Crystallization of polymophic pharmaceuticals in nanopores and Ostwald's step rule of stages

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The crystallization of the polymorphic pharmaceuticals ibuprofen and acetaminophen in controlled porous glasses (CPG) with pore diameters in the range 4-100 nm is studied by conventional DSC. In both cases growth of different polymorphs can be achieved depending on the crystallization conditions. The melting temperature T_m decreases commonly with decreasing pore size in accordance with the Gibbs-Thomson equation. Interestingly, a systematic decrease of the heat of melting ΔH_m is also observed if the pore size decreases. This can be explained by a geometrical model considering the existence of a non-crystallizable layer of the guest system with a thickness of about 1-3 nm on unmodified pore walls. We conclude that non-crystallizable layers covering hydrophilic pore walls are a common phenomenon in case of CPGs filled with pharmaceuticals. We conclude that the nanocrystals grown in nanopores can be understood as model system allowing to study early stages of crystallization of polymorphic substances. The advantage of host-guest systems is, however, that nanocrystals which are seldom and transient in bulk systems can be studied in detail. This is very interesting since more than 100 years after Ostwald postulated his step rule of stages, predictive understanding of early crystallization stages of polymorphic substances is still premature. A thermodynamic model explaining how surface energy contributions can stabilize polymorphic states which are metastable in the bulk is presented. In nanosized early-stage crystals with high surface-to-volume ratios other polymorphs may be stable than in large crystals with low surface-to-volume ratios. Accordingly, the transient occurrence of different polymorphs during crystal growth in bulk systems can be related to surface energy contributions to the total Gibbs free energy of the nanocrystals.

References

[1] M. Beiner, G.T. Rengarajan, S. Pankaj, D. Enke, M. Steinhart, Manipulating the crystalline state of pharmaceuticals by nanoconfinement, *Nano Letters* 7 (2007) 1381-1385.

[2] G.T. Rengarajan, D. Enke, M. Steinhart, M. Beiner, Size-dependent growth of polymorphs in nanopores and Ostwald's step rule of stages, *Phys. Chem. Chem. Phys.* 13 (2011) 21367-21374.

[3] N. Sonnenberger *ea*, Interfacial phenomena influencing the crystallization of polymorphic pharmaceuticals in nanopores, (2015) *to be published.*