Solution Coating of Pharmaceutical Nanothin Films and Multilayer Nanocomposites with Controlled Morphology and Polymorphism

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Supporting Information

ABSTRACT: Nanosizing is rapidly emerging as an alternative approach to enhance solubility and thus the bioavailability of poorly aqueous soluble active pharmaceutical ingredients (APIs). Although numerous techniques have been developed to perform nanosizing of API crystals, precise control and modulation of their size in an energy and material efficient manner remains challenging. In this study, we present meniscus-guided solution coating as a new technique to produce pharmaceutical thin films of nanoscale thickness with controlled morphology. We demonstrate control of aspirin film thickness over more than 2 orders of magnitude, from 30 nm to 1.5 μm. By varying simple process parameters such as the coating speed and the solution concentration, the aspirin film morphology can also be modulated by accessing different coating regimes, namely the evaporation regime and the Landau–Levich regime. Using ellipticine—a poorly water-soluble anticancer drug—as another model compound, we discovered a new polymorph kinetically trapped during solution coating. Furthermore, the polymorphic outcome can be controlled by varying coating conditions. We further performed layer-by-layer coating of multilayer nanocomposites, with alternating thin films of ellipticine and a biocompatible polymer, which demonstrate the potential of additive manufacturing of multidrug-personalized dosage forms using this approach.

KEYWORDS: coating, crystallization, morphology, polymorphism, metastable, pharmaceuticals, thin film, multilayer

INTRODUCTION

In recent years, nanocrystals have emerged as a new physical entity for enhancing the bioavailability of active pharmaceutical ingredients (APIs). At nanoscopic dimensions, molecular solids exhibit increased solubility and faster dissolution. Thus, confining the crystalline APIs at the nanoscale could provide a promising platform for drugs that demand rapid onset of action, have a poor aqueous solubility, or undergo first pass metabolism. However, current industrially compatible nanosizing processes mostly employ top-down approaches, whereby bulk crystals are broken down via mechanical forces, such as in wet media milling, high pressure homogenization, and so on. These methods require high energy input, long processing time, and are often limited in achieving consistent crystal size distributions smaller than a few hundred nanometers. The formation of nanoemulsions and polymeric micelles has also been employed to produce and accommodate nanosized crystals, but these formulations exhibit poor stability and their processing requires, respectively, high concentration of emulsifiers and expensive instrumentation to reduce the micelles to the nanoscale. Other approaches of nanosizing API crystals include freeze drying, spray drying, and microfluidic crystallization. On the other hand, methods that demonstrate nanosizing below 100 nm while being compatible with large-scale manufacturing are still urgently needed.

In this work, we apply meniscus-guided solution coating to manufacture nanoscale thin films of crystalline APIs. This facile technique, commonly used for depositing organic semiconductor thin films for printed electronic devices, enables uniform thin film deposition down to a few nanometers in thickness. Beyond precisely controlling film thickness, this approach also allows easy alternation of thin film morphology and polymorphism, which were demonstrated recently for organic semiconductors. Control of API crystal morphology is important for modulating its dissolution rate. Polymorphism is of critical importance for controlling bioavailability, processability, and stability of APIs. Controlled crystallization of metastable polymorphs is particularly advantageous for APIs that are poorly water-soluble because metastable crystal forms usually exhibit higher solubility and dissolution rate owing to their higher free energy. Solution coating can also enable layer-by-layer manufacturing of dosage forms comprised of multiple APIs, allowing for controlled and sequential release of each component. The high agility and wide tunability of solution coating further provides a novel route to manufacture personalized multilayered combination.
drugs catering to individual patient’s needs. Indeed, combination drugs are receiving increased attention because of its potential to provide synergistic effects at lower dosage. For instance, this approach could be beneficial for diseases such as certain forms of cancer and human immunodeficiency virus/AIDS. Recently, nanotechnology has been introduced to create micro- and nanostructured thin films. In particular, thermal evaporation techniques have also been developed to produce thin films for application to pharmaceuticals, where precise control of the deposit thickness and uniformity at the nanometer scale is less straightforward by varying simple processing parameters.

Solution coating has distinct advantages over existing thin-film manufacturing techniques, such as hot-melt extrusion and solvent casting. The current techniques usually produce thin films comprised of a solid-state mixture of APIs imbedded in hydrophilic matrix polymers to be administered buccally and sublingually. These thin-film formulations are sought after for improved compliance of geriatric, pediatric, and dysphagic patients. The films thus manufactured are tens of micrometers thick and offer little room for nanosizing. In addition, hot-melt extrusion, the most widely used method for manufacturing of thin film drugs, employs high pressure and temperature in film processing, which renders it unsuitable for thermostable APIs. Solvent-free thermal evaporation techniques have also been developed recently to create micro- and nanostructured thin films. However, scaling this technique is challenging because of slow deposition rates. Most recently, organic vapor jet printing was employed as a technique to deposit thin films of APIs, wherein a jet of inert carrier gas thrusts APIs in the vapor phase onto cooled substrates. However, precise control of the deposit thickness and uniformity at the nanometer scale is less straightforward by varying simple processing parameters.

Herein, we demonstrate a meniscus-guided solution coating technique, specifically solution shearing of nanoscale thin films of two model APIs—acetylsalicylic acid, a common anti-inflammatory agent better known as aspirin, and ellipticine, a poorly water-soluble plant alkaloid with anticancer properties. We chose pullulan, an edible, fast-dissolving, naturally occurring polysaccharide polymer often used in orally dissolving films for pharmaceutical formulations or novelty items such as breath-freshening strips. Pullulan serves as the biocompatible polymer substrate to support the drug thin films. By controlling the coating conditions, we demonstrate control over (i) film thickness over more than 2 orders of magnitude (30 nm to 1.5 μm); (ii) thin film morphology; and (iii) crystal polymorphism. A multilayered composite was also fabricated via coating of alternating ellipticine and pullulan layers.

RESULTS AND DISCUSSION

Meniscus-Guided Solution Coating Setup. The solution coating setup is illustrated in Figure 1. The API solution was sandwiched between a moving blade and a stationary substrate. The blade was composed of a Si or glass wafer coated with a crystalline self-assembled monolayer [octadecyltrichlorosilane (OTS)] to prevent wetting of the API solution and API deposition on the blade (Supporting Information Figure 1). The blade front was separated from the substrate by 100 μm, and the blade was tilted by 8°. The substrate consisted of a solid support [e.g., Si, polyethylene terephthalate (PET)] coated with pullulan or a free-standing pullulan film. The substrate temperature was controlled to modulate the solvent evaporation rate.

During coating, a reservoir of API solution was entrained by the blade moving at different speeds due to capillary forces. The coating speed represents a critical parameter that largely determined the film thickness and defined coating regimes. At low coating speeds, solvent evaporation from the exposed meniscus front induces crystallization of the API on the substrate, thereby depositing a film (a.k.a. evaporation regime). At high coating speeds, a thin liquid layer is first retained on the substrate because of the viscous force imposed by the substrate on the ink solution, a process known as “viscous drag-out”; solvent evaporation occurs subsequently across the entire liquid film, which induces crystallization (a.k.a. Landau–Levich regime). Even within the same regime, the coating speed...
influences the evaporation flux profile as it changes the meniscus height profile as well as the thickness of the liquid film and the dried film. These effects ultimately govern the solution concentration profile and the rate of supersaturation generation critical to crystallization. Generally speaking, in the evaporation regime, the evaporation rate sharply increases at the meniscus front (or triple phase contact line), which leads to rapid increase of the solution concentration to surpass the solubility limit and initiate crystallization and film deposition. The meniscus lengthens as the coating speed increases, pushing the triple phase contact line further away and delaying the supersaturation generation. In the Landau—Levich regime, the supersaturation is uniformly generated throughout the liquid film at constant evaporation rate. As the coating speed increases, the liquid film thickness increases, slowing down the rate of supersaturation generation at a constant evaporation rate. We note that initial solution concentration also influences the rate of supersaturation generation. For a quantitative description of the interplay of these parameters, we refer the readers to the work by Doumenc and Guerrier.33 In this work, the coating speed and the solution concentration were modulated to provide access to different coating regimes and to modulate film thickness and film morphology.

Control of Aspirin Film Thickness and Morphology. Aspirin was chosen as the first model compound because it has been studied extensively, and thus, many of its chemical and physical properties are known. Aspirin solutions of various concentrations (1–100 mg/mL) were prepared in ethanol and coated at a wide range of speeds (0.005–30 mm/s) on pullulan/Si substrates at 25 °C. The film morphology was visualized under a cross-polarized optical microscope to create a morphology “phase diagram”, expressed as a function of two dimensionless numbers: drug weight percent in the solution and capillary number (Figure 2a). The capillary number (Ca) compares the relative importance of viscous force (retaining the fluid) to capillary force (removing the fluid) and is defined as \( \frac{\mu V}{\sigma} \), wherein \( \mu \) is the solution viscosity, \( V \) the coating speed, and \( \sigma \) the surface tension of the solution. Reflected in \( Ca \), a change in the coating speed effectively modulates the viscous force relative to the capillary force.

Two distinct thin film morphologies were observed upon variation of \( Ca \): oriented ribbons (\( Ca < 10^{-6} \)) and spherulites (\( Ca \geq 10^{-3} \)). A transition region consisting of a mixture of both morphologies was also observed (\( 10^{-6} < Ca < 10^{-3} \)). The videos recorded during the solution coating of aspirin suggested two different mechanisms of film deposition that resulted in the two distinct morphologies. At lower coating speeds (\( Ca < 10^{-6} \)), growth of platelike domains closely followed the meniscus to give rise to oriented crystalline domains along the meniscus-receding direction (Supporting Information Movie 1). This phenomenon indicates that the rate of solvent-evaporation-induced crystallization matches the receding rate of the meniscus; in other words, this film was created under the evaporation regime.32 At higher coating speeds (\( Ca \geq 10^{-3} \)), the solvent evaporation was too slow compared to the meniscus receding rate. The coating entered the Landau—Levich regime,32 wherein a liquid film is first dragged out by the viscous force, followed by stochastic nucleation throughout the film resulting in spherulites (Supporting Information Movie 2). The effect of solution concentration on the film morphology was not as pronounced as that of coating speed within the concentration range studied here (1–25 mg/mL). Nonetheless, a higher concentration encouraged oriented growth, while a lower concentration favored formation of spherulites—an effect discussed below.

Next, we studied the variation of aspirin film thickness with respect to the coating speed (Figure 2b) and the solution concentration (Figure 2c). First, the coating speed was varied

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**Figure 2.** (a) Morphology diagram of aspirin thin films as a function of solution concentration and capillary number (coating speed). Representative cross-polarized optical microscopy images are shown for each morphology type with white arrow indicating the coating direction. (b,c) Aspirin film thickness was measured as a function of coating speed (b) and solution concentration (c). In (b), the concentration of aspirin used was 5 mg/mL, and in (c), the coating speed was 100 μm/s.
over almost 4 orders of magnitude from $5 \, \mu\text{m/s}$ to 30 mm/s while the concentration was held constant at 5 mg/mL. The film thickness, determined using a Dektak surface profilometer, was systematically reduced by almost 2 orders of magnitude from $\sim 1.5 \, \mu\text{m}$ down to $\sim 30 \, \text{nm}$ by increasing coating speed. We compared our experimental observation with the theory prediction by Le Berre et al.$^{32}$ In the evaporation regime at low coating speeds, the mass balance mandates that the film thickness ($h$) is defined by the coating speed ($V$) following the relationship $h = C_{Q\text{evap}}/\rho L V$, wherein C is the solution concentration, $Q_{\text{evap}}$, the evaporation rate, $\rho$ and $L$ the density and the width of the deposited film, respectively. Indeed, we observed $h \propto V^{-1.14}$ in the speed range $5 \, \mu\text{m/s} \leq V < 100 \, \mu\text{m/s}$, which closely matched the theory prediction $h \propto V^{-1}$ (Supporting Information Figure 2). For the Landau–Levich regime at high coating speeds, the film thickness is determined by the viscous drag-out instead of evaporation. Therefore, theory predicts that the film thickness would increase with increasing coating speed following the scaling relationship $h \propto V^{2/3}$. However, an increase in the film thickness was not observed in our case, which was likely due to incomplete dynamic wetting of the solution on the polymer substrate. We note that the derivation of the scaling relationship assumed the total wetting condition.$^{32}$

Besides coating speed, the solution concentration was varied from 5 to 100 mg/mL, with the coating speed held constant at 100 $\mu\text{m/s}$. In this study, two substrates were tested: pullulan and plasma-treated SiO$_2$. In both cases, an increase in concentration resulted in an almost linear increase of film thickness. We suspect that the wetting of the drug solution on the pullulan substrate was slightly better than on the plasma-treated SiO$_2$ substrate, resulting in a slight increase in the slope of the concentration–thickness graph (Figure 2c). The wetting of the drug solution on these substrates could not be quantified because the receding contact angles were too low to be measured accurately. Varying the solution concentration also effectively modulated the film morphology: a higher concentration led to oriented growth, whereas a lower concentration favored spherulite formation. Interestingly, the film thickness at which the morphology type switched closely matched the case when the coating speed was varied (Figure 2b). These observations led us to hypothesize that the thin film confinement effect played a role in defining thin film morphology together with coating regimes.

To compare the molecular packing of oriented ribbons and spherulites, we first performed powder X-ray diffraction (PXRD) of aspirin thin films in the Bragg–Brentano geometry, which provided specular diffraction patterns for thin films highly orientated out-of-plane such as observed in our case (Figure 3). We also carried out grazing incidence X-ray diffraction (GIXD) of the films equipped with a 2D detector to collect additional diffraction peaks in-plane. The original 2D GIXD images (Supporting Information Figure 3), both parallel and perpendicular to the coating direction, were converted to 1D diffraction patterns by performing azimuthal integration (see Experimental Methods). All diffraction spectra matched the simulated powder diffraction pattern for the stable polymorph of aspirin (CCDC ACSALA01). In addition, we found that the films are preferentially oriented with the (100) facet registered with the substrate plane.

Coating Ellipticine Thin Films with Controlled Polymorph. Ellipticine, a potent anticancer drug with a very low aqueous solubility,$^{34}$ was chosen as the second model compound. Preparation of nanothin films of ellipticine could potentially be beneficial for modulating its physical properties to enhance its aqueous solubility. Only one polymorph of ellipticine has been reported previously.$^{35}$ By employing our solution coating method, we discovered two distinct polymorphs, which are discussed later.

A morphology diagram of ellipticine thin films was created by varying the concentration of ellipticine solution (0.5–10 mg/mL) in dimethyl sulfoxide (DMSO) and coating speeds (10–200 $\mu\text{m/s}$) (Figure 4). The ellipticine films exhibited a wider range of morphologies compared to the aspirin films, likely due to polymorphism of ellipticine, but overall the observed trends were consistent with those observed for aspirin films. Lower coating speeds gave rise to oriented plates or needles, whereas higher coating speeds favored the formation of spherulites or dots.

Specifically, at low coating speeds ($C_{\text{a}} < 10^{-6}$) and concentration ranged $1 \leq C \leq 2 \, \text{mg/mL}$, oriented plates aligned along the coating direction were observed. The formation of plates closely traced the receding meniscus, indicating that the crystal growth rate of plates matched the solvent evaporation rate (Supporting Information Movie 3). When the drug concentration increased ($C \geq 5 \, \text{mg/mL}$) within the same coating speed range, randomly aligned yellow needles appeared on top of the highly oriented plates. From the video recordings of the coating (Supporting Information Movie 4), it is evident that while plates formed tracing the receding meniscus, yellow needles formed seconds after the meniscus passed, oriented preferentially along the grain boundaries between the plates. On the basis of this observation, we infer that the conversion of plates to yellow needles is a solid–solid polymorph transformation from a metastable to a more stable polymorph. Decreasing the concentration ($C \leq 0.5 \, \text{mg/mL}$) reduced the aspect ratio of plates into thin needles aligned in the coating direction; spherulites filled the spaces between aligned needles. The appearance of spherulites with decreasing ellipticine concentration was consistent with the case of aspirin.

At higher coating speeds ($C_{\text{a}} \geq 10^{-6}$), spherulites became dominant as in the case of aspirin, interspersed with partially
aligned needles. Video recordings of the coating showed that the needles appeared first closely following the meniscus, while the spherulites filled the gaps between the needles soon after (Supporting Information Movie 5). As the concentration decreased, the needles shortened and gradually lost orientation. Further decreasing the concentration below 0.5 mg/mL resulted in tiny dots, likely because of film/ink dewetting from the substrate.

To determine whether the diverse morphologies arose from different polymorphs, GIXD was performed on the coated thin films. The original 2D GIXD images, shown in Supporting Information Figure 4, were converted to 1D diffraction patterns for comparison with simulated power diffraction patterns (Figure 6). Interestingly, the GIXD patterns of the films did not match the powder pattern from the reported crystal structure (CCDC ELLIPT). This suggests that coating resulted in a new polymorph. Polymorph screening was performed to grow single crystals of the two forms of ellipticine. The crystal structures of two polymorphs were solved via single-crystal X-ray diffraction. Figure 5 compares the crystal structures of the two polymorphs of ellipticine, showing distinct structures that belong to two different space groups (Supporting Information Table 1). Polymorph I adopts a monoclinic $P_2_1/c$ space group and matches the previously reported crystal structure (CCDC ELLIPT). Polymorph II packs in an orthorhombic $Pbc$ space group and has not been previously reported. The crystallo-
The graphic information file for polymorph II of ellipticine has been deposited into the Cambridge Crystallographic Data Center (CCDC) under deposition number CCDC 1817466. Both polymorphs exhibit hydrogen bonding and $\pi-\pi$ stacking motifs, albeit with markedly different dihedral angles for the H-bonded pairs and molecular overlap for the $\pi-\pi$ stacking pairs. Figure 6 shows the simulated and experimental X-ray diffraction pattern of polymorphs I and II. Comparing the GIXD patterns of the thin films with these reference patterns, we determined that the yellow needles that appeared on top of the plate-like thin films belong to polymorph I, while the other observed morphologies (plates, needles with spherulites) all correspond to the new polymorph II of ellipticine. We further tested the stability of polymorph II at the coating temperature and found that polymorph II thin films converted to polymorph I yellow needles during thermal annealing and solvent vapor annealing using DMSO (Supporting Information Figure 5). This result validated that polymorph II is less stable than polymorph I at the coating temperature, which is consistent with the observations that polymorph I yellow needles transformed from polymorph II plates during coating (Supporting Information Movie 4), following the Ostwald’s rule of stages.36

Thus, in this study, by simply tuning the processing parameters such as solution concentration and coating speed, we were able to systematically arrest a new metastable polymorph of ellipticine. Although formulation of API in their thermodynamically stable polymorphs is usually preferred owing to longer shelf life and easier quality control, at times a metastable polymorph is preferred because of enhanced solubility and dissolution rate. We show that meniscus-guided solution coating can serve as a robust method to sequester metastable polymorphs of APIs in their thin-film forms.

**Layer-By-Layer Coating of Multilayer Nanocomposites.** Multilayer deposition via solution coating was demonstrated by coating alternating layers of pullulan and ellipticine thin films. The layer-by-layer coating relies on two principles that conflict with each other. On one hand, coating thin films with uniform and controlled film thickness on the nanoscale requires that the ink solution is close to total wetting on the layer beneath. On the other hand, sequential coating requires orthogonal solvents for depositing alternating layers, so that the ink for coating the subsequent layer does not dissolve the layer deposited prior. The need for using orthogonal solvents usually results in poor wetting between layers. To meet the orthogonality condition, tetrahydrofuran (THF) was chosen for ellipticine layer depositions and water for pullulan layer depositions. A 50 wt % (wrt ellipticine) poly(methyl methacrylate) (PMMA), a biocompatible polymer, was added to the ellipticine−THF solution to "seal" the grain boundaries between ellipticine crystalline domains. We observed that

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**Figure 6.** GIXD data of solution-coated ellipticine thin films of three different morphologies and simulated powder diffraction data of ellipticine single crystals of polymorph I and polymorph II. The simulated data of polymorph I correspond to ELLIPT from the CCDC, while those of polymorph II belong to the ellipticine single crystal grown in our lab. The Miller indices $(hkl)$ are labeled at the top of the graph; the black and red $(hkl)$ values correspond to peaks from polymorph I and II, respectively. The signature peaks of polymorphs I and II have been labeled as (I) and (II) for each morphology. Peaks from ellipticine films of plate morphology and of needle & spherulite morphology align well with polymorph II, whereas the plates & yellow needles correspond to a mixture of polymorphs I and II. Note that the slight offset of peak positions at higher $2\theta$ values is due to a small systematic calibration error of the GIXD setup.

**Figure 7.** (a) SEM images of the cross section of ellipticine (E)−pullulan (P) multilayer films. The composition of the multilayer from the bottom to the top of the film is labeled in each image. (b) Cumulative thickness of the multilayer films measured using AFM and SEM. Ellipticine−pullulan multilayer (4 layers) printed on free-standing pullulan (c) and flexible PET (d).
adding PMMA did not significantly alter the overall ellipticine film morphology in terms of crystalline domain size and alignment but had drastically reduced the cracks in the crystalline domains and filled the gaps between domains (Supporting Information Figure 6). As a result, adding PMMA prevented dissolution of pullulan layers beneath when depositing a new pullulan layer atop the ellipticine layer. With regard to the wettability condition, indeed, aqueous pullulan solution poorly wets the ellipticine layer. To improve wetting, a small amount of surfactant sodium dodecyl sulfate (SDS) was added to the pullulan solution, which yielded the total wetting condition without compromising the solvent orthogonality; the concentration of SDS was determined from water contact angle experiments (Supporting Information Figure 7). The binding polymer as well as the surfactant can potentially be replaced with biodegradable/biocompatible versions in practical applications.

A cross section of the multilayer was analyzed via scanning electron microscopy (SEM, Figure 7a). The images show excellent adherence between layers as no gap was observed and the interfaces were almost indistinguishable. The cumulative thickness of the multilayer thin film was determined using two methods, atomic force microscopy (AFM) and high resolution cross-sectional SEM. The two methods yielded consistent results, with cumulative average thickness of 39, 140, 253, and 334 nm from one to four layers, respectively (Figure 7b). In a similar manner, we also performed ellipticine–pullulan multilayer coating on free-standing pullulan films (Figure 7c) and transparent PET substrates (Figure 7d), which demonstrated the compatibility of our multilayer coating method with a wider variety of substrates.

The method we employed to prepare multilayer films is different from the commonly used methods of layer-by-layer deposition in terms of processing and the mechanism of assembly.37–40 In many cases, such deposition is carried out by sequentially dipping the substrate into reservoirs of desired solutions while cleaning the films in between.37–40 In these methods, hydrogen bonding,39,40 electrostatic forces,37 or hydrophobic interaction38 between the molecular layers are designed to drive the adsorption and assembly of each monolayer. In contrast, in the meniscus-guided solution coating technique reported here, assembly of the API molecules does not rely on specific molecular interactions but occurs as a result of three competing forces in the meniscus: evaporation of the solvent, viscous drag-out of the substrate by the capillary force, and capillary forces.17,32,24

**CONCLUSIONS**

Through this work, meniscus-guided solution coating was demonstrated as a new technique to fabricate films of nanometer thickness for drug formulation. Accessing different coating regimes by varying the concentration (1–100 mg/mL) and the coating speed (5 μm/s to 30 mm/s), we created thin aspirin films containing two distinct morphologies—oriented plates and misoriented spherulites, with the film thickness ranging from 30 nm to 1.5 μm. The thickness varied with the coating speed following the relation h ∝ V<sup>1.14</sup> in the speed range of 5–100 μm/s, which is very close to the theoretical prediction h ∝ V<sup>1/3</sup>. Similarly, by varying the coating speed (10–200 mm/s) and the solution concentration (0.5–10 mg/mL), polymorphic ellipticine films were produced for which the morphologies generally could be categorized as either oriented plates/needles or misoriented spherulites. More specifically, four morphology types were observed due to the complication of polymorphism—plates, plates with yellow needles, needles with spherulites, and dots. X-ray studies revealed that all observed morphologies except for the yellow needles belong to a new kinetically trapped polymorph II reported for the first time in this work, while the yellow needles correspond to the previously reported polymorph I. This example shows that meniscus-guided solution coating can offer access to and control crystal polymorphs, which was originally established in the study of organic semiconductors.17,32,41,46 Moreover, the approach reported here enables sequential deposition of alternating nanometer-sized films of pullulan and ellipticine in a multilayered fashion. Similar multilayers were also coated on free-standing pullulan and PET demonstrating the compatibility of the solution coating technique with various polymeric substrates. Solution coating of nanothin film APIs with controlled thickness, morphology, and polymorphism is not only a new approach for additive manufacturing of drugs but could also enable new solid-state properties such as controlled and sequential release, as well as large modulation of API bioavailability.

**EXPERIMENTAL METHODS**

**Coating Thin Films of Aspirin and Ellipticine.** Silicon wafers with 300 nm wet thermal oxide (University Wafer) were cleaned with swabs using toluene, acetone, and isopropanol and dried in nitrogen. The cleaned wafers were plasma-treated (Harrick Plasma PDC-001) for 6 min in 100.7 mm of Hg atmospheric pressure and high power (30 W). A 5 wt % aqueous solution of pullulan (Hayashibara Co., Ltd, Lot no. SF29) was spin-coated on the plasma-treated wafers at 1200 rpm for 30 s. Ellipticine (EMD Millipore, >99% purity) and aspirin (Sigma-Aldrich, >99% purity) solutions of various concentrations were prepared in DMSO (Macron Fine Chemicals, AR ACS) and ethanol (Decon Laboratories Inc., 200 Proof), respectively. Film deposition of the two drugs was carried out on pullulan-coated substrates by solution coating at various blade speeds. The conditions of coating unless specified were as follows: SiO<sub>2</sub> wafer (300 nm oxide layer) or glass treated with the OTS monolayer was used as the coating blade; the gap between blade and the substrate was set to 100 μm; the blade was tilted at 8°; and the temperature of the stage used was 110 and 25 °C for ellipticine and aspirin solutions, respectively. For OTS treatment of the blade, precleaned SiO<sub>2</sub> wafer or glass was plasma-treated and immersed in trichloroethylene solution of OTS (0.2 mol %) at room temperature for 20 min. The wafer/glass was then rinsed with toluene and isopropanol followed by baking at 120 °C for 20 min.32

**Multilayer Deposition of Ellipticine and Pullulan Films.** Ellipticine solution (2.74 mg/mL) in THF (Macron Fine Chemicals, AR ACS) with 50 wt % PMMA (Sigma-Aldrich, M<sub>n</sub>: 120 000) (wrt ellipticine) and 2.5 wt % aqueous pullulan solution (wrt water) were used to coat up to 4 consecutive alternating pullulan and ellipticine layers in silicon wafers. DMSO was replaced with THF for preparing ellipticine solution in the case of multilayer deposition. The replacement of the solvent was done because it was noticed that ellipticine–DMSO solution used to coat upper layers would seep into the lower layers and dissolve them. This was not noticed when THF was used as the solvent for preparing the ellipticine solution. PMMA was added to the ellipticine solution to make ellipticine films more continuous and seal the “holes” in the ellipticine layer. The pullulan water solution contained 0.025 and 0.1 wt % SDS (wrt water) (WVR Life Science, Proteomics grade) in first and third layer, respectively. SDS was added to the pullulan solution to improve its wettability on the ellipticine films. In the similar way, ellipticine–pullulan multilayer was also demonstrated on a sheet of PET (Sigma-Aldrich, 125 μm thick).

A 2.5 wt % aqueous pullulan solution with 0.1 wt % SDS (wrt water) was added to a plastic Petri dish and let to evaporate in air at room temperature for a week. A translucent free-standing pullulan was deposited on the surface.
peeled off from the Petri dish and taped to a glass slide to make it horizontal. The glass slide was placed on the coating stage, and upper layers of ellipticine and pullulan were coated in a similar manner as mentioned above.

The temperature of the substrate was set at 25 °C for ellipticine and 85 °C for pullulan using a Peltier heating plate connected to a temperature controller. The temperature controller takes stage temperature readings from a thermocouple inserted just beneath the coating stage on which the substrate was placed. The coating speeds used for ellipticine and pullulan layer deposition were 0.06 and 1 mm/s, respectively. The gap size between the substrate and blade for coating pullulan was decreased to 20 μm.

**Preparation of Ellipticine Single Crystals.** Single crystals of ellipticine polymorph I was obtained from DMSO (10 mg/mL) by drop-casting (200 μL, silicon wafer) and slow evaporation at room temperature accomplished by covering the silicon substrate with aluminum foil. Crystals of polymorph II were prepared in a similar way but by using 5 mg/mL ellipticine solution in DMSO. Crystals of both polymorphs were yellow. While crystals of both polymorphs appeared as yellow needles, those belonging to polymorph I were longer and more flexible in nature as opposed to polymorph II single crystals which were shorter and did not show flexibility.

**Characterization. Visualization of Thin Film Morphology.** The morphology of the solution coated films was visualized using a cross-polarized optical microscope (Nikon Eclipse GIPOL) and imaging software (NIS-Elements).

**Film Thickness Measurements.** The thickness of aspirin films was measured using a Sloan Dektak 3ST surface profilometer (2.5 μm radius stylus). The thickness of multilayered films was measured using an Asylum Cypher AFM with Tap300AI-G tapping mode AFM tips. To aid the thickness measurement of the multilayered films, the coating blade was offset by about 2 mm perpendicular to the direction of coating after coating each layer. This resulted in a single sample to contain separate regions with 1, 2, 3, and 4 layers (cumulative), which made it easier to measure the thickness of each multilayer assembly.

The cross sections of the multilayers were also characterized via SEM (Hitachi S4800) with an accelerating voltage of 5 kV. Considering the poor conductivity of the sample, the cross sections of the samples were covered with Au–Pd thin films with a thickness of several nanometers before taking images.

**Powder X-ray Diffraction.** The PXRD was carried out on a Rigaku MiniFlex 600 in the Bragg–Brentano geometry. The data were collected from 5° to 40°, 2θ with 0.02° steps, and an 8.00 s detection time.

**Grazing Incidence X-ray Diffraction.** GIXD of the films was executed at beamline 8-ID-E of Advanced Photon Source at Argonne National Laboratory.43 The diﬀraction data were collected with an incident beam energy of 10.86 keV on a two-dimensional detector (PILATUS 1M) at two different positions. The incidence angle was set at 0.14°. The images obtained were combined to eliminate most of the inactive pixels using the GIXSGUI package written for MATLAB.44 The 1D GIXD patterns were first converted to the q–φ plot and then azimuthally integrated from −3° < φ < −88° to yield an intensity plot across the q range measured. Using the same package, corrections were made for detector non-uniformity, beam polarization, and detector sensitivity, and the two-dimensional data were reshaped into the representation q∥ versus q⊥ (q⊥ = (q∥2 + qφ2)1/2).

**Single Crystal X-ray Diffraction.** The single crystal X-ray diffraction data were collected using Bruker D8 VENTURE equipped with a four-circle kappa diffractometer and a PHOTON 100 detector. An InS microfocus Mo source supplied with a multimirror monochromated incident beam was used. The sample was mounted on a 0.3 mm loop using paratone oil. A combination of ω and ω scans were used to collect the necessary data. The sample was cooled to 100 K in a nitrogen-supplied Oxford 700 Cryosystem. The crystallographic data were integrated using SAINT45 and absorption corrected using SADABS v2014/4.46 The final structure was solved using SHELXTL-2014-47 and refined using SHELXL-2014-7.48 The crystal data and structure refinement for ellipticine form II are tabulated in Supporting Information Table 2.

**Video Recordings of Coating Processes.** The images of coating were recorded using Pixelink PL-A, PL-B, PL-D series and AVT GigE camera fitted with the solution coating station. Sequential images were combined to form a video using ImageJ.

## Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.8b01074.

OTCs-coated blade crystallinity and water contact angle, double logarithm plot of aspirin thin film thickness and coating speed, 2D GIXD and polarized optical microscopy images of aspirin and ellipticine films, cross-polarized optical microscopy of ellipticine film annealing, AFM of ellipticine–PMMA films, contact angle of SDS-H2O on Si, comparison of unit cell parameters of polymorphs I and II of ellipticine, and crystal data and structure refinement for ellipticine (PDF)

- Oriented growth of aspirin (AVI)
- Two-step spherulitic growth of aspirin (AVI)
- Growth of plates of ellipticine (AVI)
- Growth of plates with yellow needles of ellipticine (AVI)
- Growth of needles and spherulites of ellipticine (AVI)

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**Notes**

The authors declare no competing financial interest.

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