Pharmacokinetics and Disposition of 4-Methoxydiphenylmethane in Sprague Dawley Rats

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Purpose
Methoxydiphenylmethane (4-MDM) is a new potential compound for the treatment of Chronic Obstructive Pulmonary Disease (COPD). Establishment of preclinical pharmacokinetics (PK) of 4-MDM is essential for its future clinical studies. The purpose of this study was to determine the PK and disposition of 4-MDM from a cosolvent formulation in Sprague Dawley (SD) rats after IV and oral administrations.

Methods
A 10 mg kg⁻¹ dose of a cosolvent formulation of 4-MDM containing PEG 400 (30%), Propylene Glycol (22%), Glycerol (15%) and water (33%) was administered to SD rats by both IV (jugular vein) and oral routes. For IV administration (n=3), plasma samples were collected at 0.083, 0.17, 0.34, 1, 2, 3, and 6 hour post dose. At the same time bile was collected every 0.5 hour for up to 6 hours from cannula inserted into the bile duct. On the other hand, for oral route, (n=4) plasma samples were collected at 0.25, 0.5, 1, 2, 3, 5, 8, 12, and 24 h post dose. Concentrations of 4-MDM in the plasma and the bile were quantified by LC-MS/MS equipped with a photo-ion source. Subsequently, the PK parameters of 4-MDM were derived using Phoenix Winnonlin 6.3.

Results
The plasma profiles of both IV and oral administration followed 2 compartmental model (Figure). The IV profile showed rapid distribution of 4-MDM with K₁₂ of 2.4 ± 1.23 hr⁻¹. Other IV PK parameters including K₂, t½, Vₚ, AUC₀-ₜ, AUC₀-∞, and CL were estimated as 0.79 ± 0.16 hr⁻¹, 0.89 ± 0.18 hr, 3624.14 ± 875.74 mL Kg⁻¹, 17446.19 ± 1755.86 hr*ng mL⁻¹, 18463.71 ± 1908.41 hr*ng mL⁻¹, and 577.17 ± 59.43 mL hr⁻¹ kg⁻¹, respectively. The total cumulative amount of 4-MDM excreted in bile was 614 ± 39.33 ng in 6 hours, which is less than 1% of the dose. Therefore, biliary excretion is not the major pathway for the elimination of 4-MDM. With the oral administration, absorption of 4-MDM from the cosolvent was very rapid and the absorption phase was less than 15 minutes with the highest concentration of 122.8 ± 40.1 ng mL⁻¹ at 15 minutes. Most of the PK parameters could not be estimated from this profile since the profile could not be fitted into a typical oral plasma profile. The AUC₀-∞ was approximated to be 1077.89 hr*µg mL⁻¹, and the bioavailability from the oral route was calculated as 5.83%.

Conclusion
Both oral and IV administrations of 4-MDM in cosolvent formulation followed two compartmental PK model. The low bioavailability from the oral route could be due to a rapid metabolism of 4-MDM in the liver, since biliary excretion is not a major route for its disposition and urinary excretion is not possible for its high lipophilicity.

Figure: Plasma profile of 4-MDM after (A) Oral and (B) IV dosing