Preparation and Characterization of Alectinib Amorphous Solid Dispersion Using a Novel Polymer Apinovex™ to Enhance Solubility and Dissolution

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Purpose
Alectinib (ALB) is a kinase inhibitor used to treat metastatic non-small cell lung cancer patients with anaplastic lymphoma kinase (ALK). Its bioavailability with food is only 36.9%, making it difficult to take the prescribed 600 mg dosage. The high dosage is due to ALB's limited solubility, resulting in diminished bioavailability. Amorphous solid dispersions (ASDs) could enhance ALB's solubility and decrease the dosage.

Methods
ASDs with drug loadings of 10, 20, 30, 40, 60, 70, and 80% in polymer were produced by rotary evaporation in methanol: chloroform solvent and vacuum-dried. Amorphization of ASDs was assessed by Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD). Successful ASD drug loadings were evaluated for solubility using the shake-flask method in 0.1 N HCl, pH 6.8 phosphate buffer, FaSSGF, FaSSIF-V2, and FeSSIF-V2 for 24 hours. Dissolution was performed for the drug loadings with improved solubility. Stability studies were performed at room temperature and accelerated conditions for 3 months

Results
DSC and PXRD studies showed no endothermic and crystalline ALB peaks in 10, 20, 30, 40, and 60% ASDs, indicating an amorphous state. However, endothermic and crystalline peaks were observed in 70 and 80% ASDs, suggesting the polymer could not hold all the drug. The pure ALB, 20, 40, and 60% ASDs showed the highest solubility in FeSSIF-V2 among 0.1 N HCl, pH 6.8 phosphate buffer, FaSSGF, FaSSIF-V2, and FeSSIF-V2, with a concentration of 8.81, 393.91, 347.92, and 32.66 µg/mL, respectively. Since 60% ASD solubility does not improve and 20% ASD showed similar solubility as 40% ASD, dissolution investigations were done with 40% ASD. Dissolution experiments of 40% ASD in FeSSIF-V2 media demonstrated drug release of 60 and 90% in non-sink and sink conditions, respectively, in 2 hours. 40% ASDs remained uncrystallized for 3 months at 25˚C/60%RH and 40˚C/75%RH.

Conclusion
ALB ASD was developed by solvent evaporation using ApinovexTM. The formulation increased solubility and dissolution of ALB, implying enhanced in-vivo absorption, especially in the fed state. Stability studies indicate the formulation remains stable for 3 months at 25˚C/60%RH and 40˚C/75%RH. These findings endorse the use of solid dispersion as a strategy to enhance the bioavailability of Alectinib.

Keywords: ASDs, Alectinib, solubility and dissolution