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

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ABSTRACT

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 ± 0.36 nm, 52.12 ± 0.36 nm and 59.69 ± 0.26 nm, with narrow polydispersity indices at 0.16 ± 0.03, 0.25 ± 0.03 and 0.23 ± 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 ± 0.38 μm, 7.96 ± 0.33 and 5.45 ± 0.38 μm 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 μm 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.

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INTRODUCTION

1.1 OVERVIEW

The lung represents a unique organ system in the body and is probably the most historic route of drug delivery. It has been described in Ayurvedic medicine more than 4000 years ago (Gandevia, 1975). The ancient Egyptians used to inhale vapors for treatment of a wide variety of diseases as early as 1500 BC. Bennet, a physician in Royal Infirmary, first employed inhalation therapy for treatment of tuberculosis in 1664 (Muthu, 1922). However, inhalation as a route of drug delivery was forgotten until the introduction of metered dose inhalers in 1950s to deliver albuterol for treatment of asthma (Bailey & Berkland, 2009).

The therapeutic outcome of drug delivery system depends not only on drug, delivery device and formulation, but is also significantly influenced by the route of administration. A drug delivery system should provide a therapeutic amount of drug with maximum protection from natural barriers and degradation. Oral route of drug delivery still remains dominant but other routes of drug administration like inhalation are becoming more and more popular for targeted drug delivery in the treatment of local respiratory and systemic diseases (Buttini, Colombo, Rossi, Sonvico, & Colombo, 2012).

Current research in the field of drug delivery technology mainly focuses on controlled delivery of therapeutic molecules to the lungs. This type of drug delivery minimizes drug dosage and assures improved efficacy with minimal systemic toxicity in the treatment of respiratory infections due to direct delivery of drugs to the site of action and avoidance of first-pass metabolism (Loira-Pastoriza, Todoroff, & Vanbever, 2014). Pulmonary drug delivery also improves bioavailability of drugs in the treatment of systemic infections due to large surface area, lower thickness of basement membrane and extensive vascularization of the lung (Olsson et al., 2011).

Drugs can be effectively delivered to the lungs via nebulizers, metered dose inhalers and dry powder inhalers. The choice of drug delivery device depends mainly on the site of action, the pathophysiology of lungs, the drug and the formulation