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Bioavailability enhancement of a poorly soluble lead candidate through enabling formulations and prodrugs

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Purpose

Compound A, a lead candidate of oral kinase inhibitors, showed promising potency and selectivity. However, the extensive solubility screening revealed that it had very low solubility not only in aqueous, but also in organic solvents, and solubilizing excipients including co-solvents, complexation, surfactants, and oils/lipids. The low solubility of this compound would pose a significant risk for sufficient exposure. The aim of this work was to present the enabling formulation approaches and prodrug design assessed to enable in vivo studies and identify options for reduced exposure risk.

Methods

Different exposure enhancing formulation approaches including solution, suspension, nano-suspension, salt, lipid-based formulation (LBF) and amorphous solid dispersion (ASD) were evaluated in silico, in vitro and in vivo. In addition, Compound B, a prodrug of Compound A was designed by attaching the molecule with a phosphate prodrug moiety and further evaluated for its potential for solubility and exposure enhancement via in vitro and in vivo experiments.

Results

In-silico (GISIM), in-vitro (pH-shift, advance human GI TIM-1dissolution) and in vivo data from different formulation approaches showed an overall good correlation. Low Fabs observed in NHP PK and TIM-1 studies at clinically relevant dose levels indicates high exposure risk at >200mg dose. LBF and ASD showed some improvement but unable to mitigate exposure risk due to low excipient solubility and high crystallization tendency, suggesting the development risk of an enabling formulation to achieve sufficient clinical exposure remains high.
The prodrug Compound B demonstrated significant improvement in solubility (>1000 fold) and exposure in preclinical species. Moreover, a fast and complete conversion to parent was observed in human intestine fluid suggesting an efficient bioconversion expected in human. This work has enabled in-vivo studies and the prodrug prioritized for further development.

Conclusion

Solubility-limited exposure risk has been identified for a potent kinase inhibitor. Among the options including enabling formulation approaches and prodrug design assessed in silico, in vitro and in vivo, the phosphate prodrug has demonstrated to overcome solubility limited exposure.

Keywords: Poorly soluble, Enabling formulation, Prodrug, Bioavailability