Role of the Strength of Drug-Polymer Interactions on the Molecular Mobility and Physical Stability of Amorphous Solid Dispersions
P. Mistry, S. Mohapatra, T. Gopinath, R. Suryanarayanan
University of Minnesota

Purpose
To investigate the effect of specific drug-polymer interactions (ionic or H-bonding) on the molecular mobility and the physical stability of ketoconazole solid dispersions.

Methods
Amorphous solid dispersions of ketoconazole (weakly basic drug) were prepared, with each of the three polymers - polyacrylic acid (PAA), poly (2-hydroxyethyl methacrylate) (PHEMA) and poly (vinylpyrrolidone) (PVP). These polymers differed in their ability to specifically interact with ketoconazole and their concentration ranged between 4 and 15% w/w. Drug-polymer interactions were evaluated by spectroscopy (FTIR and solid-state NMR) and thermal characterization (Tg and crystallization) was performed by differential scanning calorimetry (DSC). The structural relaxation times were determined by dielectric spectroscopy. In solid dispersions with 4% w/w polymer, the crystallization onset time (in glassy state) and kinetics (in supercooled state) were evaluated using synchrotron radiation (Argonne National Labs) and laboratory X-ray diffractometer, respectively.

Results
FTIR showed peaks at 1605 and 2500 cm⁻¹ attributable to the COO⁻ and N⁺-H stretching vibrations indicating ionization of PAA and ketoconazole in solid dispersions. Additionally, ¹³C and ¹⁵N NMR studies confirmed ionic interactions between PAA and ketoconazole. While FTIR revealed H-bonding interactions with PHEMA, no such effects were observed with PVP. Based on DSC and XRD studies, the ability of the polymer to inhibit drug crystallization was rank ordered as: PAA > PHEMA > PVP. Based on dielectric spectroscopy, the α-relaxation times of solid dispersion followed the same order. An increase in the relaxation time translated to both an increase in crystallization onset time and a decrease in the magnitude of crystallization rate constant. Ionic interaction was most effective in inhibiting crystallization followed by H-bonding interactions. PVP influenced neither the α-relaxation times nor the physical stability, presumably due to lack of specific interactions with ketoconazole.

Conclusion
Both the strength of interaction and physical stabilization of drug followed the order: PAA > PHEMA > PVP. Ionic interactions in ketoconazole-PAA solid dispersion provided enhanced physical stability via significant reduction in molecular mobility. At a given polymer concentration, the strength of drug-polymer interactions dictate the decrease in mobility obtained by addition of polymer.