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Determination of Factors Affecting Kinetics of Solid State Transformation of Fluconazole Polymorph II to Polymorph I Using Diffuse Reflectance Fourier Transform Infrared

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Abstract: It was of interest to investigate the factors affecting kinetics of transformation of fluconazole polymorph II (the metastable form) to fluconazole polymorph I (the stable form) using diffuse reflectance Fourier transform infrared spectroscopy (DRIFTS). Fluconazole polymorph I and II were both prepared by crystallization in dichloromethane. The two forms were characterized using DSC, TGA, PXRD, solubility and DRIFTS. Transformation of polymorph II to polymorph I was also studied under different isothermal temperatures using DRIFTS. Kinetic analyses of the data were done using model dependent and model independent methods. Eighteen solid-state reaction models were used to interpret the experimental results. Based on statistics, the Prout Tompkins model provided the best fit for the transformation. The activation energy (Ea) value derived from the rate constants of the Prout Tompkins model was 329 kJ/mol. Model independent analysis was also applied to the experimental results. The average value calculated using both methods were not significantly different. Factors affecting kinetics of transformation such as mechanical factors, relative humidity and the effect of seeding were also studied. Mechanical factors, which included trituration and compression, proved to enhance transformation rate significantly. Relative humidity proved to transform both polymorphs to monohydrate form. The presence of seed crystals of polymorph I was proved not to affect the transformation process of polymorph II to polymorph I. Effect of solvent of crystallization (dichloromethane) was studied. A significant change of the rate of transformation was proved in presence of solvent vapors, and a change on the mechanism was proposed.