75% cross-linked \(p(NVCL-\)

\[\text{co-DEGDVE)}\] thin films up to more than 80° for lower cross-linker amounts, as just recently determined.\(^3\) Thus, the hydrophilic cross-linker reduces the hydrophobicity. As there was no change in the EUD layer surface, this change can result in a different energetic contribution (difference in surface energies) and superimpose the strain developing during deposition.\(^2\)

**iCVD Thickness Dependence.** Intuitively, one follow-up question arises: is the induced strain already present at the beginning of the deposition, i.e., in the first nanometers, or does it vary with layer thickness of the iCVD film? To evaluate these considerations, several depositions (all being 45% cross-linked) exhibiting different iCVD thicknesses were carried out on similar EUD layers with varying thicknesses. Again, an AFM analysis has been carried out on the different systems; AFM height images are shown in Figure 6. As described earlier,
can be observed; the 50 nm samples appear to be more chaotic/inhomogeneous in terms of morphological diversity.

■ CONCLUSIONS

Wrinkling phenomena might be used in a variety of different fields. For the induction, often, prestrain is required. Wrinkling can directly be observed when the iCVD polymer is synthesized on top of another polymer layer, here made from EUD. For such a purpose, the lack of solvents used in iCVD is particularly advantageous. Changing the thickness of the underlying layer results in the ability to adjust the wrinkles induced in terms of morphology. Both the surface roughness (as a measure of the amplitude) and the wrinkle wavelength increase with increasing the spacer thickness, whereas the absolute value of the wavelength is always much larger than that of the amplitude. While this suggests that this is an effect, especially altering the surface of the layers, the variation in spacer thickness changing the surface structure over a large range of employed thicknesses hints toward a more general rearrangement of the entire layers. The iCVD technique is very versatile so that parameters like the rearrangement of the entire layers. The iCVD technique is very versatile so that parameters like the absolute value of the wavelength is always much larger than that of the amplitude.

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### NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on August 30, 2019, and due to a production error the Figure 2 graphic was incorrect. The corrected version was reposted on September 18, 2019.