Switching nitrofurantoin polymorphic outcome in solvent mediated phase transformation and crystallization using solvent and additives

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ABSTRACT

We demonstrate that several additives and solvents allow switching the polymorphic outcome of solvent mediated phase transformation experiments and crystallization of the antibacterial drug nitrofurantoin. Polymorph **β** is obtained from most of the solvents, whereas selection of alcohols as solvents or use of crystallization additives provides formation of polymorph **α**. We also demonstrate that this can be linked to reversed apparent relative solubility of nitrofurantoin polymorphs in these solvents or in presence of the respective additives. We propose that this could

be caused by different surface-additive and surface-solvent interactions formed by each of the nitrofurantoin polymorphs, which would change the relative surface energy of polymorphs.

INTRODUCTION

Industrial crystallizations of small organic molecules, including pharmaceuticals, are usually done via a solution phase, which often also serve as an important purification step.[1] It is observed that 40-70% of the small organic molecules[2-4] form various polymorphs, and polymorphic outcome of crystallization is affected by process variables such as temperature and pressure,[5-8] the crystallization approach (e.g., cooling or evaporation crystallization, crystallization from melt),[9-10] solvent choice,[11-13] particularly if the crystallization occurs close to the transition point of polymorphs,[14] and the presence of impurities.[15]

Crystallization in the presence of dissolved additives or surfaces acting as templates have been researched as a promising and useful tool for polymorph control.[16-18] Additives can differently affect crystal nucleation and growth rates of polymorphs, thus leading to the control of the polymorph obtained.[19-24] Crystallization in the presence of templates allows the nucleation to occur on an existing surface, through epitaxial matching,[25-26] matching of the surface chemistry,[27-29] or a combination of both.[30] Surfaces commonly used for polymorph and morphology control are self-assembled monolayers,[31-35] polymers,[27, 36-37] and drug-mimetic supramolecular gels.[38]

Nitrofurantoin (NF, (*E*)-1-[(5-nitro-2-furyl)methylideneamino]imidazolidine-2,4-dione, see Figure 1) is an antibacterial drug widely used for the treatment of urinary tract infections.[39-40] NF forms 2 polymorphs **α** (LABJON01)[41] and **β** (LABJON)[42] as well as 2 monohydrates,[43] and multiple solvates.[44-46] Polymorph **β** can be easily prepared in crystallization from acetone and

multiple other solvents.[47-48] In contrast, for the crystallization of pure form **α** only a rather complex stepwise procedure using acetic acid, water and acetone as solvents has been reported.[41]

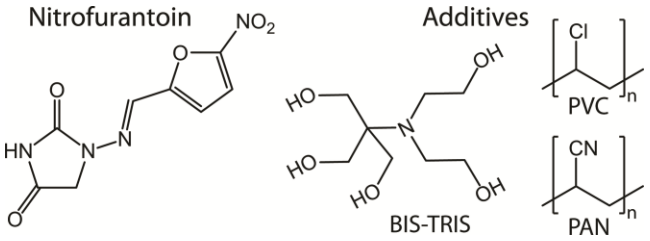

Figure 1. Molecular structure of NF and the most extensively studied additives.

In this study we explored the effect of solvent and additives on the polymorphic outcome of NF in solvent mediated phase transformation (SMPT) experiments and crystallization. We aimed to find a reliable approach for a selective crystallization of the **α** polymorph by changing the polymorphic outcome of NF crystallization via changing the solvent and using crystallization additives.

Experimental Section

Materials. NF (98%, polymorph **β**) was purchased from Alfa Aesar, organic solvents of analytical grade and all other chemicals were purchased from various commercial sources and were used without further purification. For solubility measurements and SMPT experiments polymorph **β** was prepared by recrystallization from acetonitrile without mixing. Pure polymorph **α** was produced by recrystallization from saturated 2-[bis(2-hydroxyethyl)amino]-2-(hydroxymethyl)propane-1,3-diol (BIS-TRIS) solution in acetonitrile with stirring.

Solubility determination. Solubility of both NF polymorphs at 25°C was determined in pure acetonitrile, 1,4-dioxane, THF, ethanol and 2-propanol and in the first three of these solvents in presence of selected additives using absorption spectroscopy. For these experiments ~5 mL of suspension of each polymorph in pure solvents and solvents with the respective additives were

stirred for at least 48 h at 25 °C, the suspensions were then filtered using a PTFE syringe membrane filter (0.45 μm pore size, Frisenette), and diluted 250 times in two steps (15 times in one step for ethanol and 2-propanol). The exact dilution was calculated by mass measurements. XRPD was used to confirm that no polymorph transformation had occurred. For each polymorph-solution pair two parallel suspensions were prepared, and from each of the suspensions two parallel filtrates were obtained. Absorption spectra of the obtained solutions were recorded by scanning from 300 to 400 nm with a 1 nm step using UV–Vis spectrophotometer UV-2700 (Shimadzu). The absorption value at the peak maximum (at 363 – 365 nm) was used to calculate the concentration. For acetonitrile a 5-point calibration graph from similarly prepared solutions was used, while for other solvents 2 calibration solutions were used. Solubility in 11 mg mL^{-1} solution of polysorbate 80 (and also *n*-octyl-β-D-glucopyranoside (OGP) in acetonitrile) as well as in suspensions of BIS-TRIS, polyvinylchloride (PVC) and polyacrylonitrile (PAN, only in acetonitrile) were also determined.

Crystallization experiments. Initial crystallization experiments were performed by preparing hot NF solutions with concentration corresponding to supersaturation ratio $S=c/c^* \approx 2\text{-}3$ (c^* - concentration of saturated solution at 25 °C) in selected solvents and after filtration transferring the solutions to ambient temperature and in case of no crystallization for 8 h further to –5 °C (see details in Table S5) and allowing NF to crystallize.

Further, hot NF solutions in acetone, acetonitrile, 1,4-dioxane, 1,3-dioxolane, THF, and nitromethane with exact concentration were prepared and after the filtration were transferred to 25 ° and stirred with 700 rpm using magnetic stirrer bars in glass vials. The solid products were collected within a couple of hours after the crystallization.

Crystallization in presence of several soluble and also slightly soluble or practically insoluble additives were performed using solutions of different NF concentration in several solvents, using different amount of the additive. Solutions were prepared by dissolving the corresponding amount of NF in solvent by stirring close to the boiling point, the hot solution was filtrated and ~5-6 mL of the solution were transferred to preheated 10 mL vials. In most of the experiments the vials were transferred to ambient temperature and stirring with PTFE coated magnetic stirrer bars at 700 rpm was immediately started. In some experiments, however, the vials were transferred to ambient temperature and allowed to crystallize without stirring. For each experiment two parallel crystallizations were carried out. Blank control experiments where no additive was used were always conducted. In most of the cases nucleation occurred within a few hours and the solid products were collected within a couple of hours after the crystallization. For acetonitrile we used NF solutions with concentration 6.0, 8.0, 10.0, 12.0 and 14.5 mg mL^{-1} (all the additives were tested using 8.0 mg mL^{-1}), for THF we used 6.0 mg mL^{-1} solution, and for 1,4-dioxane we used 14.9 mg mL^{-1} solution.

In the case of insoluble or poorly soluble additives (solubility below ~5 mg mL^{-1}), ~50 mg of the additive was weighed in each vial prior to the adding of the NF solution. Soluble additives were added identically, and their dissolution was easily achieved after adding the hot NF solution to the vial and shaking the obtained mixture, but two sets of experiments were performed, so that the final weight fraction of the additive in the solution would be ~1% (corresponding to ~9 mg mL^{-1}) and ~5% (~45 mg mL^{-1}). Weight fraction of 0.2% was additionally tested for water, ethanol and 2-propanol.

Crystallization from saturated solution of BIS-TRIS, PVC and PAN was also tested. For these experiments saturated acetonitrile solution of these additives was prepared at 25 °C. NF was

dissolved in corresponding amount of this solution by heating the solution close to the boiling point, the hot solution was filtrated and then transferred to empty preheated glass vials. The crystallization was achieved as described above.

Solid phase characterization. X-ray powder diffraction (XRPD) patterns were measured at ambient temperature on a D8 Advance (Bruker) diffractometer using copper radiation (CuK_α) at the wavelength of 1.54180 Å, equipped with a LynxEye position sensitive detector. The tube voltage and current were set to 40 kV and 40 mA. The divergence slit was set at 0.6 mm and the antiscatter slit was set at 8.0 mm. The diffraction patterns were recorded using a 0.2s/0.02° scanning speed from 3° to 35° (for new phases and standard samples) or 9° to 29° (for routine analysis of crystallization products) on 2θ scale. In several cases where the amount of the obtained product was very low selected narrow regions were scanned at a slower scanning speed.

DSC analysis of NF polymorphs was performed with DSC 25 (TA Instruments). Crimped 70 µL aluminum pans were used. Heating of the samples from 200 °C to melting was performed at heating rates 2, 5, 10 and 20°C·min^{-1}. Samples of ~2 mg mass were used, and the nitrogen flow rate was 50±10 mL·min^{-1}.

Solvent mediated phase transformation. SMPT experiments were performed in pure solvents as well as in acetonitrile in the presence of additives. In these experiments 11 mg mL^{-1} solution (corresponding to ~1.4% by weight) was used for all the soluble additives (polysorbate 80, OGP, polyethylene glycol (PEG), polycaprolactone (PCL), picolinic acid, and 2,6-dimethoxybenzoic acid (dOMeBA)), saturated solution was used for BIS-TRIS, 1% solution (by weight) was used for water and 5% for ethanol. For solid poorly soluble or insoluble additives microcrystalline cellulose (MCC), PVC and PAN suspension was prepared by using ~10 mg of additive per mL of solvent. Approximately 100 mg of a mixture of NF polymorphs **α** and **β** (~50% w/w) was added

to ~10 mL of pure solvent, additive solution in acetonitrile or a mixture of acetonitrile and the poorly soluble or insoluble additive so that the NF amount in the mixture would correspond to ~10 mg per mL of solution. The suspensions were stirred with PTFE coated magnetic stirrer bars at 700 rpm at 25 °C in the dark, and after a selected time part of the suspension was taken, filtrated, and XRPD pattern of the solid product recorded. Phase composition was determined based on intensities of all the characteristic peaks of polymorphs using XRPD patterns of pure polymorphs **α** and **β** as standards.

FTIR spectroscopic investigation of NF solutions. FTIR spectra of NF solution in acetonitrile, 1,4-dioxane, nitromethane, THF and 1-propanol were collected on a Frontier FTIR (PerkinElmer) spectrometer using a liquid transmission cell with a path length of 250 μm and KBr windows. The spectra were recorded from 600 to 4000 cm^{-1} at a 2 cm^{-1} spectral resolution with 16 scans. Saturated NF polymorph **β** solution was prepared and additional solutions were prepared by dilution, all spectra were recorded shortly afterwards. For solid samples a Universal ATR Sampling Accessory with a diamond window was used.

RESULTS

As an early study states that **α** is slightly more stable,[47] whereas later **β** was reported as the stable polymorph,[45] initially we investigated the relative stability of NF polymorphs. An endothermic transition of **α** into **β** just before the melting at 251 °C (using heating rate of 10 °C min^{-1}, Figure S1, Supporting Information) confirmed an enantiotropic relationship between both polymorphs, with **β** being the stable form above the transition temperature. However, information allowing to estimate the transition temperature could not be accessed because the melting was accompanied by a decomposition process preventing determination of the melting point and the heat of fusion

(see Figures S2 and S3, Supporting Information). Moreover, solubility of both NF polymorphs in several solvents were nearly identical in all the measured temperature range, see Figures S4 – S7 Supporting Information.

SMPT experiments of a w/w ~50% mixture of NF polymorphs (in acetonitrile, THF, nitromethane and 1,3-dioxolane, see Figure 2) indicated that **β** is the thermodynamically stable polymorph at room temperature of ~25 °C. The same outcome was also observed in SMPT experiments at 5° (in acetonitrile) and 80 °C (in acetonitrile, 1,4-dioxane, nitromethane, and ethanol). Surprisingly, however, in SMPT experiments in ethanol and 1-propanol at ~25 °C we observed transition to polymorph **α**. Moreover, slow transformation to **α** also occurred in SMPT experiment in 1,4-dioxane at ~25 °C, see Figure 2.

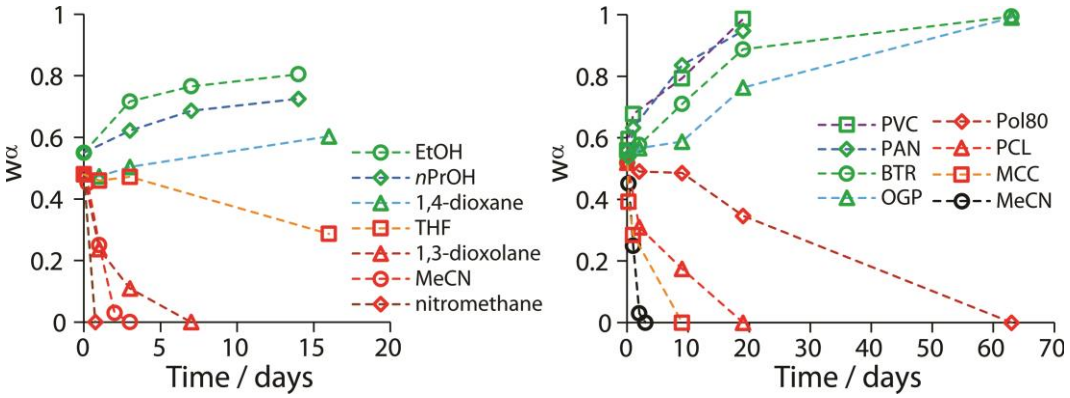

Figure 2. The weight fraction of NF polymorph **α** during a SMPT experiment (as determined using XRPD) in pure solvents (on the left) and in acetonitrile in presence of additives (on the right).

As **α** was obtained in SMPT in alcohols, we additionally studied SMPT at room temperature of ~25 °C in acetonitrile in presence of several soluble and also slightly soluble or practically insoluble additives most containing hydroxyl groups. While in presence of many of the additives we obtained **β** as in pure acetonitrile, serendipitously we noticed that part of the tested additives in fact provided formation of **α** in the SMPT. This occurred in presence of the practically insoluble

PAN, the poorly soluble PVC, in saturated solution of the slightly soluble BIS-TRIS, see Figure 1, and in 11 mg mL^{-1} solution of the soluble OGP. In presence of other tested additives **β** was the final product of the SMPT, but additives altered the transformation kinetics, with some additives noticeably decelerating the transition, e.g., polysorbate 80 (Pol80), and some accelerating it, e.g., dOMeBA, see Table S4.

We also measured the solubility of NF polymorphs at 25 °C in pure solvents and in acetonitrile, 1,4-dioxane and THF in presence of part of the used additives, see Figure 3. In agreement with the SMPT experiments, in pure acetonitrile, THF, and 1,4-dioxane **β** is the polymorph with lower solubility, whereas in ethanol and 1-propanol it is polymorph **α** (see Figure S8). In presence of additives the solubility of NF generally increased by up to 0.5 mg mL^{-1}. Furthermore, in presence of additives providing formation of polymorph **α** in the SMPT experiments in acetonitrile, the solubility of **α** becomes nearly identical (within the limits of experimental uncertainty) to that of **β** in acetonitrile and, moreover, lower than that of **β** in 1,4-dioxane and THF.

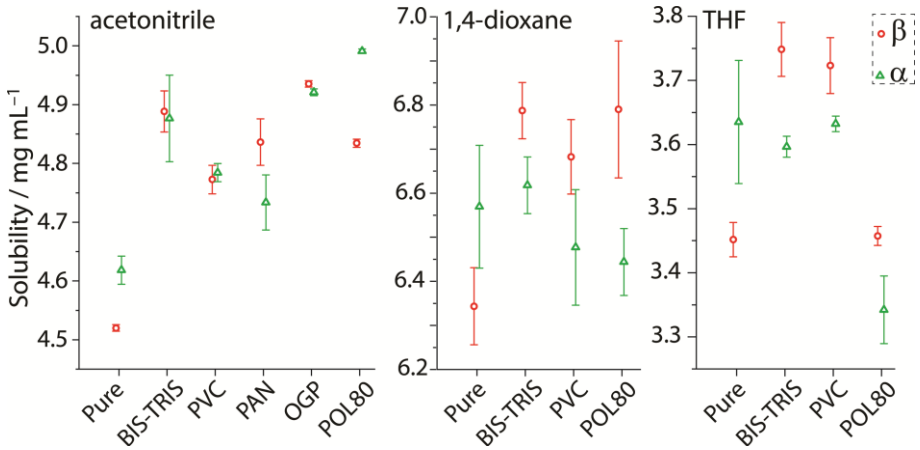

Figure 3. Solubility of NF polymorphs at 25 °C in pure acetonitrile, 1,4-dioxane and THF and in these solvents in presence of selected additives.

Considering the identified solvent and additive ability to control the polymorphic outcome of SMPT experiments, we also investigated their effect on the polymorphic outcome in

crystallization. We initially crystallized NF from a diverse series of pure solvents. We performed cooling crystallization without stirring from all of the tested solvents using solutions with supersaturation ratio S=c/c* ≈ 2-3. From solvents in which NF solubility was more than ~2 mg mL^{-1} we also performed cooling crystallization with stirring using solutions with supersaturation ratio S = 1.5-4.0. Summarized results of the crystallization experiments from selected solvents are given in Table 1.

Table 1. Summary of crystal forms obtained in crystallization of NF from selected solvents. See Tables S5 and S6 for more details and full list of the tested solvents.

Solvent	Solvent class[a]	Phase obtained
acetone	AP	**β**
acetonitrile	AP	**β**
THF	EPD	**β**
1,3-dioxolane	(AP/EPD)	**β**
2,2,2-trifluoroethanol	HBD	**β**
nitromethane	AP	**α + β / β**
1,4-dioxane	AP/EPD	**α + β / α / β**
1-butanol	HBD	**α (+β)**
ethanol	HBD	**α**
1-propanol	HBD	**α**
isobuthanol	HBD	**α**

[a] – Classification as reported in the literature: AP = aprotic polar, EPD = electron pair donors, HBD = hydrogen bond donors.[49]

Based on the polymorphic outcome of the NF crystallizations, solvents can be divided in three groups: 1) from most of the aprotic polar and electron pair donor solvents **β** was obtained, 2) from nitromethane and 1,4-dioxane a mixture of **α** and **β** was usually obtained, and 3) from most

alcohols and also from 1,4-dioxane in −5 °C (by cooling a solution with low supersaturation) **α** was obtained. The polymorphic outcome of NF crystallization is therefore mostly selective and controlled by the solvent, consistent with trends reported earlier.[48] We, however, note that the crystallization outcome is not always fully selective neither in terms of the solvent groups, nor considering each solvent individually, as higher supersaturation and enhanced crystallization induced by stirring reduced the selectivity of the polymorphic outcome, see Table S6, Supporting Information. Nevertheless, many of the solvents provided good selectivity (acetonitrile and THF for **β**, ethanol and 1-propanol for **α**) whereas some solvents provided poor selectivity (such as 1,4-dioxane and nitromethane). Additionally, from part of the alcohols we obtained solvates, including new solvates with 2-propanol, *tert*-butanol, cyclohexanol, and benzyl alcohol, see Table S5 and Section 3.2, Supporting Information.

We highlight that there is a strong correlation between the polymorphic outcome of NF crystallization and SMPT experiments, as in both experiments **β** was obtained from most of the tested aprotic polar and electron pair donor solvents, **α** was obtained from alcohols, and **α** tended to form from 1,4-dioxane.

We then crystallized NF from acetonitrile, THF, and 1,4-dioxane in presence of additives. As crystallization from most pure solvents resulted in formation of **β**, and **α** could be selectively crystallized from alcohols, many of the tested additives contained hydroxyl groups. All of the additives were tested in cooling crystallization of 8.0 mg mL^{-1} NF acetonitrile solutions ($S \approx 1.75$) with stirring. In all the experiments from pure acetonitrile as well as in the presence of part of the tested additives polymorph **β** was obtained, see Tables S9 and S10, Supporting Information. In contrast, we selectively obtained polymorph **α** in crystallization from acetonitrile in the presence of PVC, PAN, BIS-TRIS, and sorbitan monolaurate (Span 20), see Table 2 and Figure 4. Similarly,

some of the tested soluble polymers (PEG), soluble medium sized non-ionic surfactants (polysorbate 80, polysorbate 20, and OGP), soluble small molecules (picolinic acid, dOMeBA), and three compounds structurally similar to BIS-TRIS (see Tables S9 and S10, Supporting Information) also facilitated or provided formation of **α**. Alcohols as additives, however, did not facilitate formation of **α**, whereas water additive allowed formation of **α** only in some of the experiments (Table S11, Supporting Information).

Table 2. Summary of crystal forms obtained in crystallization of NF (8 – 10 mg mL^{-1}) from acetonitrile in presence of selected additives.

Additive	State of additive	Phase obtained
–	(pure acetonitrile)	**β**
Picolinic acid	1 or 5% soln.	**β** / **α** + **β**
PEG	1% soln.	**α** + **β**
Polysorbate 80	1 or 5% soln.	**α** / **β**
Polysorbate 20	1 or 5% soln.	**α** / **β**
OGP	1 or 5% soln.	**α** / **β**
dOMeBA	5% soln.	**α** / **β**
PAN	suspension	**α**
PVC	suspension	**α**
BIS-TRIS	sat. soln. / suspension	**α**
Span 20	1 or 5% soln.	**α**

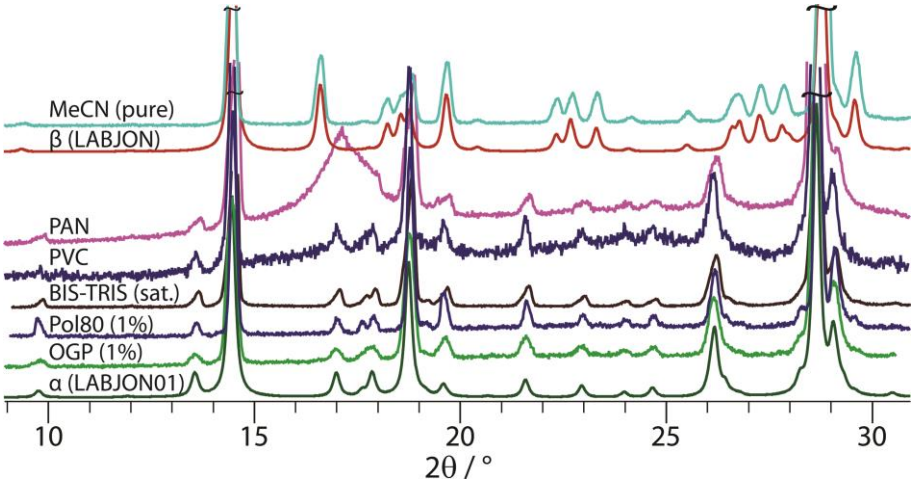

Figure 4. Example of XRPD patterns of crystallization products from pure acetonitrile and acetonitrile in presence of BIS-TRIS, polysorbate 80, OGP, PAN and PVC compared with XRPD patterns simulated from crystal structures of NF polymorphs.

Overall, using ≤10 mg mL^{-1} NF solution in acetonitrile several of the tested additives ensured selective crystallization of NF polymorph **α**, although the exact crystallization conditions where this was observed varied among additives. Pure **α** was obtained in all >25 performed crystallizations from saturated BIS-TRIS solution or BIS-TRIS suspension. Pure **α** was also obtained in all 10 crystallizations from PVC suspension and in most of crystallizations from saturated PVC solution. Similarly, pure **α** was obtained in all 10 crystallizations from PAN suspension. Using 12 – 15 mg mL^{-1} NF solution in acetonitrile **α** was still obtained in most of the cases in presence of PVC and BIS-TRIS, but crystallization in presence of PAN became unselective. Polymorph **α** was also obtained in unstirred cooling crystallizations in presence of BIS-TRIS and PVC, but not in the presence of PAN.

Selected additives were tested also in crystallization from THF (NF concentration 6.0 mg mL^{-1}, $S \approx 1.7$) and 1,4-dioxane (14.9 mg mL^{-1}, $S \approx 2.35$) solutions. In presence of PVC, BIS-TRIS, polysorbate 80 and PEG **α** crystallized from both solvents in most cases, confirming the overall

ability of these additives to provide formation of the **α** polymorph. However, addition of PAN did not result in formation of **α**, likely because of its lower solubility. Full results are available in Tables S12 and S13, Supporting Information.

We emphasize that also considering the effect of additives there is a strong link between the polymorphic outcome of NF crystallization and SMPT experiments, see Figure 5. Additives providing crystallization of polymorph **α** from acetonitrile, THF and 1,4-dioxane and PAN providing crystallization of **α** from acetonitrile resulted in formation of **α** in SMPT experiment in acetonitrile. OGP providing formation of **α** in SMPT experiment facilitated crystallization of **α** from acetonitrile, and polysorbate 80 facilitating crystallization of **α** from all three solvents notably decelerated the SMPT rate to **β** in acetonitrile.

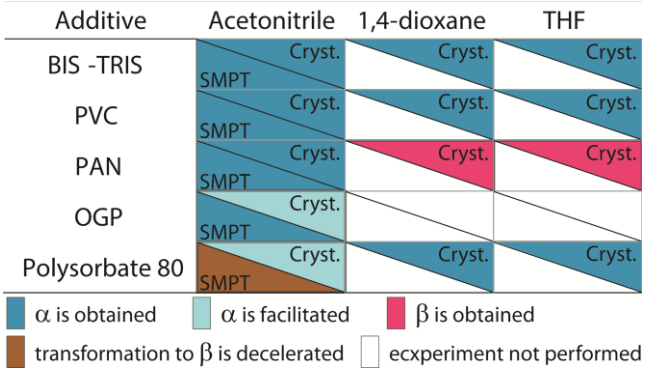

Figure 5. Summary of polymorphic outcome in crystallization (Cryst.) and SMPT experiments from acetonitrile, 1,4-dioxane and THF in presence of selected additives.

DISCUSSION

Control of the polymorphic outcome by the additives or solvent in the crystallization is usually provided by kinetic factors,[19] including the stability of associates in solution[11, 50-51] or interference of additives or solvent with the growth rates or nucleation rates of polymorphs by providing

formation of a particular polymorph.[17] Therefore, in a search for the potential mechanism of NF polymorph control by the additives and solvent we explored the effect of solvent and additives on nucleation induction times and solution speciation. Some of the additives notably altered nucleation kinetic parameters (results given in Section S4, Supporting Information), but these changes do not correlate with the crystallization polymorphic outcome and therefore appears not to be the factor switching the NF polymorph obtained in the crystallization.

For investigation of solution speciation we recoded FTIR spectra of NF solution in selected solvents. The spectra were notably different in two regions: carbonyl group stretching region (1820 – 1700 cm^{-1}) and –N–H stretching region (3700 – 3500 cm^{-1}). In most of the solvents (except for the THF and 1,4-dioxane) two stretching frequencies are observed for each of the two carbonyl groups, see Figure 6. The relative intensities and therefore the appearance of the spectra in this region is solvent dependent, and based on this solvents can be divided into three groups: a) aprotic polar acetonitrile and nitromethane, b) electron pair donors THF and 1,4-dioxane and c) hydrogen bond donor 1-propanol. These differences and doubling of the stretching frequencies therefore could be because of the hydrogen bonding with solvent, which affects the C=O stretching frequency and is significantly different in each of the solvent groups. This is also confirmed in the –N–H stretching region, where two peaks are observed in acetonitrile, 1,4-dioxane, nitromethane, and THF, see Figure S27, Supporting Information, with peak position overall correlating with the hydrogen bond acceptor propensity of the solvent. As the peak positions and peak area ratio is concentration independent (see Section S5, Supporting Information), there are no hydrogen bonded NF associates in the solution.

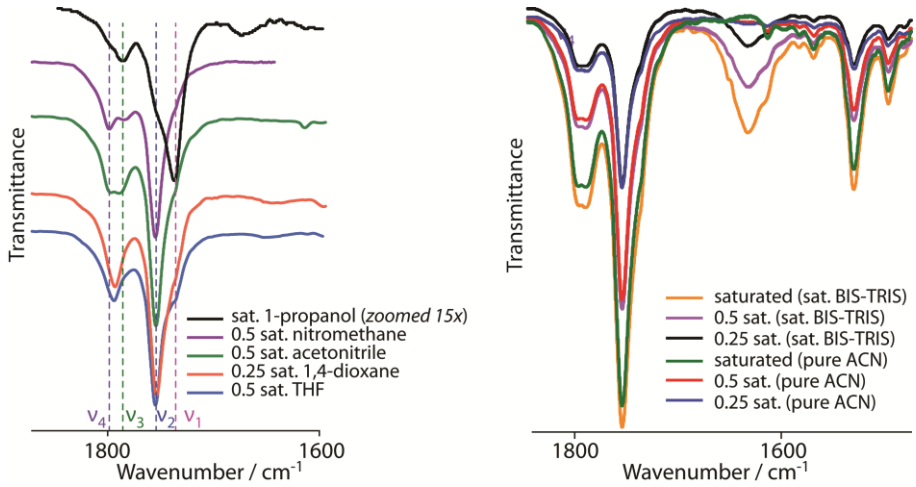

Figure 6. FTIR spectra C=O stretching region of NF solution in different solvents (on the left) and NF solutions of different concentration in pure acetonitrile and in saturated BIS-TRIS solution in acetonitrile (on the right).

Therefore, no clear differences in association in solvents favoring formation of polymorph **β** (acetonitrile, THF) and polymorph **α** (1,4-dioxane, nitromethane and 1-propanol) were detected, and the observed differences appear because of the differences in hydrogen bonding with the solvent. Moreover, the FTIR spectrum of NF in acetonitrile solution is not altered by the BIS-TRIS additive which selectively switch the NF polymorphic outcome in SMPT experiments and crystallization, see see Figure 6. These results demonstrate that the crystallization polymorphic outcome is not regulated by the associates present in the solution.

Instead, the results presented above show that the switching of the NF polymorph forming in the SMPT experiments by the additives and solvent can be linked with reversed relative solubility and thus the apparent stability of NF polymorphs. We are not aware of other examples where such change of apparent relative stability of polymorphs of an organic molecule would be demonstrated.

In a recent report[52] the ability of an additive used in cross-seeding to affect the relative thermodynamic stability of polymorphs and therefore to alter the crystallization outcome has been

demonstrated. However, this effect was caused by the formation of a solid solution. In contrast, crystallographic and LC-MS analysis of polymorph **α** obtained in presence of BIS-TRIS, the smallest of the additives used, confirmed the sample being pure NF with no changes in the crystal structure, see Section S7, Supporting Information. Additionally, the recorded XRPD patterns of the crystallization products do not indicate that solid solution would be formed between the NF and any of the used additives.

Other studies show that also very small crystal sizes can reverse the stability of polymorphs because of the contribution of the surface energy: if the surface solvation for each polymorph is different, this would result in different surface energy effect which would depend on the solvent.[53-54] It is possible that the surface-solvent and surface-additive interactions for each NF polymorph are different, and if surface energy of polymorph **α** in some conditions would be notably lower, it could be that the relative apparent stability of polymorphs changes.

The crystal structures NF polymorphs contain different hydrogen bonding motif, but the conformation is identical and molecular packing in both structures highly similar, which also results in nearly identical Hirshfeld surfaces and lattice energy. However, more detailed analysis of Hirshfeld surfaces and intermolecular interaction energies show that hydrogen bonds have slightly higher importance in **α**, whereas dispersion interactions – in **β**, see Section S6, Supporting Information.

Comparison of **α** and **β** BFDH morphologies [55] showed that both polymorphs would form prism-shaped crystals with 4-5 dominant facets. In both polymorphs the growth of most of the facets is associated with linking new molecules both by conventional hydrogen bonds and also weaker interactions formed by nitrofuryl groups, while growth of one of the facets for each polymorph is partly associated with π···π interactions. Growth of the (10-1) facet of polymorph **α** is associated

with attaching molecules by dispersion interactions and thus grow by adding new layer of mutually hydrogen bonded molecules (see Figure 7). This is the most differing interaction type exposed by any facet of NF polymorphs (see Tables S18 and S19, Supporting Information). The presence of such a surface in theory could facilitate formation of polymorph **α** from specific solvents, particularly alcohols, which in general are able to form hydrogen bonds with all the other exposed surfaces of NF polymorphs and therefore at least partly solvate them. The effect of hydroxyl group containing additives could be similar.

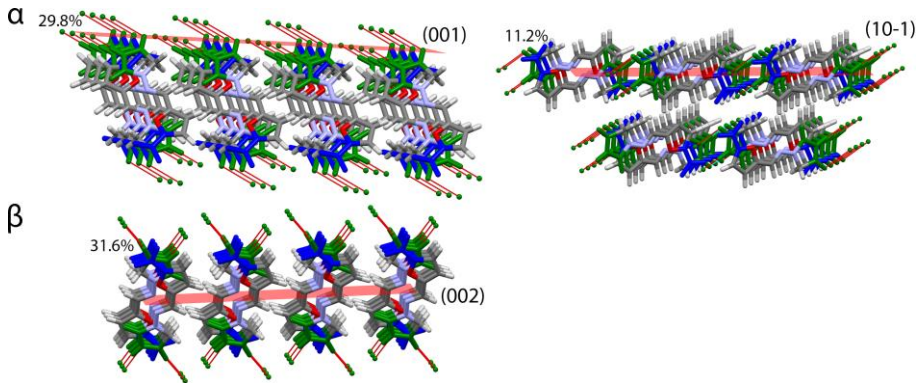

Figure 7. Molecular packing at the largest NF polymorph facets (on the left) as well as the most divergent facet ((10-1) of polymorph **α**, on the right) exposed in the crystal as predicted by the BFDH method. Nitro group is colored blue and outward placed atoms of hydantoin ring are colored green.

Nevertheless, the theory that surface energy differences in different solvents or in presence of additives could alter the relative stability of NF polymorphs is challenged by the fact that surface effects become important only for nanometre-sized particles. Therefore, this could be decisive in controlling the polymorphic outcome of crystallization, as the relative energy of nuclei of each polymorph could be affected, but for larger particles as used in the SMPT and solubility determination experiments the surface energy contribution is usually negligible, even though

crystals size is reduced by the applied stirring and crystallite sizes as determined from the Rietveld analysis are in order of 50 – 100 nm.

Therefore, we believe that the switching of the polymorphic outcome of SMPT experiments in presence of additives or specific solvent could occur through a mechanism similar to Viedma ripening,[56-57] which is influenced by additives.[58] The surface energy would be influenced with the additive or solvent used, and the polymorph with the lowest surface energy would be obtained as a final product, particularly considering that the potential temperature fluctuations during the experiments could have resulted in unintentional temperature-cycling.[59]

The proposed mechanism of switching the polymorph outcome by the additives and crystallization outcomes under the tested conditions indicate that the additives provide the polymorph control in solution.

We emphasize that a surprising aspect of the additive controlled crystallization of NF is the highly selective formation of pure polymorph **α** in all the crystallizations in presence of BIS-TRIS, PVC and to some extent also PAN. Despite the very subtle change of relative solubility by the additives, the formation of polymorph **α** is highly selective. Therefore, it is likely that also some aspects of the nucleation process or crystal growth rate of polymorphs might be altered under these conditions. This is supported by the observation that in, e.g., nitromethane, both polymorphs often crystallized concomitantly, even though in SMPT experiments a fast (< 1 day) transformation to **β** occurred.

CONCLUSIONS

In summary, we demonstrate that the NF polymorphic outcome can be switched by selecting appropriate solvent or additive. Solvent mediated phase transformation experiments and crystallizations from most of the solvents produce polymorph **β**. In contrast, the polymorphic

outcome can be selectively switched to polymorph **α** by selecting alcohols, such as ethanol and 1-propanol, as solvent, or by using crystallization additives, such as BIS-TRIS, PVC, PAN, non-ionic surfactants, or few others. The solubility measurements indicate that the switching of the polymorphic outcome can be caused by a reversed relative solubility and thus the apparent relative stability of NF polymorphs in presence of these additives and in alcohols as solvents. We believe that this is a result of different surface-additive and surface-solvent interactions present for each of the NF polymorphs, resulting in a change of the relative surface energy of polymorphs.

ASSOCIATED CONTENT

Supporting Information. More detailed and additional information on determination of the relative stability of NF polymorphs, crystal form outcome of crystallizations from pure solvents and in presence of additives. Results from characterization of the obtained NF solvates, nucleation induction time measurements, FTIR investigation of solution speciation, crystal structure analysis, and crystal structure information and determination of BIS-TRIS content by LC-MS for crystals obtained in the crystallization in presence of BIS-TRIS. (PDF)

Accession Codes. CCDC 2210518 – 2210521 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Funding Sources

This work was supported the European Regional Development Fund, project no.

1.1.1.2/VIAA/1/16/195.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Kristīne Krūkle-Bērziņa for LC-MS measurements and Kristaps Saršūns for performing the DSC measurements of NF polymorphs.

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Switching nitrofurantoin polymorphic outcome in solvent mediated phase transformation and crystallization using solvent and additives

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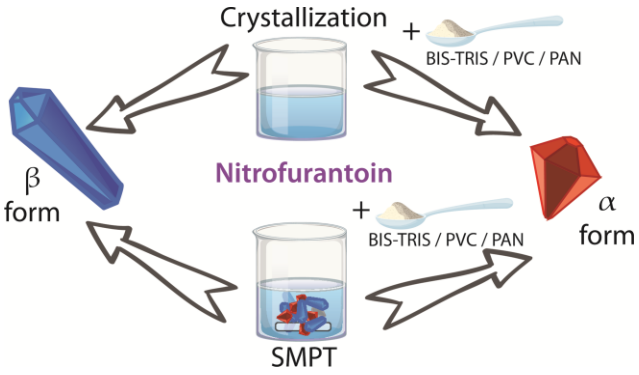

Several additives and solvent allow reversing the polymorphic outcome of solvent mediated phase transformation experiments and crystallization, as well as the apparent relative solubility of polymorphs of the antibacterial drug nitrofurantoin.