The Use of Small Molecule Excipients for Improving the Physical Stability and Dissolution Performance of Ketoconazole Spray Dried Dispersions

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**Purpose**

A large fraction of active pharmaceutical ingredients (API) currently in development have low aqueous solubility but high permeability, making their oral absorption dissolution rate limited. Amorphization has been widely used as a strategy for improving the oral bioavailability of poorly soluble APIs. However, physical instability of amorphous API, leading to crystallization, can negate the solubility advantage and lead to product failure. Amorphous solid dispersions (ASD), wherein an API is molecularly mixed with a hydrophilic polymer, have generally been used to impede drug crystallization. The use of excipients other than polymers in enhancing the physical stability of amorphous pharmaceuticals has largely been unexplored. The current study aims to evaluate the use of several small molecule excipients that are generally regarded as safe (GRAS) for the purpose of improving the solid-state physical stability and dissolution performance of amorphous APIs. Our ultimate goal is to gain a mechanistic understanding of the impact of small molecule excipients on the physical stability of amorphous pharmaceuticals and offer insights into rational excipient selection for ASD formulations.

**Methods**

Ketoconazole (KTZ) ASDs were prepared with each citric acid, tartaric acid and succinic acid in 1:1 molar ratio via spray drying. Thermal characterization was performed using differential scanning calorimetry (DSC). Specific interactions between drug and excipient play an important role in the stabilization of amorphous pharmaceuticals and were investigated by FT-IR and ssNMR. One important kinetic factor that contributes to crystallization, molecular mobility, was studied using frequency domain dielectric spectroscopy (DES). Drug crystallization in presence of small amount of dissolution medium was characterized using synchrotron source XRD. Dissolution performance of ASDs was evaluated using USP type II apparatus and KTZ concentrations were analyzed using HPLC.

**Results**

DES revealed that the addition of organic acids resulted in reduction in the molecular mobility of the solid dispersions. Addition of citric acid or tartaric acid caused a pronounced increase in the overall glass transition temperature (Tg) and no crystallization was observed within the timeframe of the DSC experiments. FT-IR spectra revealed interactions between KTZ and organic acids. Preliminary studies of KTZ-citric system by C13 ssNMR confirmed this finding. The synchrotron XRD results suggested that KTZ-citric and KTZ-tartaric SDDs are much more stable than KTZ-succinic and amorphous KTZ in presence of dissolution media. All KTZ-acid ASDs initially exhibited high apparent solubility. However, KTZ concentration decreased over time.

**Conclusion**

The current study highlighted that small molecule excipients that can significantly reduce molecular mobility are good candidates for improving physical stability of amorphous pharmaceuticals. KTZ-acid ASDs increased physical stability of amorphous KTZ in the solid-state, an effect attributed to a reduction in molecular mobility of the system. This suggested that the molecular mobility could be used as an excipient screening tool for improving solid-state stability of amorphous pharmaceuticals. However, since the solid-state stability could not directly translate to dissolution enhancement, the synchrotron XRD studies done in presence of dissolution media was used for predicting dissolution behavior.