MECHANICAL ACTIVATION TO MANIPULATE THE PHYSICAL STATE OF MOLECULAR AND PHARMACEUTICAL COMPOUNDS

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The industrial formulation processes used to prepare drugs impose high energy mechanical constraints which involve dynamic aspects in addition to temperature or pressure variations. These specific perturbations are, for example, the frequency of the shocks upon milling or the rate of desolvatation during spray drying or freeze-drying. Dynamic aspects are also clearly important during extrusion. Materials which are driven by dynamic stresses undergo modifications of their physical state which affect solubility and bioavailability: amorphizations or recrystallizations [1], forced nucleation or rejuvenation [2], interconversions between polymorphic crystalline states [3]... Physical and chemical stabilities can be modified either in the bad or good direction [4]. In this presentation we illustrate the variety of modifications that can be observed. Basically they are non equilibrium phase transformations for which no general framework is available. Some operational rationalizations however emerge which offer possibilities to control and manipulate the nature of the end product. The role of the temperature and the intensity of grinding are discussed. In particular the effect of the relative position of the milling temperature and the glass tansition temperature (Tg) of the milled compound is highlighted [1,4]. The low temperature character of the process gives opportunity to create new chemically pure solid states but also to force molecular alloying [5]. This provides new tools for investigating multi-component states and phase diagrams, either involving small or (and) macromolecules [6]. They may help finding solutions to the challenging issue of poorly soluble drugs.

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