CONCLUSIONS

The supercritical anti-solvent (SAS) method was carried out in order to fabricate rifampicin biodegradable loaded microparticles for pulmonary delivery. The polyhydroxy acid [50:50 poly(DL-lactide-co-glycolide) copolymer (PLGA), poly(DL-lactide)(DL-PLA), and poly(L-lactide)(L-PLA)] were used for preparation of drug-loaded microparticles. Rifampicin and polymer in various mixing ratios were dissolved in methylene chloride and sprayed into supercritical carbon dioxide.

The amorphous biodegradable polymer, DL-PLA and PLGA, provided film or agglomerated mass. This indicated that carbon dioxide acted as a plasticizer for the polymer resulting in agglomeration of the polymer. No particle formation was obtained when using DL-PLA and PLGA at 50-100 % polymer content. Polymer or polymer-drug film was observed on the wall of the vessel. Drug loaded DL-PLA and PLGA microparticles were formed only at 20-40 % polymer content. Those microparticles prepared from PLGA and DL-PLA had volumetric median diameter larger than 18 μm and exhibited irregular shape particles forming large and porous agglomerates.

The semicrystalline polymer L-PLA provided small and spherical microparticles. Drug loaded microparticles of L-PLA polymer provided spherical microparticles at high polymer content (70-90 %). At 60 % L-PLA polymer content, both spherical and irregular microparticles were observed. When using low polymer content of L-PLA, the irregular and agglomerate microparticles were obtained.

Type and content of polymer in microparticles had a pronounced effect on morphology and size of the final products. Only the semicrystalline polymer L-PLA provided spherical rifampicin microparticles in the size range (1-5 μm) suitable for use as powder inhalation. While the amorphous polymer DL-PLA and PLGA formed agglomerated microparticles. The semicrystalline polymer generally had higher glass transition temperature than the amorphous polymers. The carbon dioxide acts as plasticizer and reduces the glass transition temperature of the polymer. The amorphous polymers have rather lower transition temperature than semicrystalline polymer, which can easily be lowered below operation temperature by supercritical carbon dioxide.

$D_{10\%}$, $D_{50\%}$, $D_{90\%}$ and span of rifampicin L-PLA microparticles were measured by laser diffraction. Operating temperature influenced on volumetric median diameter of microparticles produced at high temperature (50 ^{o}C). The operating pressure of supercritical carbon dioxide and solution feed rate slightly affected volumetric median diameter of microparticles. The higher concentration of solution provided larger microparticles.

The microparticles prepared from 60 % L-PLA and 40 % rifampicin had good drug loading (23.30 %) with mean size of 4.07 μm but their release of drug was rather rapid. The microparticles prepared from 70 % L-PLA and 30 % rifampicin were the preferred formula because it had good drug loading (16.33 %) and mean size of 3.40 μm. In addition, it showed sustained release property throughout 24 hours. Those microparticles contained only 11.82 ppm of methylene chloride.

The microparticles prepared from 80% L-PLA and 20% rifampicin had low drug loading (8.13 %) and mean size of 3.37 μm but their release of drug was rather low. The dissolution release rate was decreased by increased percent polymer content in drug loaded microparticles. The initial burst release did not occur for 70 % and 80 % L-PLA rifampicin microparticles. The three consecutive batches had similar dissolution profiles and no significantly different particle size. The reproducibility of SAS process could be achieved.

The mass median aerodynamic diameter and geometric standard deviation of formulation containing 70% L-PLA rifampicin loaded microparticles with lactose (< 45 μm) in 1:2 ratio and lactose (45-90 μm) in 1:2 ratio were 4.86 μm, 4.29 μm, 0.63 and 0.66, respectively. It was confirmed that L-PLA rifampicin loaded microparticles prepared by SAS process was of a suitable size to be used in dry powder inhaler formulations.

SAS process showed that no decomposition of rifampicin occurred during the processing. The data of XRD, FTIR and DSC indicated that processed rifampicin produced by SAS technique was not corresponding to that of rifampicin in the previous reports.

The higher molecular weight of polymer provided slower dissolution rate. Not only molecular weight of polymer but also source of polymer influenced the characteristic of microparticles. In addition, high molecular weight of polymer (150,000 Da) produced fiber instead of microparticles.

The bactericidal efficacy of rifampicin loaded microparticles against *Mycobacterium Tuberculosis* was similar to those of unprocessed rifampicin. It was shown that the SAS process produced rifampicin loaded microparticles did not change the bactericidal efficacy of rifampicin.