Nanodisc Based Targeted Antiretroviral Drug Delivery to the Brain for the Treatment of HIV-1

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Abstract

HIV-1 treatment has been revolutionized by the use of combination antiretroviral therapy (cART). However, HIV-1 remains persistent in organs that do not allow easy penetration of anti-HIV drugs, such as the brain. Inaccessibility of the blood-brain barrier (BBB) allows for persistent CNS HIV-1 infections and inflammation to progress into HIV-1 associated neurological disorders (HAND). Nanotechnology-based drug carriers, such as nanodiscoidal bicelles, offer an attractive solution to access HIV-1 within the brain to reduce viral load and prevent further neurodegeneration. **This study characterized nanodiscoidal bicelles as a potential method to deliver extended-release of an anti-HIV drug for long term inhibition of HIV-1 within infected cells in the brain.**

Background

- According to UNAIDS, an estimated 38 million people globally are currently living with HIV.
- Despite advanced therapeutic options, HIV-1 remains concentrated in organs, known as "latent reservoirs".
- The BBB is a selectively permeable barrier, however, HIV-1 is able to bypass the BBB by infecting cells such as monocytes that traffic across.
- Nanomedicine has become more research as nanostructures have the potential to be utilized as delivery agents by encapsulating drugs.
- The nanodisc, a nanodiscoidal bicelle, offers an optimal system for a lipid-based drug delivery that can preserve the drug within its formulation until metabolized by the body.
- This study observed the encapsulation of the widely used anti-HIV drug tenofovir in the nanodisc formulation.

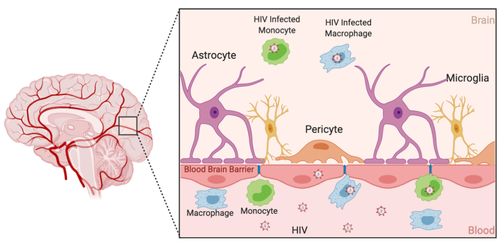

Figure 1: Schematic overview of HIV-1 infection within the BBB.

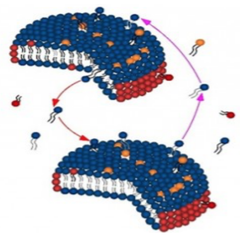

Figure 2: Model view of the nanodisc.

Hypothesis

A nanodiscoidal bicelle based anti-HIV drug delivery targeted towards the brain will be able to effectively release and control dosages over an extended period and eliminate HIV residing within the brain.

Methodology

- **Cell cultures:** Human embryonic microglial clone 3 cells (HMC3) and human neuroblastoma cells (SH-SY5Y) were cultured to make sure that the formulation overall would not be toxic to neuronal cells.
- **Chemical Characterization:**
  - **Small Angle X-ray Scattering**: SAXS was utilized to study the overall shape and structure of the nanodisc. **Dynamic Light Scattering**: DLS was utilized to determine the size and population distribution of the nanodisc formulation.
- **Biological Characterization:**
  - **Cell viability assay of nanodisc (MTS):** Cell viability of the nanodisc was determined via an MTS Assay on HMC-3 and SH-SY5Y cells and measured by a microplate reader. **Reactive Oxygen Species (ROS) Assay:** The ROS production following treatment of the nanodisc was determined by a ROS assay on HMC3 and SY5Y cells and measured by a microplate reader.

Results

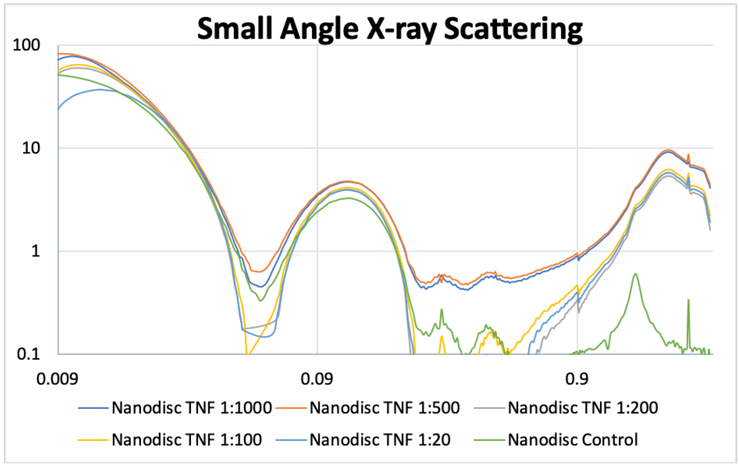

Figure 3: SAXS graph of various drug-to-lipid concentration of nanodisc formulated tenofovir.

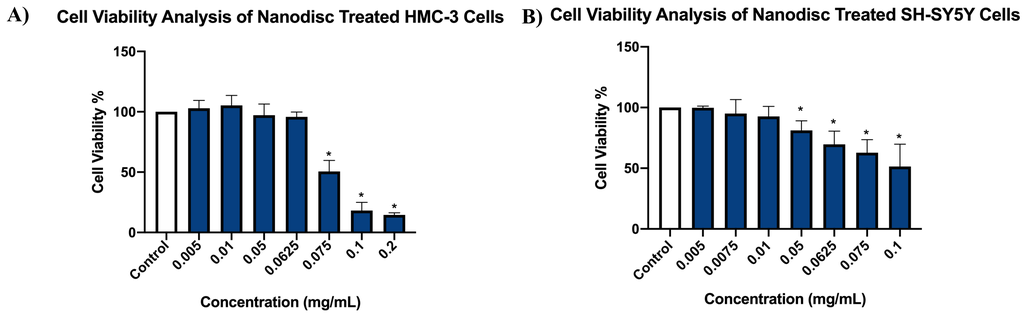

Figure 4: A cell viability analysis of A) microglia (HMC-3) and B) neuroblastoma (SH-SY5Y) cells when treated with nanodisc formulated tenofovir at a drug-to-lipid ratio of 1:20.

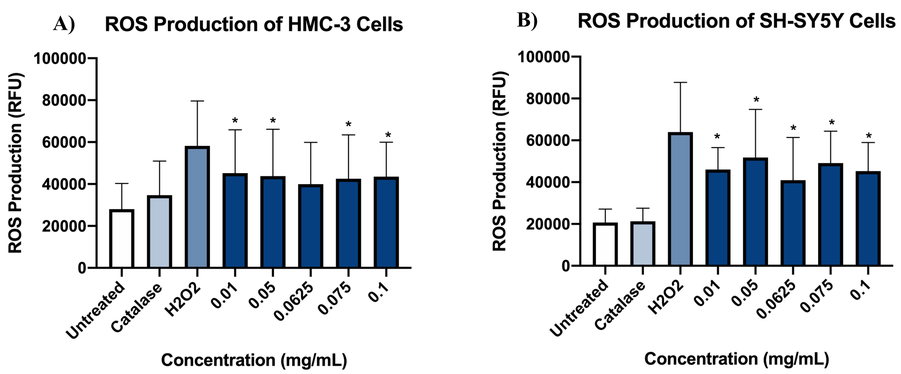

Figure 5: A ROS Assay of A) microglia (HMC-3) and B) neuroblastoma (SH-SY5Y) cells when treated with nanodisc formulated tenofovir at a drug-to-lipid ratio of 1:20.

Results (cont.)

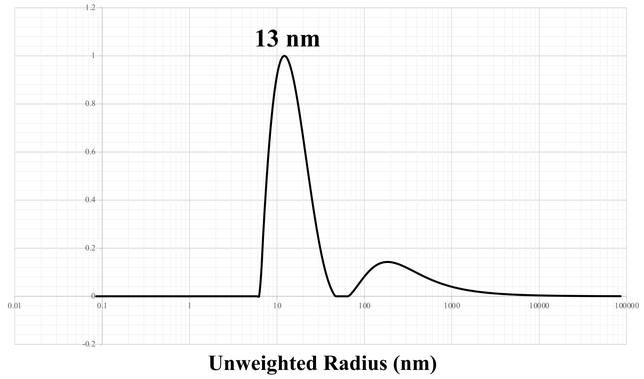

Figure 6: DLS results of newest formulation of nanodisc formulated tenofovir at a drug-to-lipid ratio of 1:4.

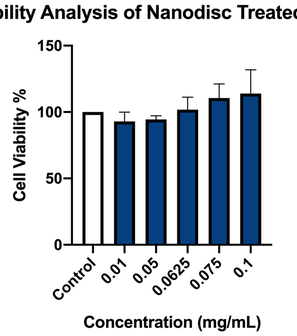

Figure 7: A cell viability analysis of microglia (HMC-3) cells when treated with nanodisc formulated tenofovir at a drug-to-lipid ratio of 1:4.

Summary

- At different drug-to-lipid ratios, the nanodisc retains its overall internal structure, shape and size.
- We observed the lipid content of our nanodisc formulation to be too high and cause significant cytotoxic effects as well as induce an increase in ROS production.
- The lipid content of the nanodisc determines the toxicity of the formulation. The new nanoformulation is showing to be promisingly safe, nontoxic and extended release properties.

Acknowledgments

This study was supported by the University of Texas Rio Grande Valley and partial NIH Grants #1R15NS108815-01 and #1R01AI147731-01A1.