Microparticles specific for lung delivery: *in-vivo* drug distribution in monkeys

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INTRODUCTION

Inspite of extensive research in tuberculosis (TB), it is still one of the major infectious diseases and cause of high mortality world wide [*Brewer et al. 2005]*. To enhance efficacy with lower dosing, newer drug delivery systems has been developed which provide targeted drug delivery and controlled release at the primary site of infection, i.e., the lung macrophage. Our lab has previously reported *poly(*D, L-lactic acid) (PLA) microparticles containing rifabutin (RFB) and isoniazid (INH) for pulmonary delivery and explored various facets of treatment with microparticle DPI *Muttil et al. 2007*]. The aim of present study was to evaluate pharmacokinetics, biodistribution and toxicity parameters of RFB and INH incorporated in DPI microparticles after ninety days of repeated dosing in rhesus macaques in order to establish steady-state pharmacokinetics and preclinical safety of the formulation prior to humans clinical trials.

OBJECTIVE

To evaluate pharmacokinetic and biodistribution of anti-tuberculosis drugs in rhesus monkeys

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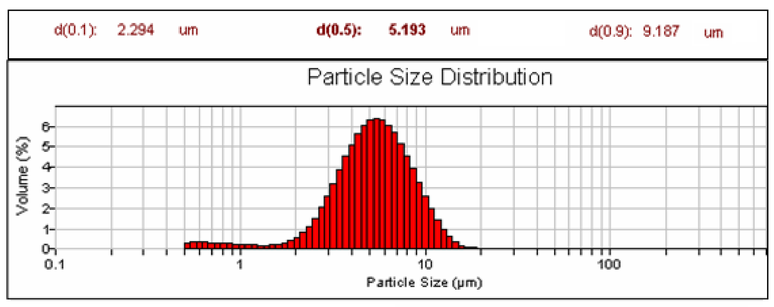
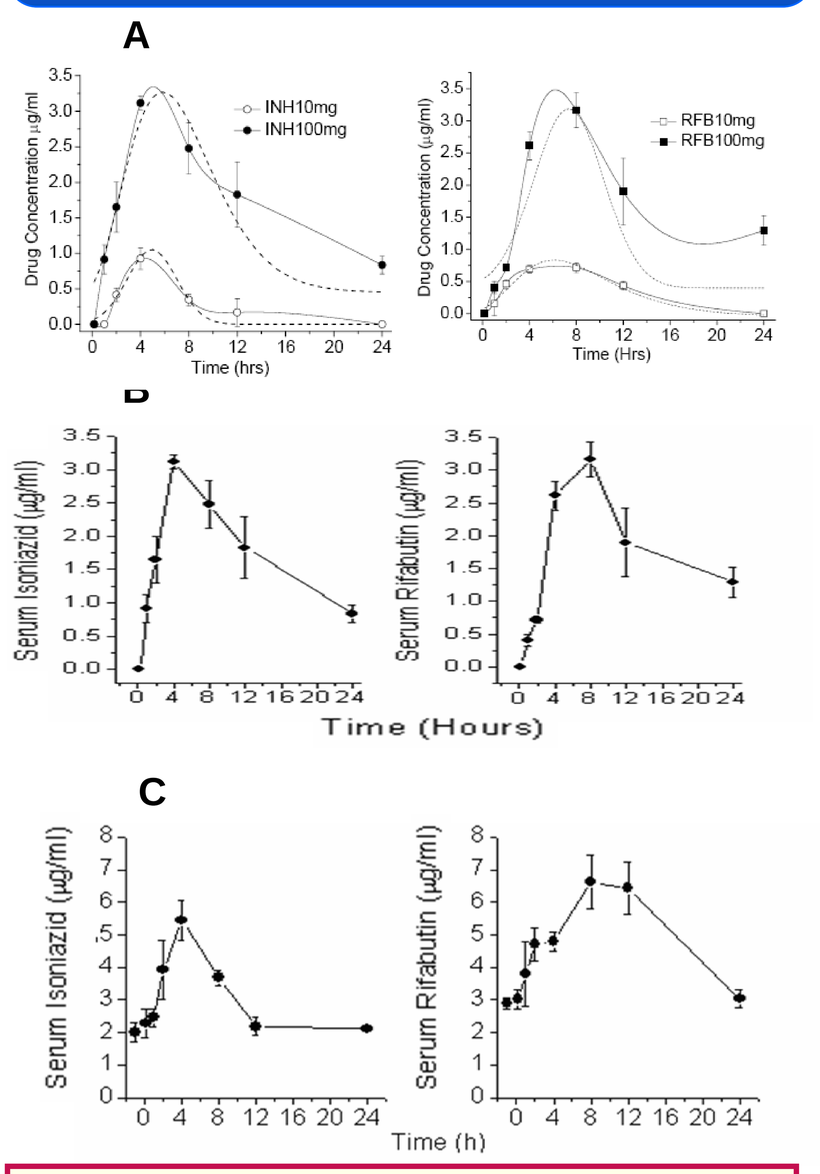


DOSING

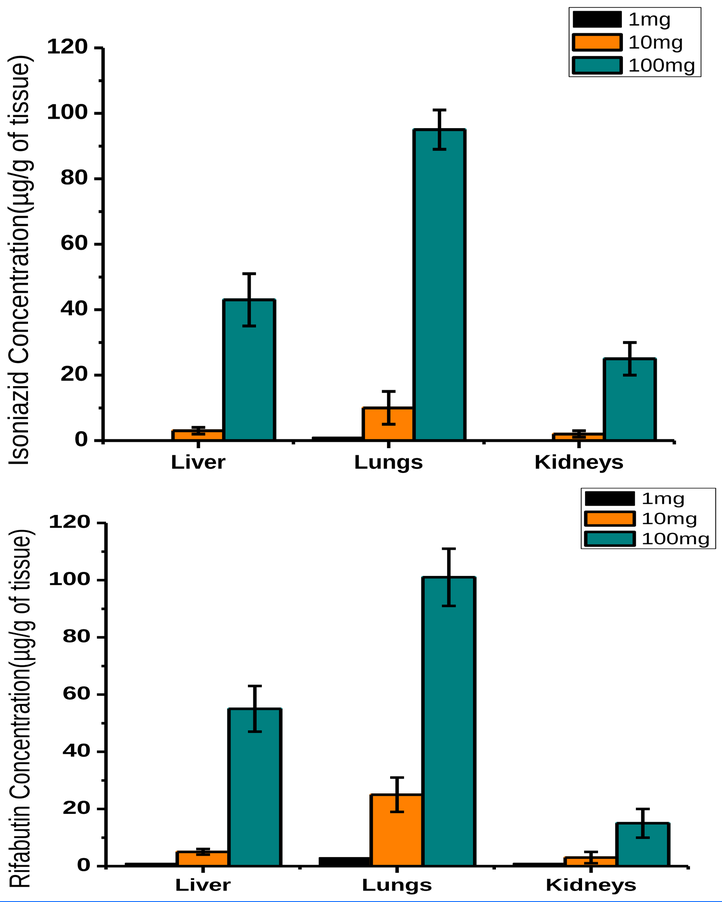
Prepared microparticles formulation has physicochemical properties that render it suitable for administration as a dry powder inhalation (DPI). Microparticles containing 0.25(1mg MP), 2.5(10mg MP) or 25 mg(100mg MP) each of isoniazid (INH) and rifabutin (RFB) were administered daily for 90 days to rhesus macaques (n=4/group). Another group received single intravenous doses.

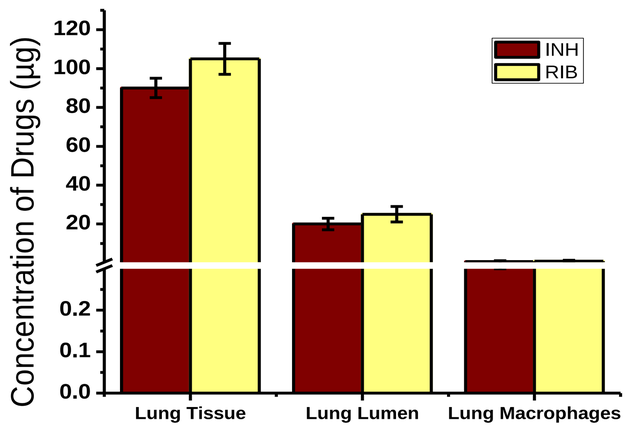
PHARMACOKINETIC PROFILE



Serum was separated from blood samples of each time point. After 90-day study, various tissues of interest (lung, liver and kidney) were harvested from twenty monkeys, minced into pieces, homogenized and analyzed for drug content. Validated HPLC method were used for assay in serum, alveolar macrophages and homogenates of lungs, liver and kidneys. Pharmacokinetics were investigated using WinNonlin. Biodistribution in cell lysate and tissues was established at terminal sacrifice.

BIODISTRIBUTION





DISCUSSION

Plots representing the mean drug serum concentration–time data after intravenous administration of rifabutin and isoniazid to monkeys are shown in figure-A. In contrast to inhalation [Fig-B(100mg MP) & C (10mg MP)], i.v. administration resulted in hasty clearance of drugs from the blood, significantly shorter half-lives and mean residence times. Dose-dependant enhancement of all parameters was observed, as expected from the order of magnitude differences in doses. It could be seen from figure that concentration of both the drugs descends in order of lungs, liver and kidney. As evident from figure, level of rifabutin and isoniazid in lungs were much higher than tissue than other tissues (Liver & Kidney). Serum Cmax was 5.4 to 7 times greater with intravenous compared to pulmonary delivery, while serum t1/2 was 3.5 to 5.7 longer after inhalation, demonstrating targeted as well as controlled delivery. The biological half lives of both agents were enhanced up to almost six times by incorporation in inhalable MP. The higher i.v. doses were retained longer, but much less as compared to equivalent doses from inhaled MP. Compared to mice, Tmax was prolonged by ~2 h while t1/2 was shorter: ~10 h for INH and ~14 h for RFB after DPI. The results of this report suggests microparticles lead to the deposition of drugs into the lungs of monkeys by means of inhalation and maintain high therapeutic concentration.

CONCLUSION

The data obtained from rhesus monkeys with good therapeutic concentration in target organ and negligible toxicity (data not shown) strongly recommends for the further human clinical trails

REFERENCES

•Brewer et al. (2005) *Long time due: reducing tuberculosis mortality in the 21st century.* Arch Med Res 36(6) 617-621

•Muttil et al. (2007) Inhalable microparticles containing large payload of anti-tuberculosis drugs. Eur J Pharm Sci 32(2) 140-150

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