Drug-loaded cyclodextrin-based polymers to treat pulmonary infections

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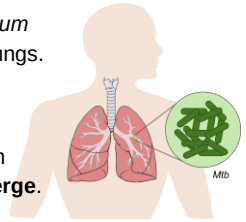
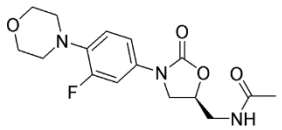
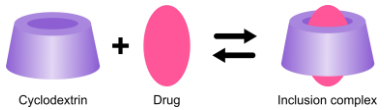
Introduction

- **Tuberculosis** (TB) is caused by *Mycobacterium tuberculosis* (*Mtb*), and primarily affects the lungs.
- TB remains the world's **deadliest infectious disease**
- Antibiotic-based treatments exist, but *Mtb* can mutate and **drug-resistant strains may emerge**.

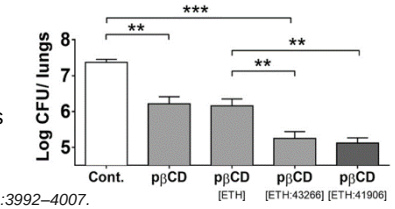


- Drug-resistant TB require the use of **second-line drugs** that are generally:
  - Less effective
  - More toxic
  - Much more expensive
- **Linezolid**, a recently repurposed antibiotic for drug-resistant TB, is **limited** by its
  - Low solubility
  - Systemic toxicity





- **Cyclodextrins** (CDs) are cyclic oligosaccharides that can host drugs in their hydrophobic cavities.
- CDs can be **polymerized** to produce **pCDs** with:
  - Host guest-complexation capabilities.
  - Increased solubility due to the introduction of cross-linking groups.
- pCDs increase solubilization, stability, and controlled release of anti-TB drugs.
- pCDs have shown to possess **intrinsic anti-TB properties**



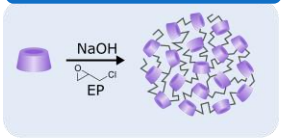
Machelart et al., ACS Nano, 2019;13(4):3992–4007.

Objective

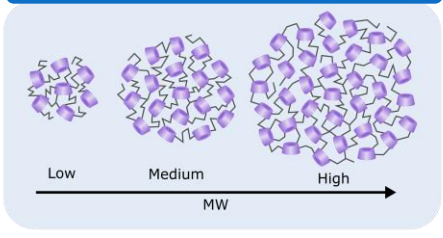
To develop **water-soluble CD polymers** and **evaluate the effect of their molecular weight** on the encapsulation of small hydrophobic drugs, specifically the anti-TB drug linezolid.

Results

Synthesis of pCDs

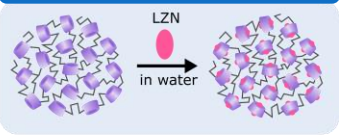


Dialysis of pCDs



Characterization

Complexation of pCDs with LZN

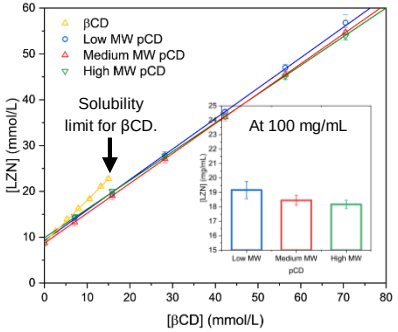


→ pCDs are water-soluble and have a wide molecular weight (MW) range.

MW Range	Membrane cut-off	MW (g/mol)[1]	CD content[2]
Low	20 – 100 kDa	47,100	80% wt.
Medium	100 – 1000 kDa	97,200	80% wt.
High	> 1000 kDa	230,000	80% wt.

→ pCDs are more than 10 times more soluble than native βCD, and therefore solubilize more LZN.

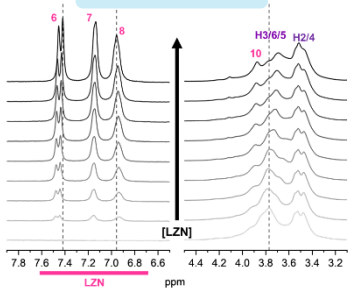
→ Although all polymers have a similar CD content, a low MW allows more LZN to be solubilized.



Phase solubility diagrams of native βCD, and pCD of different molecular weight ranges with linezolid (LZN).

NMR of the pCD-LZN complex

Titration of LZN

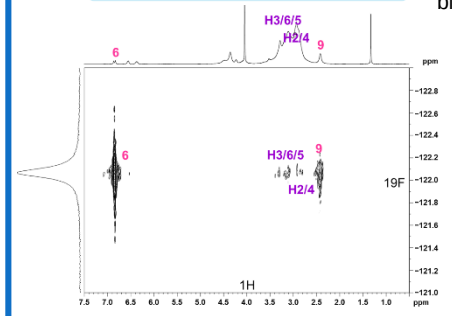


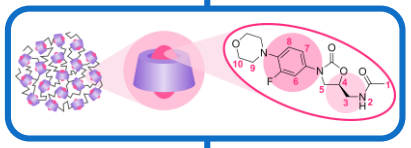
→ Titration of LZN in pCD shows a change in the chemical shift of:

- The drug, specially at protons 6 and 8.
- In the area of pCD (protons H3/6/5 are normally involved in complexation).

→ LZN diffuses with pCD, supporting the binding hypothesis.

^1H-^{19}F NOESY of pCD-LZN complex

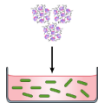


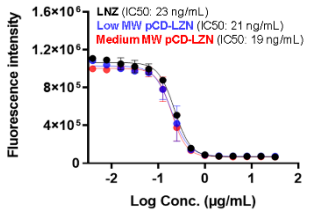


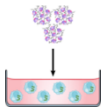
→ LZN fluorine is in close proximity with protons H3/6/5 and H2/4 of pCD.

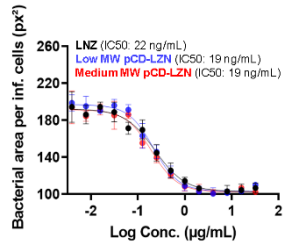
Anti-TB efficacy of pCD-LZN complex

- Infected cells or *Mtb* alone were incubated for 5 days with different concentrations of LZN or pCD-LZN complex.





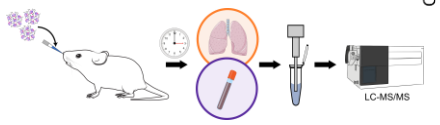


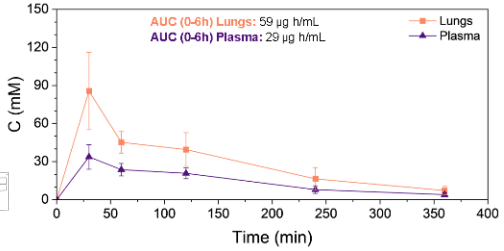


→ LZN encapsulation does not hinder antimicrobial efficacy of LZN.

Pharmacokinetic of pCD-LZN complex

- Mice received pCD-LZN intranasally. Lungs and plasma were collected and analyzed for LZN quantification.





Conclusions

- CD-based polymers (pCDs) were successfully synthesized and characterized.
- Lower molecular weight pCDs enhanced linezolid (LZN) solubility more effectively.
- LZN forms inclusion complexes with pCDs through its aryl and amide groups.
- Encapsulation does not reduce LZN's anti-TB activity, and the pCD-LZN complex delivers sustained drug levels in the lungs with minimal toxicity.