Milling of amorphous molecular and pharmaceutical compounds: accelerated aging or rejuvenation

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The industrial formulation processes used to prepare molecular materials (drugs, foods, cosmetics...) impose high energy mechanical constraints which involve dynamic aspects in addition to temperature or pressure variations. Materials which are forced by dynamic stresses undergo modifications of their physical state which affect their subsequent properties (solubility, bioavailability, stability etc...). Due to their structural peculiarities and sensitivity to external perturbations, molecular materials are also excellent model systems to investigate the influence of forcing factors [1]. In the presentation we are concerned with the effect of milling which is the prototype of such forcing processes.

Upon milling, molecular compounds reveal a wide range of behaviours. Milling can induce amorphisation of crystals. In contrast milling of an amorphous compound can sometimes induce recrystallisation towards phases of various degrees of stability. In other circumstances, it can modify the nature of the amorphous state itself [2]. It can provide glasses of different degrees of energy, looking like either an hyperquenched liquid, a rejuvenated or an over-aged glass. Depending on intensity, temperature and duration of the milling, the local structure of the amorphous state appears to be possibly modified such that it is able to promote recrystallisation into various crystalline varieties upon reheating. The microstructure itself may be modified and changes the balance between surface and bulk crystallization. Even if a lot remains to be done at the fundamental level to understand and efficiently control the various transformations, milling appears to be a promising methods for manipulating the amorphous state for specific uses.

What the experimental results suggest, is that, the various mechanisms, which combine to achieve the forced molecular motions, compete with a thermally activated restoration. Effective temperature concepts and energy landscape formalism can be tentatively used to rationalise the whole observed behaviour.

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[1] J. F. Willart, and M. Descamps *Solid State Amorphisation of Pharmaceuticals***.**
Mol. Pharmaceutics, **2008**, 5 (6), 905-920

[2] M. Descamps, and J.F. Willart *Perspectives on the amorphisation/milling relationship in pharmaceutical materials* Advanced Drug Delivery Reviews (Available online 27 January **2016**) doi:10.1016/j.addr.2016.01.011 .) Volume 100, 1 May 2016, Pages 51-66.