# A Tiered Formulation Approach for Screening Poorly Soluble, Discovery-Stage Compounds

## Purpose

We describe a formulation approach 1) to give developable compounds the best chance for success in the initial preclinical pharmacokinetic study, and 2) to advance the simplest formulation possible. Potential dosing vehicles are separated into tiers, with each tier adding potential complexity for subsequent formulation development. We examined this approach using two poorly soluble marketed drugs with reasonably good bioavailability in humans.

## Methods

Potential dosing vehicles were first evaluated based on solubility, precipitation on aqueous dilution, and conformance with IACUC guidelines. Various formulations of each compound were then dosed \textit{in vivo} in fasted rats. Plasma sample analysis was performed using LC/MS/MS with internal standard after protein precipitation.

## Results

Carbamazepine was not completely soluble in the Tier 1 (aqueous solution or suspension) formulations tested, but was soluble in the Tier 2 (primarily aqueous with solubilizing agents) formulations. The Tier 1 methylcellulose suspension formulation provided 50% oral bioavailability. When carbamazepine was dosed using Tier 2 (40% HPbCD), or Tier 3 (DMA/PEG) dosing solutions, bioavailability was complete. Carbamazepine represents an example of a compound for which formulation can influence bioavailability, but it has sufficient solubility such that acceptable properties in a discovery PK study could be obtained using the most basic formulation. Itraconazole was not soluble in the Tier 1 or Tier 2 formulations tested, and a Tier 3 formulation was required for complete solubilization. A methylcellulose suspension formulation (Tier 1) resulted in variable and low oral absorption. The Tier 2 (HPbCD) formulation was dosed as a suspension and resulted in improvement of oral bioavailability to 15 ± 7%. The Tier 3 formulation (PEG 400) improved oral bioavailability further to 56 ± 21%. Itraconazole represents an example of a compound for which formulation not only influences bioavailability, but could have been critical to the identification of this as a developable compound.

## Conclusions

Here we propose a tiered approach for assessing discovery stage formulations and identifying the simplest formulations that can maximize oral absorption of poorly water soluble compounds.