

Characterization, Stability and Structure of Pharmaceutical Hydrates

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Many pharmaceutical salts, such as cromolyn sodium (CS) and metal salts of nedocromil, including nedocromil sodium (NS), form various hydrates. Whereas NS and its bivalent metal counterparts, nedocromil magnesium (NM), nedocromil zinc (NZ), and nedocromil calcium (NC), form various stoichiometric hydrates [1], CS forms a series of non-stoichiometric hydrates [2]. These hydrates were characterized by thermal analytical methods, dynamic aqueous solubility measurements, ^{13}C solid-state nuclear magnetic resonance (SSNMR) spectroscopy, and X-ray diffractometry (both powder and single-crystal), supplemented by molecular modeling of the crystal lattice.

For the nedocromil salts, ^{13}C SSNMR data provided information on the number of non-equivalent sites of the nedocromil anions in the unit cell and on the dihedral angle of the out-of-plane carboxylate group. For hydrates of NM, NC, and NZ, the (metastable) solubility in water increases, and the associated negative free energy of aqueous solution decreases, with increasing water stoichiometry. This unusual behavior is explained by the greater structuring of the water molecules in the crystals of the higher hydrates, which is reflected in their lower entropy, as the water stoichiometry increases.

In NS and NM, the carboxylate oxygens provide the primary coordination sites for the sodium and magnesium ions, whereas in NZ, the carbonyl oxygen in the pyridone ring provides that for the zinc ions. In NC, both the carboxylate and the carbonyl oxygens provide coordination sites for the calcium ions. In the nedocromil salts, most of the water molecules are coordinated to the metal ions, which accords with the fixed stoichiometry of the nedocromil hydrates. In CS, one of the sodium ions is disordered over three sites, the other sodium ion has a fixed position, while some of the water molecules are disordered and the others are fixed [2]. This structural variability helps to explain the variable water content of CS in response to the environmental relative humidity that reflects the water activity.

References

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