**Rational Development of Sildenafil-Curcumin Nanoagglomerated dry powder as Nose-To-Brain Therapy for** **Alzheimer's Disease**

**Xinyue Zhang1,2**, Shing Fung Chow1,2.

1Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China;

2Advanced Biomedical Instrumentation Centre, Hong Kong Science Park, Hong Kong Special Administrative Region, China.

**Background and aims.** Alzheimer's disease (AD) remains a significant challenge due to the lack of effective treatments that can halt disease progression. Sildenafil (SIL) has been shown to suppress tau hyperphosphorylation (1), while curcumin (CUR) has demonstrated the ability to regulate Aβ levels (2). Hence, this study aims to develop SIL-CUR nanoagglomerated dry powders as nose-to-brain therapy for halting Aβ- and tau-driven progression of AD.

**Methods.** SIL-CUR nanosuspensions were fabricated by flash nanoprecipitation with N-polyvinylpyrrolidone as the stabilizer. The formulation parameters were optimized using a three-factor Box-Behnken design. The optimal SIL-CUR nanosuspension was converted into nanoagglomerated powders using combined *in-situ* thermal gelation and spray drying (3). The spray drying processing parameters were optimized using a 2-level, 2-factor full factorial design. The nasal deposition studies of the dry powder were conducted using an anatomically realistic Alberta Idealized Nasal Inlet model at an inspiratory flow rate of 15 L/min. The safety of the optimized SIL-CUR dry powder was evaluated in cytotoxicity studies with nasal (RPMI 2650) and brain related cells (SH-SY5Y and U-87 MG).

**Results.** The optimal SIL-CUR nanosuspension (Figure 1 (A) and (B)) exhibited a z-average particle size of 122.32 ± 1.92 nm, PDI of 0.18 ± 0.03, acceptable colloidal stability, zeta potential of 0.30 ± 0.29 mV, and encapsulation efficiency of 80.33 ± 2.44% (SIL) and >99.99% (CUR). The optimized dry powder (Figure 1 (C) and (D)) exhibited satisfactory redispersibility (Redispersibility index = 1.16 ± 0.01), buckled morphology and excellent drug deposition in the olfactory region (18.62 ± 0.85%). The drug content of SIL (6.63 ± 0.14%) and CUR (13.43 ± 0.38%) were consistent with the theoretical values. Furthermore, the cytotoxicity studies confirmed that SIL-CUR dry powder was safe within a clinically relevant SIL concentration range of 50–2,000 nM.

**Conclusion/Discussion.** The production and optimization of SIL-CUR dry powders, tailored for nose-to-brain delivery, were successfully achieved using a Quality-by-Design approach. Studies on the *in-vivo* pharmacokinetics and efficacy are currently underway. This study holds potential for advancing the development of innovative nanotherapy targeting anti-Aβ and anti-tau for patients with AD.

**Acknowledgements.** This study was financially supported by the Health and Medical Research Fund (Reference number: 21223381) from Health Bureau, Hong Kong SAR Government.

**References:**

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**Figure 1.** (A)Exemplary intensity-weighted size distribution of nanosuspension; (B) Colloidal stability profile of nanosuspension (n = 3); (C) Exemplary intensity-weighted size distribution of the nanosuspension and SIL-CUR nanosuspensions reconstituted from the optimal nanoagglomerated powder formulation; (D)Scanning electron microscopy images of the optimal SIL-CUR nanoagglomerated powder at \*5000.