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Communication

Crystal engineering: effects of amide/lactam containing additives on the crystallization behaviour of nitrofurantoin monohydrate

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Abstract: Crystal engineering is of great interest for many drug manufacturers in order to improve their products. It is a possible way to modify the physiochemical properties of raw materials and thereby smoothen the way to the optimized product. The objective was to investigate the modified crystallization behaviour of nitrofurantoin monohydrate (NFMH) in presence of additives containing amide/lactam moieties. Nitrofurantoin (NF) was chosen as a model API as it is poorly water soluble and it forms needle-shaped crystals in aqueous environment. NF was crystallized using evaporate crystallization from acetone/water mixtures on glass-slides in presence of both polymers and corresponding monomers. The crystal morphology of NFMH can be significantly modified when it is crystallized in presence of poly(N-isopropyl acrylamide) PNIPAM, polyvinylpyrrolidone PVP and Soluplus® SOL, resulting in crystals with dendritic shaped morphology. Presence of SOL results in smaller crystals than presence of PNIPAM and PVP. Presence of a monomer was not found to affect the resulting crystal morphology. The molecular size of the additive together with the presence of amide/lactam moiety seems to have a key role in modifying the crystal morphology, indicating the dentritic crystal growth could be related to steric hindrance or to the decreased diffusion of the additive in solution and the possibility of the additive to interact with NF. Three different concentrations of the additives were investigated, which did not change the growth habit.

Keywords: Crystallization, Additive, Morphology, Polymer, Monomer, Amide, Lactam, Nitrofurantoin

1. Introduction

Crystal engineering is of great interest for drug manufacturers to modify properties of solid materials. A large number of active pharmaceutical ingredients (APIs) are poorly water soluble affecting the bioavailability, likewise they can have challenging physical properties such as unfavourable particle shape (e.g. needles) and surfaces affecting powder flowability and mixability. By designing crystals with optimized particle size and shape the API performance can be improved. If possible this should be done during production of raw material for instance at the crystallization step; this approach will smoothen the further development into the final dosage form. Many APIs can exist in different solid state forms, which often can be controlled by the crystallization condition used [1-2]. Likewise the achieved morphology of the crystalline material can change under different crystallization condition, such as choice of solvent, temperature, pH and presence of additives. It is therefore of great interest of the pharmaceutical industry to investigate the possibilities of controlled crystallization to optimize the properties of crystalline material in order to overcome technical difficulties during processing and to improve the solubility of especially poorly water soluble drug molecules. Modification of solid material has previously been shown to be achievable e.g. the particle shape of L-lysine monohydrochloride were modified using specific solvents resulting in tablets with improved crushing strength[3] and the dissolution rate of siramesine hydrochloride was increased by using additives in the crystallization process to change the particle morphology[4]. It has previous been shown that the use of poly(N-isopropyl acrylamide) (PNIPAM) as crystallization modifier can change the morphology of nitrofurantoin (NF)[5]. The amide group in the side chain of PNIPAN enables the polymer to interfere with the crystallization processes in different ways, e.g. by hydrogen bond formation or absorption to API, or by disrupting the solvent structure around the growing crystals.

In this study nitrofurantoin was chosen as model compound since it has a low solubility, it can form different solid state forms and has the possibility of forming hydrogen bonds. A range of polymeric and non-polymeric additives with an amide or lactam functional group were selected to investigate their effect as crystallization modifiers, and to identify which types of additives that typical can interfere in crystallization of NF.

2. Materials and methods

2.1. Materials

Nitrofurantoin anhydrate form β (NFAH) (Ph.Eur. 5ed standard) was purchased from Unikem, Denmark. Following additives were used: atactic poly(*N*-isopropyl acrylamide) (PNIPAM), methacrylamide (MAA), dimethylacetamide (DMAA), N-isopropylacrylamide (NIPAM), N-methylpyrrolidone (NMP) were obtained from Sigma Aldrich, Germany. Soluplus® (SOL) and polyvinylpyrrolidone (PVP, type: Kollidon 30) were manufactured by BASF, Germany. HPLC grade acetone and MilliQ water were used as solvents. All materials were used as received.

2.2. Crystallization

Glass-slides crystallization of NF in presence of additives was performed at ambient temperature with 3 different additive concentrations: 1, 3.3, and 10 mg/ml. 2.0 mg NFAH was dissolved in 1 ml additive solution containing two parts acetone and one part water. 40 µl drops of this solution were placed on a glass-slide and the solvent mixture were allowed to evaporate freely to create the necessary supersaturation for crystallization to occur. When most of the solvent were evaporated the achieved crystal was analysed using optical microscope for morphological changes. After complete solvent evaporation attenuated total reflectance fourier transformed infrared (ATR-FTIR) spectroscopy was used to identify the solid state form.

3. Results and discussion

The presence of specific additives during crystallization of NF from aqueous solution can significant change the nucleation and growth habit resulting in modified crystal morphology[6]. The usage of additive represents one method among many of controlling and modifying crystallization processes. In presence of water NF crystallizes as a monohydrate (NFMH), with the possibility of forming two different crystal structures termed nitrofurantion monohydrate form I (NFMH-I, plate-shaped) and nitrofurantoin monohydrate form II (NFMH-II, needle-shaped)[7-9]. Usually NFMH crystallizes as NFMH-II (figure 1A) or as a mixture of NFMH-II and NFMH-I. The nucleation rate of NFMH-I increases with decreasing water activity and supersaturation[9]. The solid state form of NFMH crystals depends therefore on the crystallization condition used.

3.1. PNIPAM used as crystallization additive

The morphology of NFMH crystals grown in the presence of thermosensitive poly(N-isopropyl acrylamide) (PNIPAM) are different from the morphology obtained when NFMH crystals was grown from an acetone-water mixture without additive. When NFMH was grown in presence of PNIPAM the growth habit changed to dendritic growth with intense branching (figure 1B), similar to NFMH crystals grown in presence of HPMC[6].

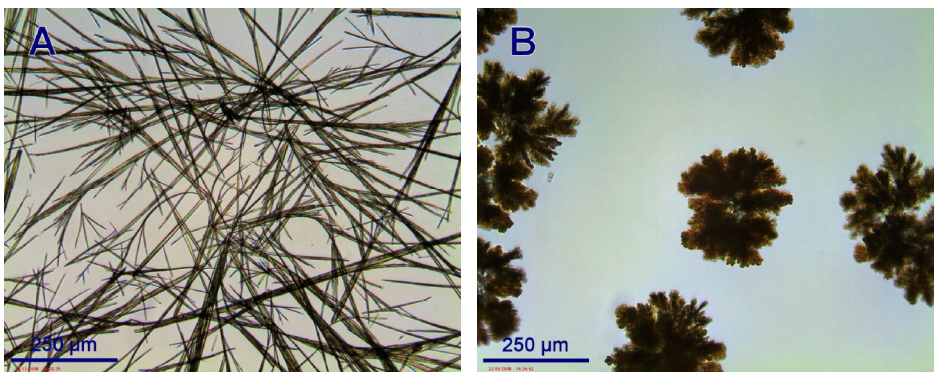


Figure 1. Nitrofurantoin monohydrate crystallized from acetone:water mixtures in presence of **(A)** no additive, **(B)** PNIPAM.

Each NFMH cluster consists of many needle sections defined as the part between two branches, each needle-section are significantly shorter and thinner compared to the needle-shaped crystals (figure 1A). PNIPAM interfere with the growing crystals probably by adsorbing temporary to the surface of the crystal, either through hydrogen bond formation or by hydrophobic interactions. The presence of foreign molecules can interrupt the crystal growth and possibly force the crystal to grow in another direction; this could explain the dendritic and retarded crystal growth.

Solid state identification of the dendritic crystals using ATR-FTIR spectroscopy revealed that the NFMH crystals crystallized in presence of 3.3 mg/ml PNIPAM were either NFMH-I or NFMH-II (figure 2) as well as a mixture of NFMH-I and NFMH-II (spectra not shown). The morphological changes are not accompanied by solid state changes in the case of dendritic growth of NFMH and thus a specific crystal form can not be selectively achieved by using PNIPAM as an additive.

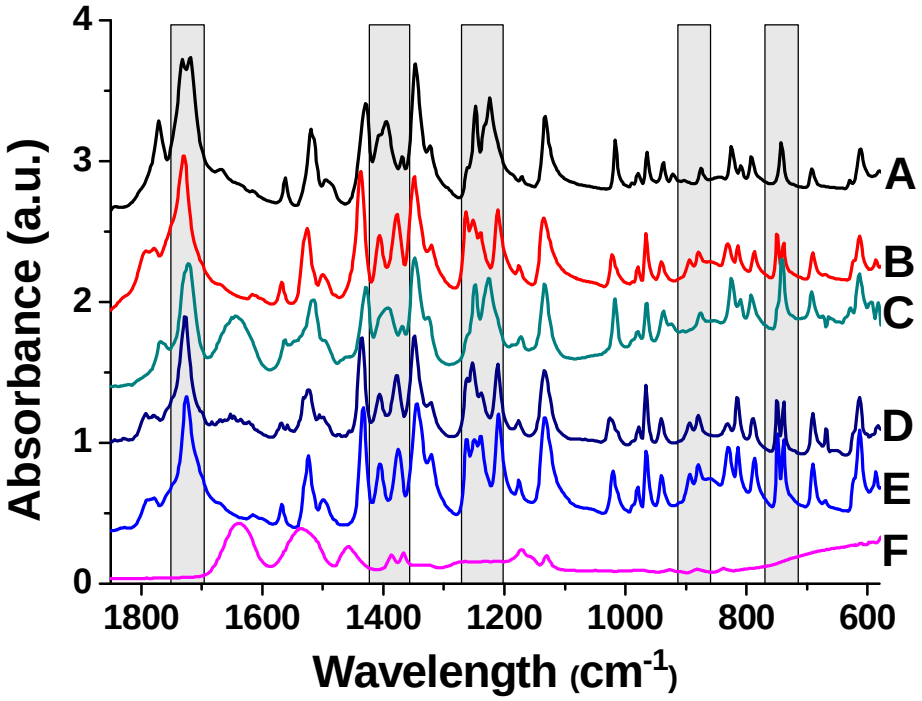


Figure 2. Identification of nitrofurantoin monohydrate (NFMH) crystallized in presence of 3.3 mg/ml PNIPAM using ATR-FTIR. **(A)** Reference spectra of NFMH-I, **(B)** Reference spectra of NFMH-II, **(C)** NFMH (form I) crystallized in presence of PNIPAM, **(D)** NFMH (form II) crystallized in presence of PNIPAM, **(E)** NFMH crystallized from acetone-water, **(F)** PNIPAM.

3.2. Chemistry and molecular size of additives

In the previous section it was shown that presence of PNIPAM can change in growth habit from needle to dendritic shaped morphology. In our previous work it has been shown that cellulose derivates have a significant influence on morphology whereas polyethylene glycol and poloxamer 407 have not[6 10].

These observations lead to the hypothesis that the morphological changes could be related to specific structural/chemical elements in the additives. Different additives with structural elements similar to PNIPAM were screened to investigate if the morphological changes could be related to presence of certain chemical groups in the additive and if the molecular size of the additive has a role to play. Additives with following types of chemical groups were selected for the investigation: group 1: monomers containing lactam and amide moieties, group 2: polymers containing lactam and amide moieties. All crystallization experiments were done using 1, 3.3 and 10 mg/ml additive.

3.3. Monomers containing amide/lactam moieties

To investigate the hypothesis of the importance of chemical elements and additive size NFMH was first crystallized in presence of monomers containing amide or lactam groups for comparison with PNIPAM. Examples of the resulting crystals are shown in table 1. Four small monomers were selected containing a primary, methacrylamide (MAA), secondary, N-isopropyl acrylamide (NIPAM), tertiary, dimethylacetamide (DMAA), amide or a lactam group, N-methylpyrrolidone (NMP), respectively. None of the monomers resulted in a dendritic like growth habit, which were observed using PNIPAM as an additive. The achieved crystal morphology was in all cases needle shaped crystals and thus the presence of the amide/lactam group alone is not the sole reason for the dendritic growth. This could either be due to the fast diffusion rate of the small monomers and therefore the interaction with NFMH could be too short-lived to influence the growth morphology, or the size of monomer is too small to disturb the crystal growth enough to cause visual changes. The solid state form the NFMH needles were usually NFMH-II, but NFMH-I or a mixture of NFMH-I and NFMH-II were occasional observed.

3.4. Polymers containing amide/lactam moieties

NFMH was further crystallized in presence of different polymers containing amide/lactam moieties, polyvinylpyrrolidone (PVP) and Soluplus® (SOL) were chosen as additives in addition to PNIPAM. Presence of any of these three additives resulted changed growth habit, where the crystal morphology was changed from needle to dendritic shaped crystals. Examples of the resulting crystals are shown in table 2. Using SOL as an additive resulted in significant smaller dendritic crystal compared to PNIPAM and PVP. Therefore, the change from monomer to polymer together with the presence of amide/lactam moieties seems to play a key role in the changed growth habit.

Similarly to the results for the monomeric additives, the solid state form of the dendritic NFMH crystals achieved in presence of the polymers were usually NFMH-II, but NFMH-I or a mixture of NFMH-I and NFMH-II were also found, probably affected by localized crystallization condition.

The morphology of the achieved NFMH crystals were not affected the concentration of the additive used, all three investigated concentration resulted in similar morphology. The concentration differences could result in varying viscosity possible affecting the crystallization. All solution had low viscosity, and no change in the crystallization habit was observed. The dendritic crystals, that were achieved using the polymeric additives, will potentially have changed physiochemical properties compared to the needle-shaped crystals. Since the shape and surface area are changed, this could influence product performance, such as dissolution rate and flowability. Additionally, the thin crystals in the dendritic

cluster are weaker and thereby could facilitate particle size reduction steps if necessary. However, further investigation is needed.

Table 1. Group 1 additives: monomers containing lactam and amide moieties

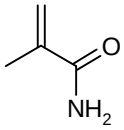
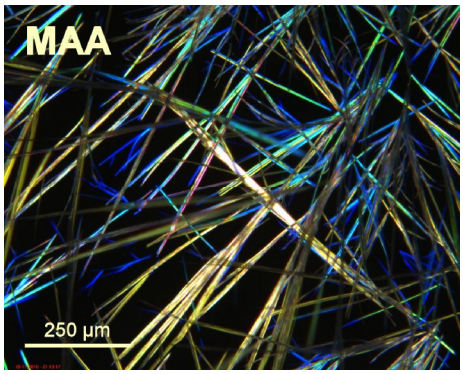
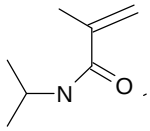
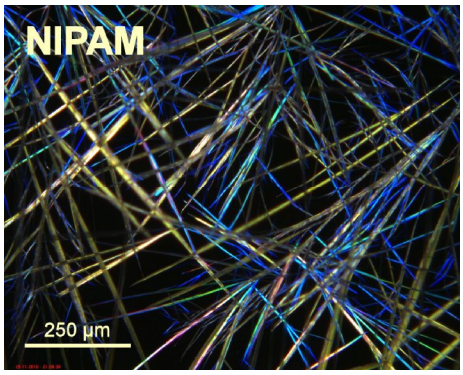
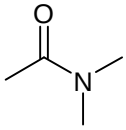
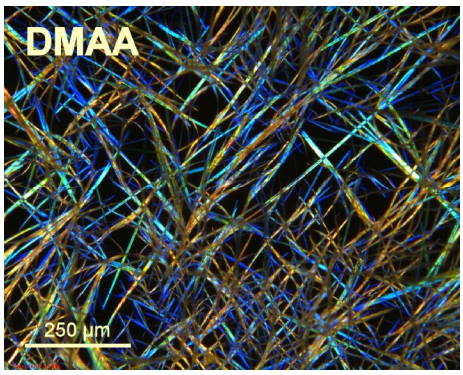
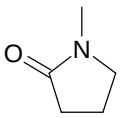
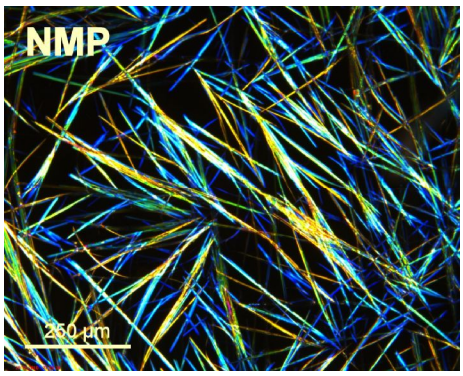
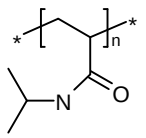
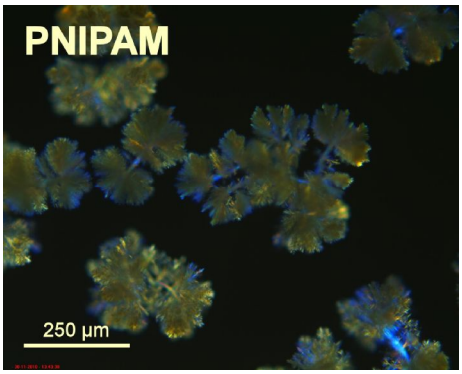
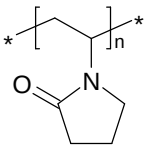
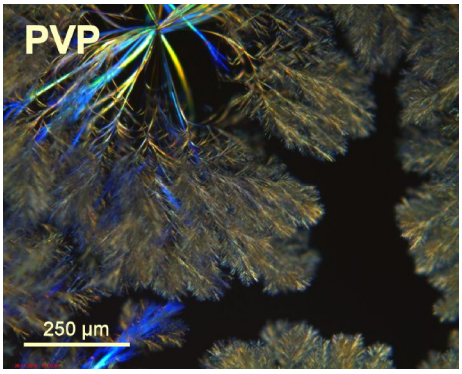
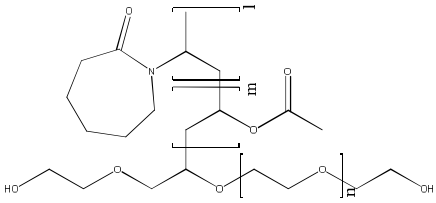
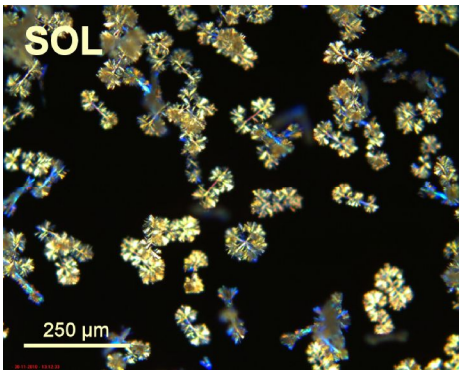
Additives	Chemical structure	Visual crystallization outcome
Methacrylamide (MAA) - primary amide		
N-isopropyl acrylamide (NIPAM) - secondary amide		
Dimethylacetamide (DMAA) – tertiary amide		
N-methylpyrrolidone (NMP) - lactam		

Table 2. Group 2 additives: polymers containing lactam and amide moieties

Additives	Chemical structure	Visual crystallization outcome
Poly(N-isopropyl acrylamide) (PNIPAM)		
Polyvinylpyrrolidone (PVP type: K30)		
Soluplus®		

4. Conclusion

Dendritic-shaped NFMH crystals were achieved using amide or lactam containing polymers as additives, whereas presence of amide/lactam containing monomers did not result in morphological changes. The crystallization outcome in presence of monomers were independent of if a primary, secondary, tertiary amide or a lactam containing monomer were chosen, in all cases needle-shaped crystals were gained. Dendritic crystal growth was observed using both amide and lactam containing polymers as additives. Presence of SOL resulted in smaller dendritic crystals compared to the dendritic crystals achieved in presence of PNIPAM and PVP. The combination of large molecular size of the polymeric additive and the presence of amide or lactam moieties were found to be important to achieve the dendritic growth habit. The investigated additive concentrations were not found to influence the growth habit. Controlling the solid state form of NFMH is challenging and could not be achieved completely using the investigated additives.

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