Effect of Compression on the Crystallization of Amorphous
Indomethacin in Tablets

Naveen K. Thakral¹², Sarat Mohapatra², Gregory A. Stephenson¹, Raj Suryanarayanan²

The goal of this work is to evaluate the effect of compression on the physical stability of amorphous drugs, using indomethacin as a model compound. Tablets of amorphous indomethacin (200 mg; 8 mm round flat) were compressed at 25, 50 or 100 MPa using a materials testing instrument (Zwick-Roell, Germany) and stored individually in Mylar pouches at -20, 4, 25 and 35 °C. At different time points, tablets were analyzed using synchrotron radiation (Argonne National Laboratory, IL) to detect drug crystallization and, under select conditions, the crystallization kinetics was studied. Immediately after compression, no crystallization was observed in tablets compressed at 25 and 50 MPa. While compression at 100 MPa revealed crystallization, storage at -20 °C and 4 °C did not show any further increase in crystalline content up to 14 days. In the tablets stored at 35 °C, drug crystallization was rapid and accelerated as a function of compression pressure - crystallization was most rapid in tablets compressed at 100 MPa. Using an X-ray microdiffraectometer with an area detector, we obtained spatial information by monitoring tablets from the surface to the core (depth profiling). Drug crystallization was not uniform throughout the tablets. Crystallization was more pronounced on the upper and lower surface and in the radial regions facing the die wall.

1. Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285
2. Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455