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Structural origin of superior plasticity and tabletability of theophylline monohydrate

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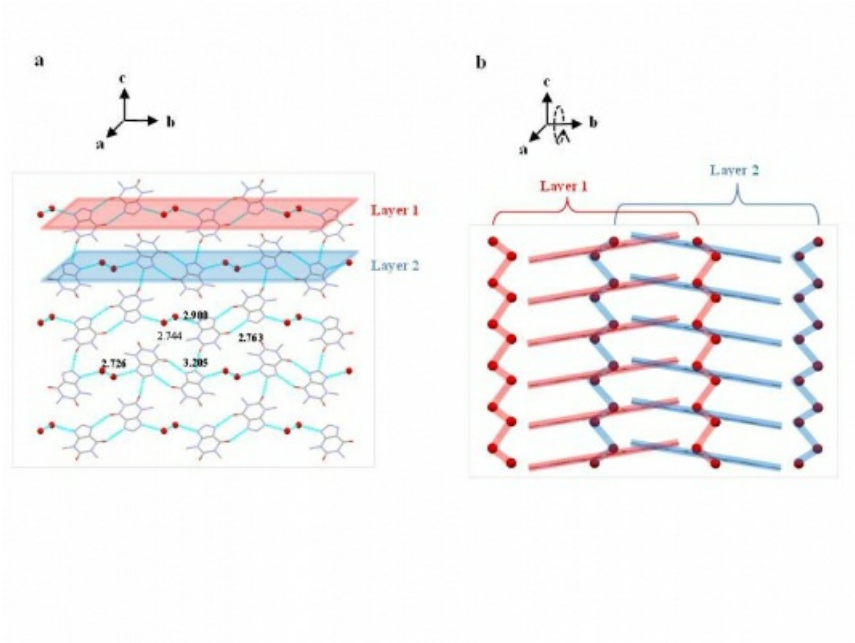
Material mechanical properties influence tableting performance of pharmaceutical powders. Mechanical properties of crystals are, in turn, influenced by crystal structure. A clear understanding of the relationship between crystal structure and mechanical properties is key to effective crystal engineering for improving tableting performance of drugs. Hydrate formation is one way to modify crystal structure and mechanical properties of drugs. Theophylline anhydrate (THa) transforms to theophylline monohydrate (THm) when exposed to sufficiently high relative humidity. THa was previously shown to be very plastic and exhibited excellent tabletability due to its structural features that lead to multiple slip mechanisms. Surprisingly, we recently observed that THm exhibited even better tableting performance than THa. We examined structural origin of the superior plasticity of THm. In this study, a THm powder with particle size and shape closely similar to a THa powder was prepared by vapor mediated phase transformation. The elimination of possible contributions by particle size and shape to tableting properties made it possible to unambiguously identify the role of bonding area and bonding strength on powder tableting performance. It was also shown that accurate true density is essential for correct analysis of compressibility data and clear understanding of tableting behavior of THm. Experimental evidences from compressibility analysis and macroindentation hardness measurements confirmed the higher plasticity of THm than THa. The high plasticity of THm is explained by its unique ladder-like structure (Fig. 1a-b), where rigid theophylline dimers (rungs) weakly connecting to more rigid water chains (rails). When subjected to an external stress, the rigid ladders can be displaced along the direction from their position at rest with little resistance since only the weak N···H-O hydrogen bonds between dimers and water chains need to be overcome for plastic deformation to take place. More importantly, the displacement of the dimeric rungs will propagate through the rigid pillars easily because only a few dimers are involved for a dislocation to move along the water chains in the THm crystal (Fig. 2a-c). Hence, plastic deformation can take place under a stress much lower than that required to simultaneously move the entire column as in THa.

[1] Chattoraj, S. et al. (2010) CrystEngComm, 12:2466-2472



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