Crystallization control possibilities of para-aminobenzoic acid using crystallization additives

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Introduction

Polymorphism of active pharmaceutical ingredients has been the subject of intense investigation in the drug industry due to their influence on the properties of the drug. A better understanding of the formation of different polymorph forms and control mechanism may improve crystallization process efficiency and reduce production cost. [1-2]
In this study, *para*-aminobenzoic acid (pABA) was used as a model substance to investigate the additive crystallization control approach. pABA has four polymorph forms, which have different types of hydrogen bonding and aromatic interactions. Forms α and γ are similar. Although forms have the same acid homodimers and stacking related by translation, forms have differ in the position of the layers. Forms β and δ contain identical hydrogen bond head to tail acid-amine dimers, however, they differ with aromatic interactions. α form is the stable form and enantiotropically related to the β and δ forms. [3-4]

Crystallization with the presence of additives

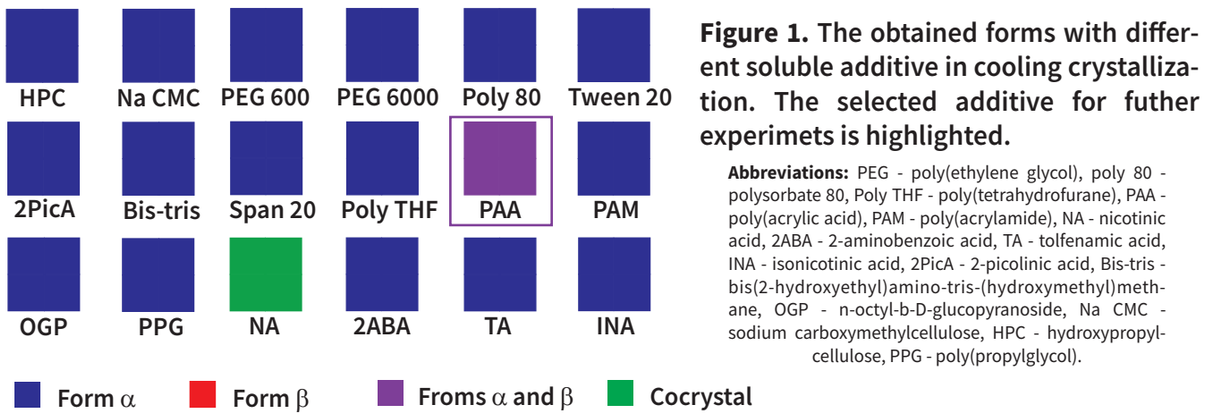

Figure 1. The obtained forms with different soluble additive in cooling crystallization. The selected additive for futher experimets is highlighted.

Abbreviations: PEG - poly(ethylene glycol), poly 80 - polysorbate 80, Poly THF - poly(tetrahydrofurane), PAA - poly(acrylic acid), PAM - poly(acrylamide), NA - nicotinic acid, 2ABA - 2-aminobenzoic acid, TA - tolfenamic acid, INA - isonicotinic acid, 2PicA - 2-picolinic acid, Bis-tris - bis(2-hydroxyethyl)amino-tris-(hydroxymethyl)methane, OGP - n-octyl-b-D-glucopyranoside, Na CMC - sodium carboxymethylcellulose, HPC - hydroxypropylcellulose, PPG - poly(propylglycol).

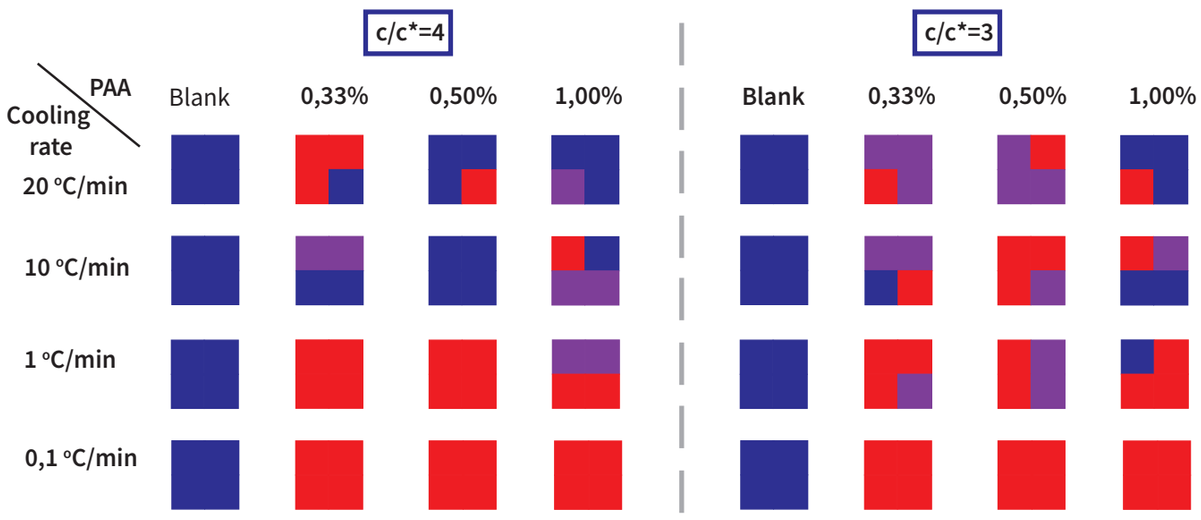

Figure 2. The obtained forms with different amount of additive wt%, pABA supersaturation and cooling rates. Each 1/4 of the square is one of the parallel experiments.

Stability of polymorphs

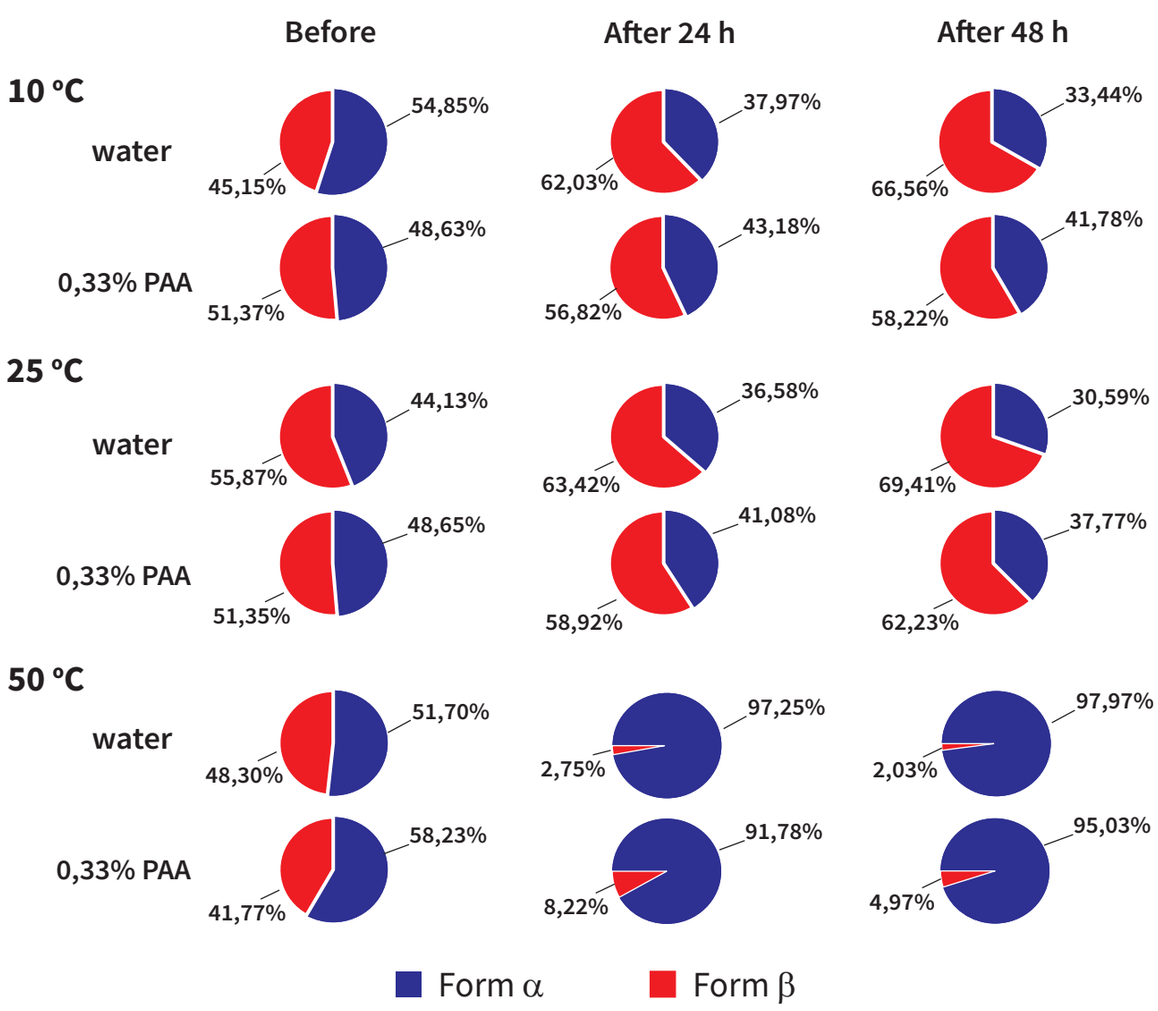

Figure 3. The quantitative content of both forms in water and 0,33 wt% PAA aqueous mixtures maintained at different temperatures after a different period of time.

References

[1] Pudipeddi, M.; Serajuddin, A. T. M. J. *Pharm. Sci.* **2005**, 94 (5), 929–939.
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[3] Cruz-Cabeza, A. J.; et. al. *CrystEngComm* **2019**, 21 (13), 2034–2042.
[4] Bobrovs, R.; et. al. *Cryst. Growth Des.* **2021**, 21 (1), 436–448.
[5] Black, J. F. B.; et. al. *CrystEngComm* **2015**, 17 (28), 5139–5142.

Induction time

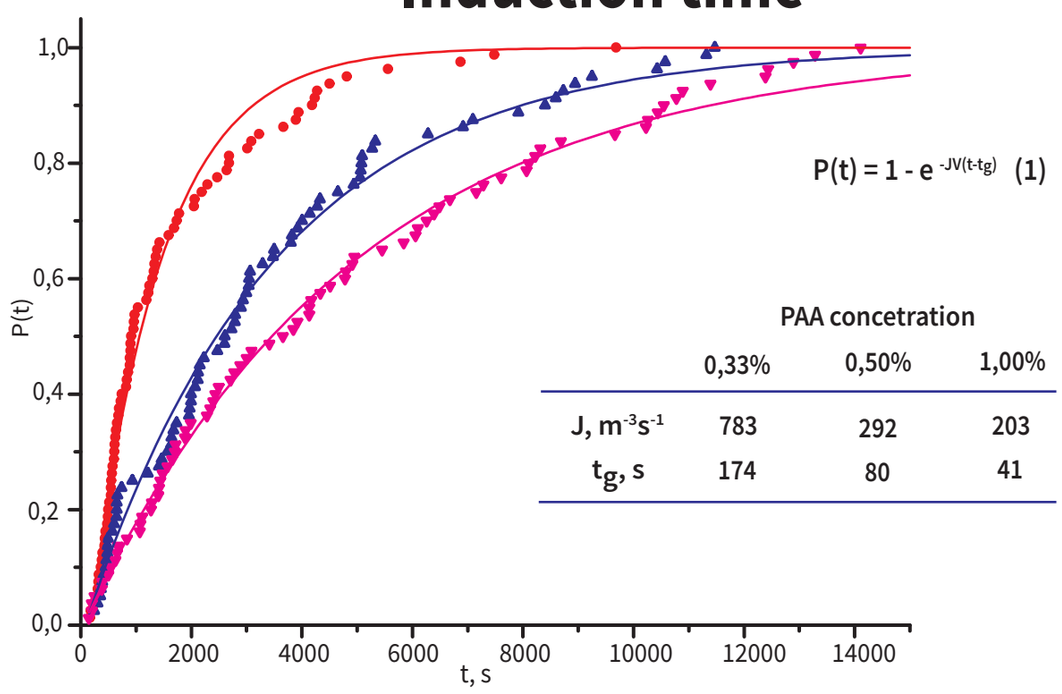


Figure. 4 Experimentally obtained probability distribution P(t) of the induction time for pABA at supersaturation ratio c/c* = 4 in 0,33 wt% PAA (●), 0,50 wt% PAA (▲), 1,00 wt% PAA (▼) aqueous mixtures at 41 °C temperature. The nucleation rate (J) and delay time (t_g) were obtained by fitting the experimental data to eq. (1).

Solubility

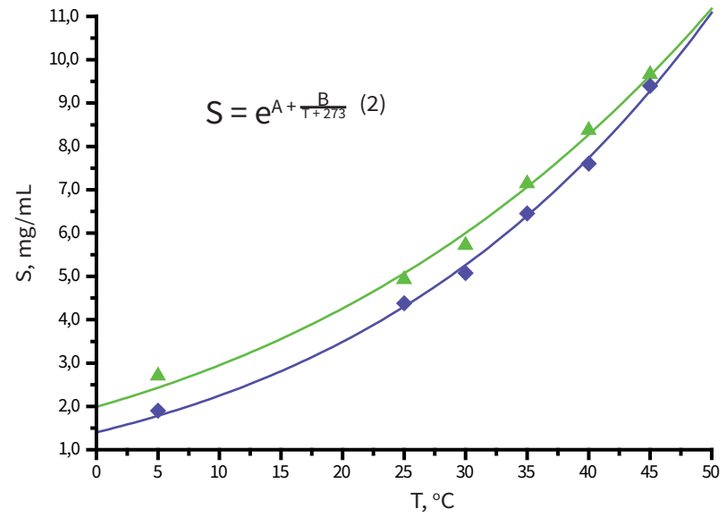
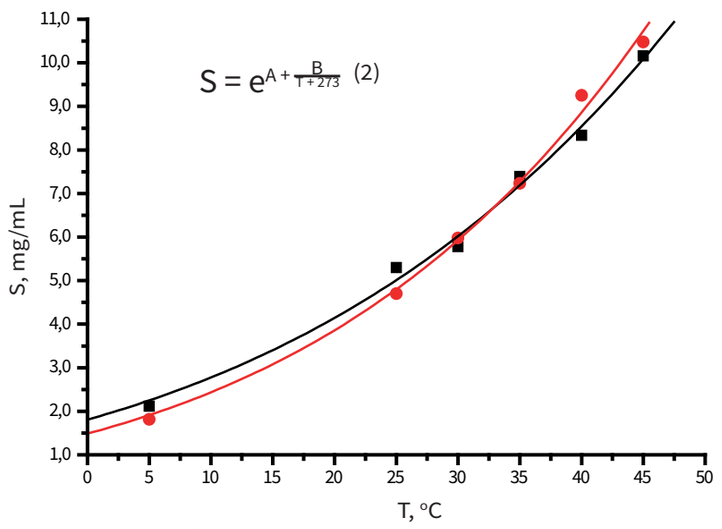


Figure. 5 The solubility of pABA α polymorphic form in water (▲) and 0,33 wt% PAA (◆) aqueous mixture. Triangles and diamonds represent experimental data, while lines were calculated using eq. (2) with coefficients A and B found in the fitting using the least-squares approach.

Figure. 6 The solubility of pABA β polymorphic form in water (■) and 0,33 wt% PAA (●) aqueous mixture. Triangles and diamonds represent experimental data, while lines were calculated using eq. (2) with coefficients A and B found in the fitting using the least-squares approach.



Conclusions

- The greatest influence on the crystallization of the pure β form of *para*-aminobenzoic acid in the presence of polyacrylic acid is a low cooling rate (0,1 °C/min), a small supersaturation of the *para*-aminobenzoic acid solution (c/c*≤4) and a 0,33 wt% polyacrylic acid concentration.
- Polyacrylic acid slows down both forms phase transition compared to the phase transition in deionized water.
- Polyacrylic acid reduces the solubility of both forms of *para*-aminobenzoic acid in deionized water and also inhibits its crystallization.
- Increasing the concentration of polyacrylic acid from 0,33 wt% to 1,00 wt% further delays the nucleation of *para*-aminobenzoic acid (increases the nucleation induction time).
- Polyacrylic acid decreases the nucleation rate of *para*-aminobenzoic acid and increases the nucleation induction time compared to the nucleation rate and induction time in deionized water, but does not necessarily result in the formation of the pure β form.

Presented at: The 4th International Online Conference on Crystals, 18.-20.09.2024