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"Isoenergetic" Polymorphs of Cimetidine

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Relevance of polymorphism in the field of pharmaceutics is variation of bulk properties of powders, i.e. different behaviour of crystal modifications e.g. under granulation, milling and compression and during dissolution processes. Furthermore, transition from one modification to another under stress conditons may also alter such properties significantly. Cimetidine, a H_2-antagonist, has been discussed in the literature as a relevant example of a polymorphic substance: Four solvent-free modifications of Cimetidine have been described [1,2]; the explicite structure of three of them are resolved [4,5,7]. The aim of the present study was to investigate modifications of Cimetidine with respect to differences structure and in crystal energies.

Material and Methods

Four modifications of Cimetidine (A, B, C, D) were prepared in pure form according to published protocols [1.2,3]. The polymorphs were characterised by x-ray powder diffraction (Stoe, Darmstadt, Germany), IR spectroscopy (Perkin Elmer 841, Norwalk, CT, USA), heat flow DSC (DSC 600 TABase (WSK); 10 mg, 0.2 K/min), power compensating DSC (Perkin Elmer Pyris 1; 2.5 mg, 5 K/min), and solution calorimetry in water and in methanol for A, C and D: (Thermometric Thermal Activity Monitor; 0.05 - 0.1 g Cimetidine in 100 ml of water or methanol respectively).

Results and Discussion

Using heat flow DSC and power compensating DSC on samples of modifications A, B, C and D, melting temperatures as well as enthalpies of fusion were found to be extremely next to one another, almost within the tolerance of the respective method. Therefore only data within one series are compared. Data were used in order to calculate Gibbs free energy functions. Furthermore, solution calorimetry, by avoiding experimental drawbacks with respect to heat capacity of powder samples (packing density, contact to the sample pan etc.), is regarded as particularly useful for the present problem. Measurements in two solvents yielded significant crystal energy information corresponding to the findings in the respective DSC methods. Conformations of molecules in the various crystals the explicite structures of which are resolved (A, C and D) are discussed with regard to the small differences in crystal energies.

Conclusion

Gibbs free energy functions are useful tools for the discussion of energy relationships of modifications, because they point out the one preferred, most stable form at each given temperature and as well as conditions for possible transitions. In the case of Cimetidine, however, as energetic differences between the modifications are so extremely small, all of the modifications are regarded practically isoenergetic. In many cases the modifications crystallise more or less at random from aqueous solutions, whereas in some cases two modifications even crystallise simultaneously from the same solution. DSC on powder samples as well as high precision solution calorimetry have proven to be suitable methods for studying small differences given a particularly careful calibration.

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