

Morphologies of Phenytoin Crystals at Silica Model Surfaces: Vapor Annealing versus Drop Casting

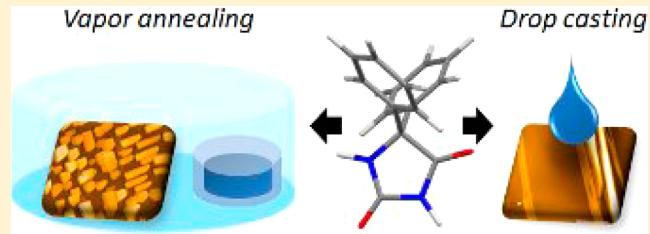
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ABSTRACT: The controlled preparation of different crystal morphologies with varying preferential orientation with respect to the substrate is of crucial importance in many fields of applications. In this work, the controlled preparation of different phenytoin morphologies and the dependency of the preferential orientation of those crystallites is related with the preparation method (solvent annealing vs drop casting), as well as the physical–chemical interaction with the solvents in use. While solvent annealing induces the formation of particular structures that are partially dewetted, the drop casting technique from various solvents results in the formation of needle-like and elongated structures, with each having a distinct morphology. The morphologies are explained via the Hansen solubility parameters and correlated with the solvent vapor pressures. X-ray diffraction experiments reveal preferential orientations with respect to the solid substrate and indicate the surface-mediated stabilization of an unknown polymorph of phenytoin with an elongated unit cell in the *b*-axis.



INTRODUCTION

Defined thin film preparation of organic molecules on solid surfaces is of great importance in a variety of fields, including pharmaceuticals,^{1,2} organic electronics,^{3–5} and colloid science,^{6–8} among many more. Typically the preparation method and the surface properties of the substrate have a decisive impact on the morphology and the polymorph forming with each having specific physical and chemical properties. For instance, small particles can be obtained from phenytoin sitting on a solid silica surface via a spin-casting process, which results in an increased solubility and dissolution rate, both being strongly enhanced compared to the bulk material.¹ Another example is the achievement of surface-mediated polymorphic structures by changing the preparation condition within alkyl-terminated terthiophene thin films.^{9–11} Small crystals may also be obtained via atomic force microscopy, which initiates crystallization during scanning.¹²

Within pharmaceutical applications, the deposition of drug molecules or active pharmaceutical ingredients (APIs), as well as aid substances, allows to achieve new application routes like buccal^{13,14} or transdermal,¹⁵ *in vivo* drug targeting,^{16,17} acidic resistant coatings,^{18,19} and many more. The ways the molecules are deposited are various. For instance, spray drying²⁰ or electrospinning²¹ are shown to achieve pharmaceutically relevant molecular coatings. Surprisingly, the deposition via physical vapor deposition or drop casting is hardly recognized even though such processes are fast and reproducible, allowing the preparation of defined API layers on solid surfaces.

Deposited solid organic layers can be manipulated using temperature treatments, which often result in changes in their polymorphic structures²² or morphologies.^{23,24} Higher temperatures mean that the unit cell thermally expands and that a system has more energy present, allowing an adaption into different confinements. Similarly, the usage of solvent annealing is a way to induce similar changes compared to temperature treatments.^{25–27} In such an experiment, the sample is in contact with a solvent vapor, resulting in additional interactions being present. Even small portions of the sample can be dissolved during such an experiment. This additional interaction induces alterations of the solid; in the case of an amorphous film, defined crystallization may be induced, and in crystalline films, recrystallization is often observed,²⁷ which makes this technique a perfect choice for an identification of possible morphologies and polymorphic structures.

Within this study the preparation of thin layers of a model API is investigated at a solid, flat silica substrate, providing the opportunity to study interactions with various surface-sensitive methods like atomic force microscope (AFM) and X-ray diffraction. The model API used is 5,5-diphenyl-2,4-imidazolidinedione (phenytoin), which is typically used due to its anticonvulsive, antiepileptic, and antiarrhythmic properties within solid oral dosage forms (i.e., capsules and chewable tablets) or parenteral formulations. The API is chosen as it is

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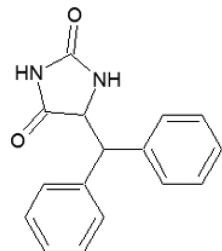
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known to be isomorphic, that is, only one crystalline phase was observed.²⁸ Samples are prepared via vacuum deposition technique revealing amorphous thin films at a silica surface. For the induction of crystallization, the samples are exposed to various solvent vapors. The resulting films are investigated by AFM and X-ray diffraction experiments, and the resulting crystalline morphologies are explained by solvent-API interactions using the concept of Hansen-solubility parameters.^{27,29} Furthermore, the resulting films are benchmarked versus dropcasted thin films and differences are elucidated.

MATERIALS AND METHODS

Phenytoin was purchased from Sigma (Germany, pharm. grade) and used without further treatment. The chemical structure is shown in Figure 1. Various solvents (toluene,



5,5-diphenylimidazolidine-2,4-dione (Phenytoin)

Figure 1. Structure of phenytoin.

tetrahydrofuran, 2-propanol, ethanol, acetonitrile, and acetone) were purchased from various suppliers in spectroscopic grade. As substrates, conventional glass slides (Roth, Germany) were cut in $2.5 \times 2.5 \text{ cm}^2$ pieces. Prior to the experiments, the substrates were cleaned in ethanol, acetone, and a 0.1 M NaOH solution and were rinsed with isopropanol. Finally, the pieces were dried under a nitrogen stream.

Vacuum deposition of phenytoin was performed in a custom-made setup. At a sublimation temperature of 115°C and a pressure 10^{-4} mbar, a deposition rate of 3 nm/min was achieved. The samples were kept at room temperature. This resulted in amorphous films being present after the preparation process.

Solvent annealing of the amorphous films was performed by exposing each phenytoin film to a different solvent vapor. A solvent vapor atmosphere was achieved by putting an open glass vessel containing the solvent next to the sample and a common enclosure. A direct contact of the liquid solvents with the samples is prevented with this method. Annealing times of 60 h at 25°C were used for all solvent annealing steps.

Drop casting films were prepared by placing a $200 \mu\text{L}$ drop containing the solute onto the glass slide. A Petri dish covered the sample to reduce the evaporation rates resulting in homogeneous film formation over the entire glass slide.

Atomic force microscope (AFM) measurements were performed with an Easyscan 2 (Nanosurf, Switzerland). All scans were performed in noncontact mode using a TAP – 190 (Budgetsensors, Romania) with a nominal resonance frequency of 190 kHz. A scan rate of 0.5 s per line was used.

Specular X-ray diffraction experiments were performed with a Siemens D500 in Bragg–Brentano configuration. The radiation was provided by a copper sealed tube (wavelength $\lambda = 0.154$

nm) and the beam was guided through a slit system. A secondary graphite monochromator was used prior the scintillation detector. The angular measurements were recalculated into scattering vector notation via $q_z = 4\pi \sin(\theta)/\lambda$. Theoretical spectra were generated using Mercury software package.

RESULTS

The vacuum deposition of phenytoin onto a silica surface results in an amorphous film. This amorphous film has a thickness of about 50 nm and is stable up to about 24 h after which crystalline structures are present (see Figure 2). The film

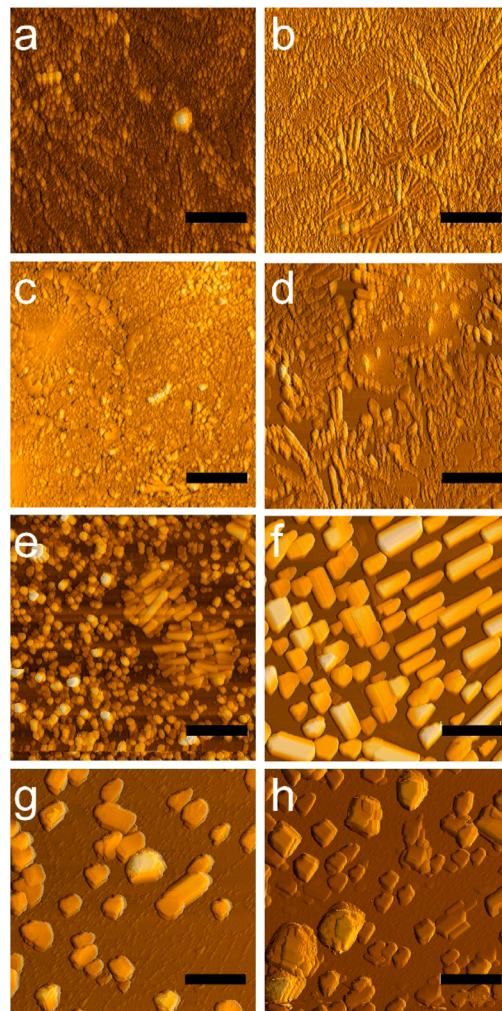


Figure 2. AFM height images of various phenytoin thin films after spontaneous crystallization (a) and the exposure to water (b), toluene (c), tetrahydrofuran (d), 2-propanol (e), ethanol (f), acetonitrile (g), and acetone (h) solvent vapors (scale bar = $5 \mu\text{m}$).

consists of small particular crystallites which pack closely together. The morphology of phenytoin crystallites drastically changes as the samples are exposed to a solvent atmosphere (compare in Figure 2). After water vapor exposure a film consisting of similarly small particles is observed but other than in the spontaneously crystallized film a certain long-range order is present. This is typical for spherulitic growth. Using a TOL vapor results in the formation of more plate-like structures and some areas still exhibiting particle-like structures. Changing the solvent to THF results in the observed morphology of

phenytoin being larger elongated structures. In addition, the film has areas where the substrate can be identified showing that THF vapor assists in dewetting of the film from the surface; thus, holes in the film form during the solvent vapor annealing process. This dewetting of the surface is even more pronounced using alcohols. The sample exposed to the IPA vapor exhibits various small separated particles as well as some elongated structures. In the sample annealed in an EtOH vapor, bar-like shape structures are present with a width up to $1.6\text{ }\mu\text{m}$, a length of $5.0\text{ }\mu\text{m}$ and a height of 340 nm . In MeCN and DMK, respectively, the phenytoin molecules assemble in structures which have an even smaller contact area with the surface, that is, the lateral extension is reduced compared to the other samples. In addition, the shape of the crystallites is more square-like compared to those observed in EtOH vapor.

For the determination of the crystalline structures of the films specular X-ray diffraction scans were performed and the data is depicted in Figure 3. Within such a scan net planes

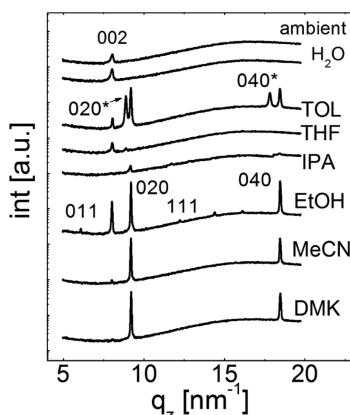


Figure 3. Various X-ray diffraction patterns of phenytoin thin films after the exposure to solvent vapors.

which are parallel to the surface are investigated giving information on the net planes which are in contact with the silica surface. The measurements on samples which were either spontaneously crystallized, vapor annealed in water or THF annealed reveal one peak over the entire scan range at 8.0 nm^{-1} . A comparison of this peak position with the only known crystal structure of phenytoin with its orthorhombic packing in $a = 0.62\text{ nm}$, $b = 1.36\text{ nm}$, and $c = 1.55\text{ nm}$ spanning unit cell reveals that this peak results from the 002 reflection. This means that phenytoin crystallizes preferentially with this net plane parallel to the surface.

Within all other samples, the 002 peak is less intense than the 020 peak at 9.2 nm^{-1} , which shows that phenytoin vapor annealed in TOL, IPA, EtOH, or DMK assembles preferably in a direction different to the previous samples; the solvent annealing process is able to alter the interaction with the substrate, which results in a deviating assembling of the phenytoin molecules with respect to the silica surface. Some of the X-ray patterns show different peaks with varying relative peak intensities. This means that the phenytoin crystals have a preferred orientation, but the solvent annealing is not able to induce a unique direction. Only within DMK and IPA a solely 020 is present, which suggests that the flat surface of the plate-like crystallites consists of this net plane. Within the TOL sample, two peaks at 8.9 and 17.8 nm^{-1} are visible, which are not explainable by the unit cell shown above. This strongly

indicates that this is due to a second polymorph or a solvate having formed during the vapor annealing process.

The vapor annealing process consists of film deposition and a subsequent annealing process requiring a large experimental and time-consuming effort. Drop casting is a simple technique for which a drop is placed on, typically, a solid surface, followed by solvent evaporation. The formed morphologies within phenytoin films prepared from various solvents are depicted in Figure 4. The low water solubility of phenytoin prevented the

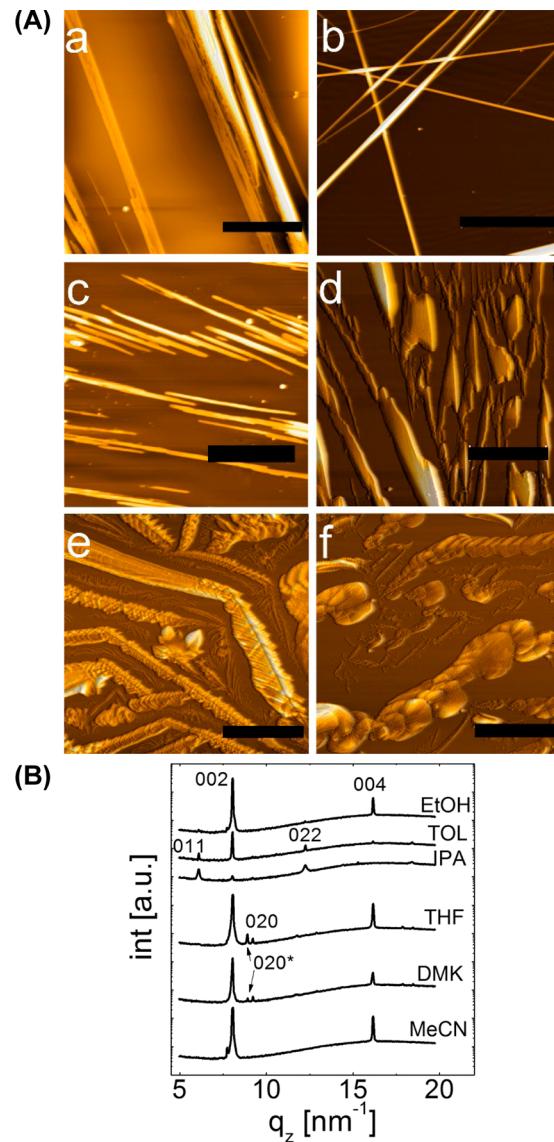


Figure 4. (A) AFM height images of phenytoin samples prepared via drop casting from ethanol (a), toluene (b), 2-propanol (c), acetonitrile (d), tetrahydrofuran (e), and acetone (f) onto silica surface (scale bar = $30\text{ }\mu\text{m}$, except for c for which the scale bar = $10\text{ }\mu\text{m}$). (B) X-ray diffraction patterns of phenytoin thin films prepared via drop casting from various solutions.

usage of water within this method. The AFM height images of the samples are prepared from EtOH, TOL, and IPA and reveal the formation of long needle-like structures. The needles expand beyond the image, showing that needles longer than $100\text{ }\mu\text{m}$ have formed. The MeCN sample shows a morphology that is deviating to the previous samples. The needle-like structure shows a more pronounced tendency to form a two-

dimensional network. These two-dimensional morphologies are even more dominant for samples prepared from THF or DMK, whereby plate-like structures form during the drop casting process. The X-ray investigation on the drop casted films reveal a preferential order of the 002 net plane being parallel to the surface. Only the IPA sample shows a reduced probability for this alignment, and the 011 is more dominant. Within the THF and DMK annealed samples, a peak at 8.9 nm^{-1} is present, indicating that a second polymorph has again formed. Surprisingly, this second polymorph is absent in the sample prepared from the TOL solution, which in the vapor annealing experiment showed the formation of this additional polymorph.

■ DISCUSSION

Vacuum deposition of phenytoin results in completely amorphous films. Such amorphous films are stable up to 1 day after which the entire film is converted to a crystalline form. While the amorphous form is expected to be preferable in the dissolution behavior,^{30,31} the shelf-life is not sufficient for any relevant application purpose; recrystallization on storage may result in strongly changed physio-chemical properties and therefore on the *in vivo* behavior. Within the dropcasting experiments, an amorphous phase could not be identified that suggests that the solvent assisted in the rapid formation of phenytoin crystals; a solution means that diffusion processes are easily accessible. In addition, the evaporation of the solvent takes about 1 min for the fasted samples (DMK solution) and about 30 min for TOL, in accordance with their differences in vapor pressures (see Table 1). These differences in crystal formation time aid in the formation of different crystalline structures.⁹

Table 1. Summary of Various Parameters and Crystal Orientations^a

mater.	HSP			cryst. orientation	
	δ_d	δ_p	δ_h	p_v (torr)	VA
H ₂ O	15.5	16.0	42.3	24	001
TOL	18.0	1.4	2.0	28	010
THF	16.8	5.7	8.0	162	001
IPA	15.8	6.1	16.4	44	010
EtOH	15.8	8.8	19.4	59	010/001
MeCN	15.3	18.0	6.1	91	010
DMK	15.2	7.4	4.8	230	010
SiO _x	17.0	19.0	15.0		
pheny. lit.	22.8	6.7	7.74		
pheny. calcd.	15.6	7.4	13.5		

^aDispersive (δ_d), polar (δ_p), and H-bonding (δ_h) Hansen-solubility parameters and vapor pressures (p_v) are listed.

The amorphous films transit on ambient storage spontaneously into its crystalline form after a day. The resulting film consists of small particles which pack closely together. The high number of particles suggest that the formation of nuclei and their growth into crystals is taking place simultaneously. This is further supported by the fact that the size of these particles is very similar indicating again a nearly identical crystal initiation. These structures are similar to structures observed previously which however were obtained via a spin-casting process.¹ However, such small particular films clearly showed a favorable dissolution behavior.

By solvent annealing a process is meant where the solvent vapor fills the entire glass vessel and that a certain amount of the solvent is able to condensate/interact with the amorphous phenytoin film. As a result, the crystal morphologies within the various films exposed to the various vapors are distinct. For the understanding of the various interactions of the solvent vapors with the phenytoin molecules or the silica surface, the polar (δ_p), apolar (δ_d), and H-bonding (δ_h) contribution have to be taken into account (note: the electrostatic interaction is of no importance, as charges within the solute and solvents are not present). An estimate for the different contributions can be obtained by the comparison of the Hansen-solubility parameters. These values are either tabulated³² or can be determined by solubility testing or calculations and are summarized for the materials used in this work in Table 1. The literature value taken for phenytoin overestimates the dispersive contribution.³³ Therefore, the mean value of those solvents in which phenytoin shows a good solubility are chosen for further considerations. Water is a poor solvent for phenytoin. Its large polar and H-bonding contribution results in bad solvent compatibility. This is also reflected in the affinity radius of two substances which is³²

$$R_a = \sqrt{4(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2}$$

A large R_a value means a poor affinity and a bad solvent quality are likely present. For water–phenytoin, a value of about 30 is obtained (see Figure 5), which is large in accordance with the

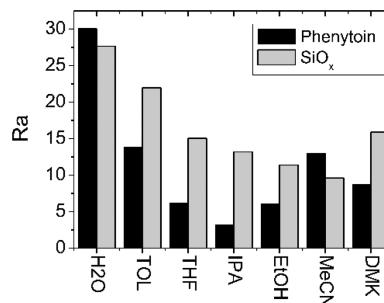


Figure 5. Calculated solvent interaction radii for the various solvents either for phenytoin or the silica surface.

low solubility of phenytoin in water.³⁴ In addition, the affinity of the solvent for the substrate surface can be estimated. A R_a value of about 27.5 indicates that an equally poor interaction strength is present for water with the substrate surface. From this follows that the nucleation of phenytoin is weakly influenced by the presence of water vapor. However, the spherulite-type structures suggest that crystallization within some spots along the surface is taking place earlier, inducing crystallization of adjacent fractions of phenytoin; the poor solubility means that when dissolution takes place, supersaturation is easily obtained by solvent evaporation, which commonly takes place in such an experiment.

X-ray diffraction experiments of the spontaneously grown and the water-treated samples show a preferential growth, with the 001 net plane being parallel to the substrate surface. By visualizing the arrangement of the phenytoin molecules in the unit cell (Figure 6) with respect to the 001 net plane, it can be seen that H-bonds from the terminal oxygen and van der Waals interactions of the phenyl rings are alternating in contact with the silica surface. Such an arrangement seems to be reasonable

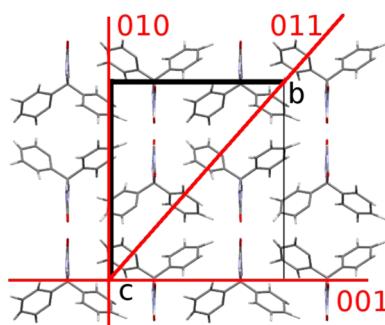


Figure 6. Arrangement of the phenytoin molecules within the unit cell. The view is along the *a* axis together with most prominent net planes.

by means of the silica substrate, which has both polar and apolar contributions. From this follows that the interaction with the silica surface causes an alignment of the molecules with this specific direction.

Contrarily, the solubility of phenytoin in TOL is enhanced. An interaction radius of 13.8 is calculated for toluene–phenytoin and for silica–phenytoin $R_a = 22$, thus, TOL preferentially interacts with the API molecules. As a result of better solubility, the crystallites forming during the annealing process are larger; a higher saturation concentration means that crystallization is slowed down, which typically results in the formation of less but bigger crystallites. Interestingly, the X-ray diffraction measurements reveal a preferred orientation of the 010, which is different to the sample annealed in H_2O or crystallized under ambient conditions but with some fraction still crystallizing in a 002 orientation. The inspection of the unit cell in terms of a 010 contact plane shows that in this orientation only the phenyl rings are in contact with the surface, which indicates that the silica–phenytoin interaction is weakened. This might be due to TOL being able to penetrate the amorphous phenytoin film and to assemble at the silica surface. This provides new interactions and the formation of crystallites with a 010 orientation results.

The preparation of drop-casted films from a TOL solution results in the formation of needle-like structures, while plate-like structures are absent. A drop casting process means that the entire API is dissolved and individual molecules are present in the solvent. As the vapor pressure is relatively low for TOL (see Table 1), evaporation of the solvent is slow. This results in API molecules having sufficient time to assemble into a low energetic crystal site which for phenytoin is located at the front of the needle. In addition to the change in the morphology compared to the vapor annealing process, the X-ray diffraction experiments show that these needles have a preferable 010 texture, indicating that the phenytoin molecules have a preferable interaction of the polar and H-bonding sites with the silica surface. The additional 011 peak in the pattern suggests that some crystals grow on account of another interaction. Possibly, crystals forming in the solution just assemble after solvent removal. This is further supported by the fact that the crystals are lying across each other (see Figure 4).

The vapor annealing process with other solvents reveals the formation of structures with a more or less strong tendency for dewetting. Again this can be explained by the fact that the interactions of the solvent with either the API or the substrate has changed. THF has a small R_a value together with phenytoin in accordance with a high solubility of the API in this solvent. In addition, the interaction of the solvent molecules with the

silica surface is more favorable compared to water or TOL. This enhances the ability for dewetting and a different morphology is observed. In the same manner, IPA, EtOH, and MeCN are good solvents and have an increasing tendency to interact with the surface. This results in even stronger dewetting from the surface and morphologies with separated structure form. Further, a stronger dewetting means that more material is present for the formation of crystal structures. It seems that within most of the dewetted structures, which are typically drop-like, a single crystal forms. This results in the crystal size being larger in EtOH or MeCN vapors compared to the IPA vapor. Within the DMK annealed sample, also a strong dewetting is present. This is surprising, as the interaction with the silica surface is weaker. However, DMK exhibit still a good solvent quality for the API, which together with the high vapor pressure means that more solvent is present, favoring the dissolution of a higher mass of phenytoin, which are able to crystallize into larger crystals.

The corresponding X-ray diffraction pattern shows that the THF sample has a preferred 001 orientation, while the others show a 010 orientation. This means that in THF the polar sites of phenytoin favor a contact with the silica surface. Within the other solvents a 010 orientation suggests that the silica–phenytoin interaction is weak, which suggests that the adsorbed solvents again provide an apolar surface and an assembling with the phenyl rings in close vicinity of the surface results. In EtOH, an intermediate situation is present as the 010 and the 001 orientation are even likely.

The drop casting of phenytoin from EtOH, IPA, or TOL solutions results in needle-like structures being present after the solvent evaporation. All of these solvents have relatively low vapor pressures, which means that evaporation is slow, and like mentioned earlier, growth takes place at the front of the crystal. However, as the vapor pressure exceeds 92 Torr, the morphology drastically changes. A more two-dimensional structure evolves. This is most probably a result from the molecules being not able to diffuse to the low energetic sites, which for the needle-type morphology are at the needle head or tail. As the solvent evaporates fast the API molecules adapt at crystal sites which are in close vicinity and a more two-dimensional structure results.

The X-ray diffraction experiments reveal a preferentially 001 orientation for all samples with some disorder along the 010 direction. This means that, while the morphology is completely different for the various samples, preferred alignment of the phenytoin oxygen with respect to the surface exist, that is, the solvent has no effect on the molecule alignment during the fast drop casting process. From this follows that the structures that assemble on the evaporation do most likely form in the supersaturated bulk solution where strong interactions with the surface are absent. The large structures seem to “just” fall onto the surface. As all structures show a certain extension in two lateral directions (most likely along the crystal *a* and *b* direction), this “fallen” structure assembles with the broad side with respect to the surface.

The X-ray investigations reveal the presence of a peak for some samples that is not explainable by the unit cell shown above. However, as the peak position and its higher order peak are close to the 020 and 040 peak of the known unit cell, it is likely that this peak is a result from a polymorph that has an extended *b* axis compared to the known one. As various samples show this peak, it is unlikely that this peak results from a solvate, that is, a crystal packing that contains solvent

molecules. Furthermore, this phase is observed for the vapor annealed TOL sample and is also present within the drop cast THF and DMK samples. Typically, the appearance of a thermodynamic unstable polymorph is a result from fast solvent evaporation, which causes molecules to assemble into a structure that is different to the stable low energetic phase.^{9,10} Anyway, the measurement and repeated measurements after 2 weeks did not show any deviating X-ray pattern, which shows that this polymorph is stable at least for 2 weeks. Often the substrate surface is able to stabilize such a thermodynamic unfavorable structures; the surface mediates the arrangement on account of altered API–surface interactions.

The preparation of the various morphologies for a single material typically allows to tune the physical and chemical properties. While not tested, it can be expected that the dissolution properties, which are of great interest for pharmaceutical application, are altered, as shown elsewhere for similar films.¹ The usage of a vacuum deposition technique allows depositing the material on any substrate providing the ability, for instance, to prepare patches containing a biodegradable substrate; such a process is often limited by a solvent process as it dissolves the substrate material. Introducing a proper solvent for a subsequent solvent annealing process, which does not affect the substrate surface, may assist in the formation of a desired morphology with defined properties. The HSP parameters of the substrate can be used to estimate the expected behavior, reducing the experimental effort to find a proper material combination.

CONCLUSION

Vacuum deposition of phenytoin results in completely amorphous thin films and different crystal morphologies with varying preferential orientation with respect to the silica substrate can be induced via solvent vapor annealing. The relatively slow vapor annealing process results in a preferential crystal growth in the 010 direction on vapor annealing in most of the tested solvents, while water and THF vapor induce a preferential orientation in the 001 direction. In the case of EtOH, the orientation is somehow in between 010 and 001. Contrarily, drop casting of phenytoin from different solvents results in distinct morphologies, while the X-ray diffraction experiments reveal, in general, a preferentially 001 orientation for all samples with some disorder along the 010 direction. This suggests that preferred alignment of the phenytoin oxygen with respect to the surface are present and suggests that the solvent has no or little influence on the molecule alignment during the fast drop casting process. The observed morphologies can be explained using the concept of the Hansen-solubility parameters, considering further the vapor pressure of the solvents in use. The X-ray investigations reveal the presence of peaks within the pattern of some samples (SA TOL, DC DMK, THF), which are not explainable by the known unit cell. The results indicate that these peaks are a result from a polymorph that has an extended *b* axis. The presence of this most likely thermodynamic unstable polymorph does not change even after 2 weeks, indicating the stabilization of this elusive crystal structure via the solid substrate. The finding of this study motivates the usage of a similar approach for many other organic molecules within pharmaceutical or other research areas for which the search for new morphologies and polymorphs is highly desired.

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Notes

The authors declare no competing financial interest.

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