PLA microparticles for pulmonary delivery of AntiTB drugs: biodistribution study

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INTRODUCTION

Tuberculosis (TB) is a infectious disease caused by Mycobacterium tuberculosis (MTB). Among various forms of tuberculosis, pulmonary tuberculosis is the most common with the involvement of lung macrophages containing a large number of bacilli. Effective chemotherapy of pulmonary tuberculosis has been proposed through pulmonary delivery of biodegradable microparticles incorporating antitubercular drugs. We have demonstrated administration of dry powder inhalations (DPI) of microparticles containing anti-TB drugs to various laboratory animals, which can target drugs to macrophages while decreasing bioavailability to blood and blood-perfused organs. The biodistribution of antituberculosis drugs has always remained a challenge and is responsible for the requirement of daily administration of these drugs during TB chemotherapy. In the present study, a DPI comprising antituberculosis drugs incorporated in biodegradable microparticles was delivered using a validated IPLC biocatalytic method. We studied the pharmacokinetics of the two drugs in target cells (alveolar macrophages) and lung tissue, as well as in the liver and kidneys, where their toxicity is most commonly manifested. Equivalent doses of free rifabutin and isoniazid were administered intravenously for comparison.

OBJECTIVES

- To prepare and characterize poly (DL-lactic acid) microparticles containing rifabutin and isoniazid
- To evaluate the time kinetics of biodistribution of the two drugs i.e. Rifabutin and Isoniazid in the lungs, liver and kidneys of mice

CHARACTERIZATION

- Particle Size analysis
- Differential Scanning Calorimetry

INHALATION OF PLA MICROPARTICLES TO ANIMAL USING IN-HOUSE APPARATUS

DISTRIBUTION OF RIFABUTIN & ISONIAZID IN VARIOUS ORGANS OF MICE AT VARIOUS TIME INTERVALS (n=4)

CONCLUSIONS

This study shows that drugs incorporated in microparticles generate high concentration and maintain therapeutic levels in lungs. Based on favourable biodistribution kinetics, these microparticles have the potential to reduce dosing frequency and toxicity of anti-TB drugs.

ACKNOWLEDGEMENTS

ICMR for providing financial support for the project, ICNR for providing Senior Research Fellowship(SRF) to JK and CNR for providing SRF to AJP

Differential Scanning Calorimetry

Inhaleation

Electron Microscopy of Fabricated Drug Loaded Poly Lactic Acid Microparticles

Pharmacokinetic Parameters of Rifabutin & Isoniazid in the Lungs, Liver and Kidneys of Mice After Intravenous Injection and Inhalation of Microparticles

RIFABUTIN

<table>
<thead>
<tr>
<th>Drug/ Route/ Organ</th>
<th>C0 (µg/ml)</th>
<th>t1/2 (h)</th>
<th>V1 (ml/kg)</th>
<th>CL (ml/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>16.0 ± 0.95</td>
<td>0.45 ± 0.30</td>
<td>0.60 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>8.5 ± 0.18</td>
<td>0.30 ± 0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ISONIAZID

<table>
<thead>
<tr>
<th>Drug/ Route/ Organ</th>
<th>C0 (µg/ml)</th>
<th>t1/2 (h)</th>
<th>V1 (ml/kg)</th>
<th>CL (ml/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>24.0 ± 1.78</td>
<td>16.0 ± 1.12</td>
<td>391.16 ± 1.55</td>
<td>0.47 ± 1.10</td>
</tr>
<tr>
<td>Kidneys</td>
<td>9.5 ± 0.39</td>
<td>0.30 ± 0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IN HUMANS:

- Rifabutin
  - 7.0 ± 0.05
  - 0.45 ± 0.30
- Isoniazid
  - 2.0 ± 0.05
  - 0.30 ± 0.03

In the present study, inhalation of microparticles resulted in effective accumulation of the incorporated drugs in the lungs. At the same time, intravenous administration of equivalent amounts did not result in selective accumulation in targeted organs, i.e., lungs.

All the organs examined showed detectable levels of drug. Levels of isoniazid and rifabutin in lungs (target organ) were much higher than those in the liver and kidney of mice in case of inhalation as compared to intravenous administration. Inhalation of microparticles resulted in targeting of both the drugs to the lungs. The relative bioavailability of both drugs incorporated in microparticles was significantly higher compared with free drugs.

High and prolonged drug concentrations and increased AUC values (~9-fold and ~6-fold increase of rifabutin and isoniazid in case of lungs) were observed. Significant decrease in drug concentration was found in the liver and kidneys. These results confirm that inhalable microparticles are suitable for targeting and providing sustained release of anti-TB drugs to lungs.

Targeted delivery of RFB to the lungs led to substantial reduction in first-pass metabolism of RFB. The findings suggest that polymeric microparticles prepared by spray drying process offer promise for treating pulmonary TB with reduced doses, lower dosing frequency and alleviated toxicity.