# Influence of Mechanical Stress on the Crystallinity and Molecular Structure of Piroxicam Polymorphs

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*Purpose:* To investigate the effect of mechanical stress on the amorphization of polymorphs of piroxicam (PI and PII) and to study the subsequent recrystallization. This work extends the pioneering mechanical activation studies of Shakhtschneider and Boldyrev [1,2].

*Methods:* Mechanical stress was applied using a cryogenic grinding mill. Changes in the crystallinity of PI and PII were measured by powder X-ray diffractometry using the general area detector diffraction system (GADDS). Changes in the electronic structure of piroxicam molecules in PI and PII were quantified by the Kubelka-Munk function using solid-state diffuse-reflectance UV-visible spectroscopy (DRUVS). Changes in the intermolecular interactions of piroxicam were investigated using variable-temperature solid-state $^{13}C$ nuclear magnetic resonance (VTSSNMR) spectroscopy and solid-state diffuse-reflectance infrared Fourier-transform spectroscopy (DRIFTS). These tools are excellent for this study of mechanochromism.

*Results:* Cryogenic grinding results in amorphization of both polymorphs, PI and PII. A color change, white to yellow, accompanies the above phase changes. Using HPLC and $^{1}H$ solution-state NMR spectroscopy, piroxicam was found not to undergo chemical degradation under mechanical stress. A linear relationship was found between the increase in the intensity of the yellow color and the time of application of the stress. This color change is reversed on recrystallization of amorphous piroxicam. However, the kinetics of the reverse reaction did not fit the classical solid-state reaction models. Changes in wavelength of the 400 nm band also accompanied each phase change, crystalline to amorphous, indicating that amorphization is accompanied by a change in dipole moment (zwitterionization). The structure of amorphous piroxicam depends on the polymorph from which it is prepared. VTSSNMR spectroscopy indicates that most of the amorphous piroxicam consists of unionized piroxicam molecules. The zwitterionic species comprise only about 8% of the amorphous phase. This ability to quantify the fractions of unionized and ionized molecules of piroxicam in the amorphous phase highlights the unique capability of solid-state NMR to quantify mixtures in the absence of standards.

*Conclusions:* Under mechanical stress, each polymorph (PI or PII) of piroxicam undergoes a structural change, crystalline (white) to amorphous (yellow), which is reversed on recrystallization. Amorphization and recrystallization are accompanied by proton transfer.

## References

1. T.P. Shakhtshneider. Phase transformations and stabilization of metastable states of molecular crystals under mechanical activation. Solid State Ionics. 101-103, 851-856 (1997).

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