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Publication date: 2018

Document version
Final published version

Citation for published version (APA):

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Download date: 23. Aug. 2019
Crystallization of cephradine polymorphs and hydrates from mixed solvents of methanol and water

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ABSTRACT

Cephradine is a first-generation cephalosporin antibiotic and can be used to treat different infectious diseases from both gram-positive and gram-negative microorganisms. From other studies it has been reported that cephradine can form at least 4 anhydrous polymorphs, one monohydrate and one dihydrate [1–4], which lead to significant challenges in the crystallization process as the product has to be crystallized with the desired solid form and the preferred particle size and shape.

In the current work, the relative stability of the anhydrate/monohydrate cephradine (CPA/CPH) as a function of temperature and water activity in the surrounding medium is investigated. This is investigated by measuring the solubility of CPA/CPH in different methanol-water mixtures at varying temperatures 15-55 °C. The solid phase is analyzed by Raman spectroscopy to identify which solid form is obtained under the given methanol-water mixture and temperature conditions. It is observed that the CPH transforms to the CPA at methanol mole fractions greater than 0.65 and that the CPA is a different polymorph than the anhydrous cephradine, purchased from Sigma-Aldrich. Subsequently, crystallization behavior of cephradine polymorphs and hydrates is studied by linear cooling crystallizations. Different operating conditions are investigated such as the effect of cooling rate and use of different solvent mixtures of water and methanol.

The obtained results can be used to predict the relative stability of the CPA/CPH at different temperatures and water activities of water and methanol.

Solubility and stability measurement:
- Classical isothermal technique
- Temperature: 15, 25, 35, 45 and 55 °C
- Time: 6 hours
- Solvents: Water and Methanol
- Saturated solution analyzed with HPLC
- Three repetitions
- Starting material: Cephradine monohydrate

Cooling crystallization:
- Cooling at constant rate
- Performed in an EasyMax 102
- Scale 100 mL
- Overhead stirrer and solid state thermostat
- Nucleation is detected by monitoring the turbidity of solution
- The Meta Stable Zone Width (MSZW) is measured

RESULTS

Solubility and stability measurement:

![](Figure_1.png)

Cooling crystallization:

![](Figure_2.png)

![](Figure_3.png)

![](Figure_4.png)

![](Figure_5.png)

![](Figure_6.png)

CONCLUSIONS

- Solubility of cephradine increases with temperature and water mole fraction
- CPH transforms into CPA at a mole fraction <0.4 of water and methanol
- Cooling crystallization of cephradine showed that the MSZW increases with cooling rate in pure water and with mole fraction of methanol in the solvent
- CPH was formed in all cooling crystallization experiments

ACKNOWLEDGEMENTS

This project is part of the ProPharm project which is a collaboration between Lundbeck, LEO Pharma, the Technical University of Denmark and the University of Southern Denmark. Danish Council for Independent Research (DFF) is acknowledged for the financial support (grant ID: DFF-6111-00077B).

REFERENCES