SUMMARY AND CONCLUSIONS

• Anti-TB drugs differing markedly in terms of solubility, were incorporated in a biodegradable polymer matrix to prepare inhalable microparticles (MP) containing a drug payload of 50% weight/weight. No such formulation is hitherto reported in the literature.

• Solvent systems were standardized to prepare true solutions containing all the drugs for developing industrially-scalable spray-drying processes for MP preparation.

• The incorporation efficiency of these process was close to 99%, and the product was amenable to use as a dry powder inhalation. MP had a mass median aerodynamic diameter (MMAD) of about 4 μm and comprised a (respirable) fine particle fraction (FPF) close to 79%.

• Analytical methods employing HPLC and LCMS were developed and validated for the assay of RFB and INH in various matrices.

• A simple, inexpensive and efficient ‘nose only’ inhalation apparatus was fabricated and standardized with respect to reproducibility of dose delivered. This apparatus was evaluated against a benchmark apparatus with regards to uniform dose delivery via inhalation route, and gave satisfactory results.

• Administration of MP by inhalation resulted in the development of high intracellular drug concentrations in the alveolar macrophages, and much lower drug levels in the serum of mice and Guinea pigs.

• Determination of the dose of inhalant is a difficult problem in pulmonary drug delivery. This problem was addressed using a bioanalytical approach. Accurate analytical methods enabled quantitation of drug levels in different tissue compartments, and a plausible projection of the amount of MP inhaled by rodents when the in-house or a standard apparatus was used.

• MP administered to mice and Guinea pigs by inhalation specifically targeted AMΦ and co-localized with bacteria within the same phagosome, as evidenced by flow cytometry and confocal microscopy.

• MP induced the proinflammatory cytokine tumor necrosis factor-α upon uptake by infected macrophages. This induction preceded upregulation of γ-interferon, suggesting that MP drive the innate host response to TB infection towards host cell apoptosis and the acquired response towards the T helper-1 phenotype.