**Impact of Improved Solubility and Nasal Retention of Phenytoin via Amorphous Solid Dispersions on Brain Delivery Following Intranasal Administration**

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**Background and aims.** Intranasal administration is a non-invasive and convenient dosing method that enables immediately offering an effective treatment option for urgent central nervous system disorders such as epileptic seizures and migraines. Drugs administered intranasally in in nasal mucus and permeate the nasal mucosa to reach the brain and systemic circulation. However poorly water-soluble drugs such as phenytoin (PHT) which is an antiepileptic drug may limit brain uptake following intranasal administration by the elimination caused by mucociliary clearance. This study investigated the effect of intranasal administration of amorphous solid dispersions (ASDs) with improved PHT solubility on the PHT’s nasal retention and brain delivery.

**Methods.** ASDs were prepared by dissolving PHT and various water-soluble polymers in an organic solvent, followed by solvent evaporation. The ASDs were characterized by PXRD and IR measurements. PHT solubility was assessed by quantifying the amount of PHT dissolved in simulated nasal mucus over time. To evaluate in vivo effects of PHT, ASD suspensions were intranasally administered to mice, and the residual amount of PHT in the nasal cavity and its distribution to the brain were quantified.

**Results and Discussions.** PXRD patterns of ASDs prepared with polyvinylpyrrolidone (K30) or copolyvidone (VA64) showed a halo pattern.IR measurements revealed the changes of intermolecular interactions resulting from spectral changes. These results suggested that the formation of ASD consisted of PHT and K30 or VA64. At 5 min after the start of the solubility test, the amount of PHT dissolved of VA64-ASD was 10-fold and 2-fold higher than PHT alone and that of K30-ASD, respectively. Furthermore, intranasal administration of the VA64-ASD suspension resulted in a 2.3-fold improvement residual amount of PHT in nasal mucosa compared to PHT alone. Consequently, the amount of PHT delivered to the brain and plasma significantly increased by 2.5-fold and 3.5-fold, respectively.

**Conclusion.** These findings suggest that intranasal administration of ASD is a promising approach to enhance brain and systemic drug delivery by improving solubility and nasal cavity retention. (313 word)