Mechanical activation and mechanical alloying of pharmaceuticals

M. Descamps[+], J.F. Willart, S. Desprez, A. De Gusseme, V. Caron

LDSMM, UMR CNRS 8024, University Lille1, 59655 Villeneuve d'Ascq, France
+ marc.descamps@univ-lille1.fr

The molecular materials differ from other materials by the strong contrast between the intra and intermolecular force field. The weakness of the intermolecular interactions makes them extremely sensitive to the external disturbances. We are here concerned with the effects of mechanical milling on the physical state of this type of materials. It is well known in the pharmaceutical domain that grinding may induce untimely transformations of the physical state of the materials with strong influence on the stability and bioavailability of the drug. Sometimes phase transformations are observed to occur between different polymorphic varieties and sometimes it results more or less partial amorphyzations. Our objective is to try to rationalize the behaviours in order to obtain a better control of the formulation processes. Up to now the effects of mechanical activation were mainly considered in metallurgy. However no universally accepted theoretical description of the transformation!

processes has still emerged. The situation of molecular materials differs in several ways: namely the richness of the crystalline polymorphism, the very low symmetry of the structures and above all the propensity of the compounds to amorphize with glass transition temperatures Tg close to room temperature. The molecular mobility and transport coefficients change rapidly in this temperature domain. We may thus anticipate a very strong specific influence of the grinding temperature on the state of the end product.

We present results obtained on a selection of relevant pharmaceutical molecular solids. Upon grinding new states of the compounds are reached. Their physical natures depend on the grinding temperature and intensity. However they do not depend on the nature of the initial physical state. There are convincing features to show that the states which are reached are stationary dynamical states rather than equilibrium thermodynamical states. The structural and nanostructural evolutions of the ultimate single crystalline grains were followed at different stages of the grinding process by X-ray powder analysis. This investigation enables to show how the size and the distortion of the crystalline grains as well as their anisotropies take place in the transformation process. When a solid state amorphyzation is induced by grinding it can be observed that the physical state of the amorphous solid depend on the grinding control parameters. Further more grinding the glassy amorphous stat! e itself may induce evolutions of its state corresponding to different levels of the energy landscape. This may offer new possibilities to manipulate the glassy state, either accelerating aging or inducing rejuvenation.

Finally the possibility to form molecular alloys by solid state vitrification is discussed. Emphasis is more specifically placed on the existence of a single relaxation process in the mechanically prepared alloy.