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**Name :** KIFAYAT ULLAH SHAH

**Title :** LIQUID AND SPRAY-DRIED NANOEMULSION DESIGNS FOR PULMONARY DELIVERY OF RIFAMPICIN

**Supervisor :** ASSOC. PROF. DR. WONG TIN WUI (MS)  
ASSOC. PROF. DR. CHAN LAI WAH (CS)

The study investigated the aerosolization and inhalation profiles of rifampicin-oleic acid first generation liquid and solid nanoemulsions and their respective chitosan- and chitosan-folate conjugate-decorated second and third generation nanoemulsions. The liquid nanoemulsions were prepared by spontaneous emulsification method and had their size, zeta potential, polydispersity index, morphology, pH, viscosity, surface tension, density, refractive index, drug content, drug release, aerosolization and inhalation profiles characterized. The first, second and third generation nanoemulsions had average droplet sizes of  $43.89 \pm 0.36$  nm,  $52.12 \pm 0.36$  nm and  $59.69 \pm 0.26$  nm, with narrow polydispersity indices at  $0.16 \pm 0.03$ ,  $0.25 \pm 0.03$  and  $0.23 \pm 0.01$  respectively. They exhibited desirable pH, surface tension, viscosity, refractive index, density, and viscosity attributes for pulmonary rifampicin administration. The second generation nanoemulsion was characterized by relatively low levels of burst drug release due to intimate chitosan packing at the oil globules' surfaces and viscosifying effect on continuous phase, which was unattainable by the branched folate conjugate of chitosan. All nanoemulsions demonstrated more than 95 % aerosol output and inhalation efficiency greater than 75 % when delivered by nebulization. The aerosol output, aerosolized and inhaled fine particle fractions were primarily governed by the size and surface tension of nanoemulsions in an inverse relationship. The first, second and third generation nanoemulsions were converted to their corresponding solid counterparts by spray drying method. The spray-dried solid first, second and third generation nanoemulsions achieved particle sizes of  $7.05 \pm 0.38$   $\mu$ m,  $7.96 \pm 0.33$  and  $5.45 \pm 0.38$   $\mu$ m

respectively, with sustained drug release behavior as compared to their associated nanoemulsions due to their large particle sizes and solid nature. The powder exhibited an aerosol output of > 65 % when delivered using Handihaler. The mass median aerodynamic diameters of < 5  $\mu$ m was achieved for all spray-dried solid nanoemulsions, due to their lower tapped densities resulting in inhaled fraction of > 30 %. Among physicochemical properties of spray-dried nanoemulsions, increased circularity and lower tapped density have been found to improve aerosolization of powder from dry powder inhaler, while higher span value tends to improve the FPF. Due to significantly higher aerosolization potential and inhalation efficiency of liquid nanoemulsions, they were evaluated for their cellular internalization, safety and pharmacokinetics behaviors in cell culture and animal models. A significantly higher level of cellular internalization was observed with third generation nanoemulsion when compared to second generation liquid nanoemulsion due to double receptors targeting in the former via folate and acetylglucosamine moiety of chitosan. The liquid nanoemulsions were regarded as safe and biocompatible with reference to rifampicin in therapeutic doses, because macrophages remain viable (> 80 %) following their incubation with nanoemulsions. The pharmacokinetics analysis revealed that nanoemulsion succeed in maintaining therapeutic level of drug in the plasma for 16 h after intratracheal drug administration, with higher lung drug concentration in case of third generation nanoemulsion. Thus, both liquid and solid nanoemulsions are suitable for use as rifampicin carrier in the treatment of tuberculosis.