

# Characterisation of New Solvates of Amiloride-HCl

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Amiloride (3,5-Diamino-N-(aminoiminomethyl)-6-chloropyrazinecarboxamide), a potassium-sparing diuretic, can also be used as an inhaling therapeutic agent in the treatment of mucoviscidosis. Jozwiakowski *et al.* [1] reported that amiloride hydrochloride can crystallise as dihydrate, which exists in the two polymorphic forms A and B, and as an anhydrate. The crystal structure of a methanol hemi-solvate was reported by Pretscher *et al.* [2].

In a recent comprehensive study we found three new solvates besides the already known methanol hemi-solvate, which were characterized in detail applying powder X-ray diffraction (PXRD), polarized light and hot stage microscopy, thermal analytical methods (TGA, DSC), moisture sorption analysis as well as infrared and Raman spectroscopy.

The three new solvates were obtained from ethanol, 1-butanol and 1-propanol. The solvates are stable in dry atmosphere but in a moist environment an exchange of the solvent with water occurs, resulting in dihydrate A. TGA shows that the methanol hemi-solvate is the most stable solvate, which desolvates not below 180°C, whereas the ethanol solvate desolvates at about 150°C. The desolvation step of the 1-propanol and 1-butanol solvates occurs in the same temperature range between 160 and 170°C. The ethanol solvate and the 1-propanol solvate show a stoichiometric ratio of 1:1, whereas the 1-butanol solvate contains 0.8mol of solvent. All solvate forms exhibit clearly different PXRD patterns, which points out that the structures are not isomorphic. Also IR and Raman spectroscopy show clear differences and support this assumption. However, desolvation at elevated temperatures always resulted in the same anhydrous form.

Moisture sorption/desorption studies (25°C) of the solvates with the automatic moisture balance (SPS11) showed that the organic solvents can be replaced completely by water at elevated moisture conditions. The methanol hemi-solvate is stable below a relative humidity (RH) of 50%. Above this moisture condition the solvate exchange results in a mass increase until a solvent (water) content of a dihydrate is achieved (about 13.5%), which varies less than about 2% in the entire humidity range from 0 to 95% RH. The other three solvates are unaffected at and below 20% RH but show a mass decrease in the sorption cycle between 30 and 40% RH down to about 10% solvent content. Between 50 and 70 % RH the mass then increases to a solvent content of 13.5%, indicating the formation of a dihydrate. All solvates transform to a mixture of the two dihydrate forms during this solvent/water exchange.

These results highlight the importance of a proper humidity control during harvesting and drying in solvent screening programs for crystal forms. Such a control becomes particularly crucial if a stable hydrate exists and is required in order to understand crystallization processes that involve unstable or transient solvate states.

## References

- [1] M.J. Jozwiakowski, S.O. Williams, R.D. Hathaway: Relative physical stability of the solid forms of amiloride HCl. *Int. J. Pharm.* (1993) 91, 195-207.
- [2] A. Pretscher, M. Brisander, A. Bauer-Brandl, L.Kr. Hansen: The methanol hemisolvate of amiloride hydrochloride. *Acta Cryst.* (2001) C57, 1217-1219.