Effect of Moisture on the Crystallization of Amorphous Drugs in Contact with Tableting Excipients
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Purpose
Amorphous drugs are used to improve the dissolution and bioavailability of drugs. However, these metastable forms of drugs can transform into more stable, less soluble crystalline counterparts when formulated with excipients into tablets or capsules. In this study we evaluated the effect of residual and atmospheric moisture on the amorphous to crystalline transformation of nifedipine (NIF) and indomethacin (IMC) when in contact with microcrystalline cellulose (MCC), lactose monohydrate (LacM) and magnesium stearate (MgSt).

Methods
Amorphous NIF and IMC were prepared on glass cover slips and covered with MCC, LacM and MgSt. Excipients were used as received or dried before use. Samples were stored in a desiccator or in a 50% RH humidity chamber at 30 or 40ºC. A light microscope was used to determine the number of nuclei and growth rate of surface crystals that formed on the amorphous surface in contact with the excipients as a function of time. Crystal forms were confirmed by XRD and Raman measurements.

Results
In a desiccator using dried excipients only MgSt caused significant nucleation on the surface of amorphous NIF. At 50% RH all three excipients increased the number of nuclei formed on the amorphous surface. This increase ranged from 10 to 50 times when compared to controlled samples without excipient coverage. LacM had the smallest effect. The growth rate of NIF was not significantly changed under a layer of excipients. For IMC, in addition to increasing the number of nuclei, contact with excipients appeared to induce the nucleation of a different polymorph (α versus γ).

Conclusion
The results showed that contact with certain excipients accelerates the amorphous to crystalline transformation of nifedipine and indomethacin and that this involved both an increase in the number of nucleation sites and a lesser extent crystal growth rate. These effects were significantly enhanced by an increase in moisture.