
The research was conducted in collaboration with former graduate student Hitesh Purohit, Research Scientist Niraj Trasi, Scientist at AbbVie Yi Gao, and FDA Scientists Dajun Sun, Edwin Chow, Hong Wen, and Xinyuan Zhang.

Drugs are sometimes formulated as the amorphous form in tablets and capsules. Amorphous drugs are more soluble than their crystalline counterpart and hence can increase the amount of drug absorbed by the patient when the drug is not very soluble in the gastrointestinal tract. This is very useful to make sure that the patient gets a sufficient dose such that the drug can exert its therapeutic effect. However, there is a risk that the amorphous drug will crystallize, either partly, or completely, before it reaches the patient, for example during storage. We studied the crystallization tendency of tacrolimus capsules when storing them at higher temperatures and relative humidity (40°C/75%RH). Tacrolimus, an immunosuppressant, is produced as an amorphous drug in commercial formulations. We found that the drug underwent crystallization after a few days, and that the crystallization affected how well the capsules dissolved. Next, we used the dissolution data as input into a model that enables us to simulate how much drug is absorbed. This part of the study was done by collaborators at the FDA. We found that the model predicted that small levels of crystallinity did not substantially impact how much drug was absorbed into the body. However, if more than 20% of the drug crystallized, the model predicted that the drug absorption was reduced to unacceptable levels. The use of the modeling tool thus enables us to predict the potential impact of drug crystallization on the oral absorption behavior. In the future, we will test how predictive the model actually is by dosing partially crystallized tacrolimus capsules to
volunteers and determining the amount of drug that reaches the systemic circulation. It is expected that this study will help us to better understand the effect of crystallized drug on product performance, as well as improving inputs to predicative modeling approaches.

“This research represents an exciting collaboration between academic, industry and FDA scientists, combining experimental data with physiologically based pharmacokinetic modeling,” said Dr. Taylor.