Controlling solid state properties of pharmaceuticals with polymer selection

Stefania Baldursdottir, Fang Tian, Jukka Rantanen

Department of Pharmaceutics and Analytical Chemistry, Faculty of Pharmaceutical Science, University of Copenhagen

ABSTRACT

Excipients have shown the ability to change the physical state and the morphology of drug crystals. Nitrofurantoin (NF) was allowed to recrystallize during evaporation of acetone, polymer/water solution (1.0 wt%) (2:1). The solid state of drug compound and morphology were evaluated by X-ray powder diffractometry (XRPD), Raman and IR spectroscopy and the rheological properties of the solutions were investigated using a TA AR-G2 rheometer. Three different types of polymers were used, PEG, EHEC and HPMC. In the absence of polymer, NF recrystallized as a polymorphic mixture of plate and needle-like monohydrate crystals, hydrate I and II respectively. All the polymers showed an ability to prevent the formation of plate-like hydrate I. In addition EHEC and HPMC changed the morphology of hydrate II crystals to dendrite-like. The PEG solution has only minor effect on the viscosity of the solution, while both EHEC and HPMC showed network associations that increased as the acetone evaporated. This study shows that the presence of a polymer network can influence both the final solid state form and the morphology of NF crystals - however, H-bonding between the drug compound and the polymer should be evaluated in order to successfully modify solid state properties of these systems.

INTRODUCTION

Building the quality into crystalline starting material will smoothen the way towards increased drug bioavailability of the final dosage form. Both low- and high molecular excipients, if chosen strategically, will adsorb to the surface of an early stage crystals resulting in a slower or completely blocked growth in certain crystallographic directions. The hypothesis is that these interactions can be predicted based on physicochemical properties of both the drug substance and the excipients. In this study we look at how polymers with different physicochemical properties are able to change the physical state and the morphology of NF crystals.

MATERIALS AND METHODS

Sample preparation

NF is poorly water soluble and exists in 2 anhydrate and 2 monohydrate crystalline forms[1]. Hydrate I has plate habit whereas hydrate II shows characteristic needle morphology. The monohydrates can be recrystallised from aqueous environment. A mixture of acetone, polymer/water solution (1.0 wt%) (2:1) was used for dissolving the drug at increased temperature, and the solvent was then allowed to evaporate resulting in the crystallisation of the drug. The drug solid state was evaluated by XRPD, DSC and Raman microscopy. For the rheological measurements the acetone evaporation was imitated by the addition of

various amounts of acetone to the system in the absence of the drug, diluting the initial polymer solution. Three different types of polymers were used, poly-ethylene glycol (PEG) a hydrophilic polymer M_w = 6.000, and two cellulose derivatives with hydrophobic groups, ethyl(hydroxyethyl)cellulose (EHEC) M_w = 250.000, and hydroxylpropylmethylcellulose (HPMC) M_w = 200.000.

Rheology experiments:

Oscillatory shear and viscosity experiments were conducted in a TA AR-G2 rheometer using a cone-and-plate geometry, with a cone angle of 1^o and a diameter of 60 mm. The sample was applied on the plate and a cover shield was used to reduce the evaporation of the acetone as much as possible during measurement. The temperature control unit (Peltier plate) kept the temperature at 25.0 ^{o}C during the measurement. All the oscillatory shear experiments were performed within the linear viscoelastic regime. The viscosity measurements were conducted over an extended shear rate range and the viscosity was monitored as a function of increasing shear rate.

RESULTS

As shown in Figure 1, in a solution of acetone and water (2:1) without polymer, NF crystallized during solvent evaporation and formed a mixture of plate and needle-like crystals. These were identified by solid state techniques as hydrate I and II respectively. All the polymers had an effect on the crystallization of NF, but to a different extent. The PEG showed an ability to prevent the formation of hydrate I, plate like crystals, where all the crystals were hydrate II and remained as its characteristic needle-like shape. EHEC and HPMC also inhibited the formation of the plate-like hydrate I, but more interestingly, the morphology of the hydrate II crystals was changed to be dendrite-like. When comparing EHEC and HPMC, HPMC system shows even more condensed dendrite.

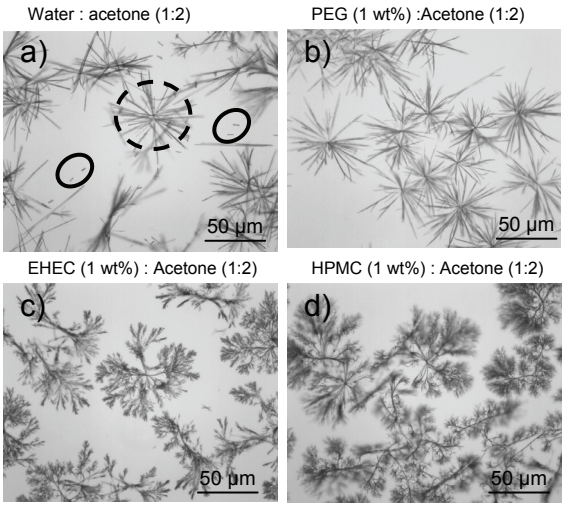

Figure 1: NF monohydrate recrystallized from solvents without any polymer (a) (dashed circle showing the needle-like crystals and the red circles highlighting the plate-like crystals); containing PEG (b); EHEC (c); and HPMC (d).

Figure 2 shows the effect of shear-rate on the measured viscosity for the different polymer systems, PEG, EHEC and HPMC (1 wt. %). The decreasing amount of acetone imitates the evaporation and thereby the beginning of the recrystallisation.

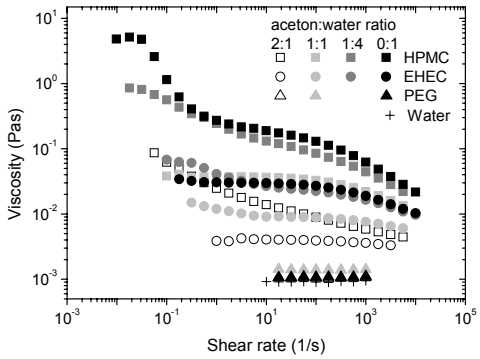

Figure 2: Viscosity as a function of shear rate for the three different polymer systems, PEG, EHEC and HPMC compared to pure water. The decreasing amount of acetone represents increasing evaporation has occurred in the system.

The shear-rate dependence of the viscosity is detected for all the HPMC systems, and the EHEC solutions except for the most diluted. The shear thinning observed, can be ascribed to disruption of entanglements and other intermolecular interactions. The PEG solutions has only a minor influence on the viscosity of the solution when compared with pure water but does not show any sigh of shear dependency, indicating a Newtonian fluid with very low viscosity.

The oscillatory characteristics were scrutinized further for the EHEC and HPMC systems.

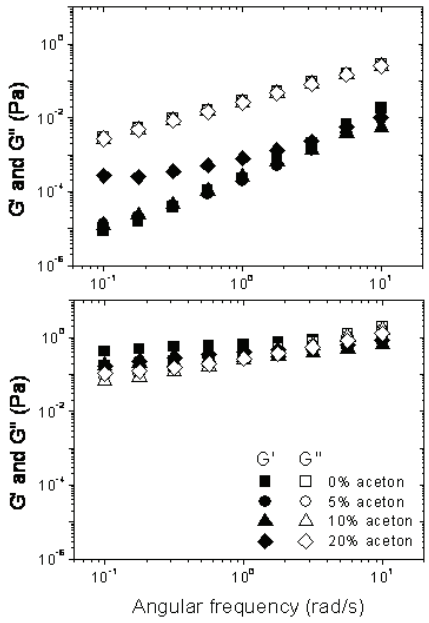

Figure 3: Frequency dependency of the dynamic moduli for the a) EHEC and b) HPMC solutions with 0%, 5%, 10% and 20% acetone added.

Typical illustrations of the frequency dependencies of G´ and G´´ for EHEC and HPMC systems with different amounts of acetone added is depicted in Figure 3. For the EHEC systems the G´´ is higher than G´ throughout the frequency domain studied at all concentrations of acetone. Less frequency dependency of the G´ and G´´ is detected for the HPMC system and a crossover from dominating elastic behavior to more viscous behavior is detected at higher frequencies.

Figure 4 shows the frequency dependency of the complex viscosity (η*) of the EHEC and HPMC systems with 0% or 20% acetone added. η* takes into account both G' and G'' as the following equitation shows:

$$\eta^*(\omega) = \frac{\sqrt{G'(\omega)^2 + G''(\omega)^2}}{\omega}$$

Much larger values of η* are obtained for the HPMC than the EHEC system and HPMC shows more frequency dependency.

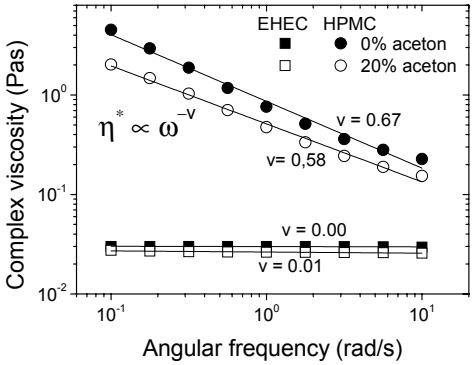

Figure 4: Frequency dependency of the complex viscosity of the two polymer systems, either without or with 20% acetone added.

The frequency dependence of the complex viscosity can be quantified by $\eta^* \sim \omega^{-\nu}$ ($0 \leq \nu \leq 1$). Low values of ν indicate viscous-like behavior, while higher values indicate a more elastic response[2]. Both the EHEC systems have a ν value of 0.0, the viscous mode dominating in the system. The values of ν are increased for the HPMC systems, indicating more solid-like behavior. This illustrates that there are relatively few cross-links in the EHEC system, while for the HPMC system shows more associations, more elastic response. The values of ν also increases with decreasing amount of acetone in the HPMC system indicating the growing associations in the system with evaporation.

No such growth was detected for the EHEC system.

EHEC and HPMC solutions both have high viscosity and associated network, which could be a possible explanation for the modification to dendrite morphology of NF hydrate formation. PEG, however, only slightly increases the viscosity without any sign of network associations, does not have that effect. The dendrites exhibited numerous branches, appearing to be produced via an abundant number of interactions between the drug and polymer. Also when comparing EHEC and HPMC, HPMC system shows more cross-links, and led to more condensed dendrite.

It is now shown that polymer network association play a role in the crystallization change of NF. But there are other influencing factors that can inspire both the change in polymorphism and the transformation to dendrite like crystals. NF has the ability to form H-bonds with the polymers, and thus inducing polymer adsorption which then affect the further growth of these faces.

The theory was supported by an evaluation of the H-bonding between the polymers and the drugs by studying the chemical structure of the polymer and with IR spectroscopy. However, crystallization of carbamazepine, which does not have the same H-bonding ability as NF, was also influenced by the presence of the polymers indicating that the network association are of importance.

CONCLUSIONS

This study provided an insight into the nature of polymer-drug interactions during crystallization. A highly associated polymer network would possibly induce complex physical interactions between drug and polymer, and thus lead to a great influence on the final crystal morphology. This effect does not require a structural match as commonly acknowledged in crystallization field[3,4].

In conclusion, the effects of polymers on the crystallization mechanism of a specific compound are in close relationship to their H-bonding with the specific compound. The network properties of polymers also play a role in influencing the crystallization phenomenon.

REFERENCES

1. Caira, M.R., Pienaar, E.W., Loetter, A. P. (1996), "Polymorphism and pseudopolymorphism of the antibacterial nitrofurantoin", *Mol. Cryst. Liq. Cryst. Sci. Technol., Section A: Mol. Cryst. Liq. Cryst.* **279**, 241-264.

2. Winter, H.H. (1987), "Evolution of rheology during chemical gelation", *Prog. Coll. Pol. Sci.,* **75**, 104-110.

3. Weissbuch, I., Addadi, L., eiserowitz, L. L. (1991), "Molecular Recognition at Crystal Interfaces", *Sci.* **253**, 637-645.

4. Giordani, P., Modenesi, P., Tretiach, M. (2003), "Determinant factors for the formation of the calcium oxalate minerals, weddellite and whewellite, on the surface of foliose lichens", *Lichenologist* **35**, 255-270.