

# **Risperidone-loaded Microplates Ameliorate The Temporal Order Recognition Memory In A Murine Model Of Schizophrenia**

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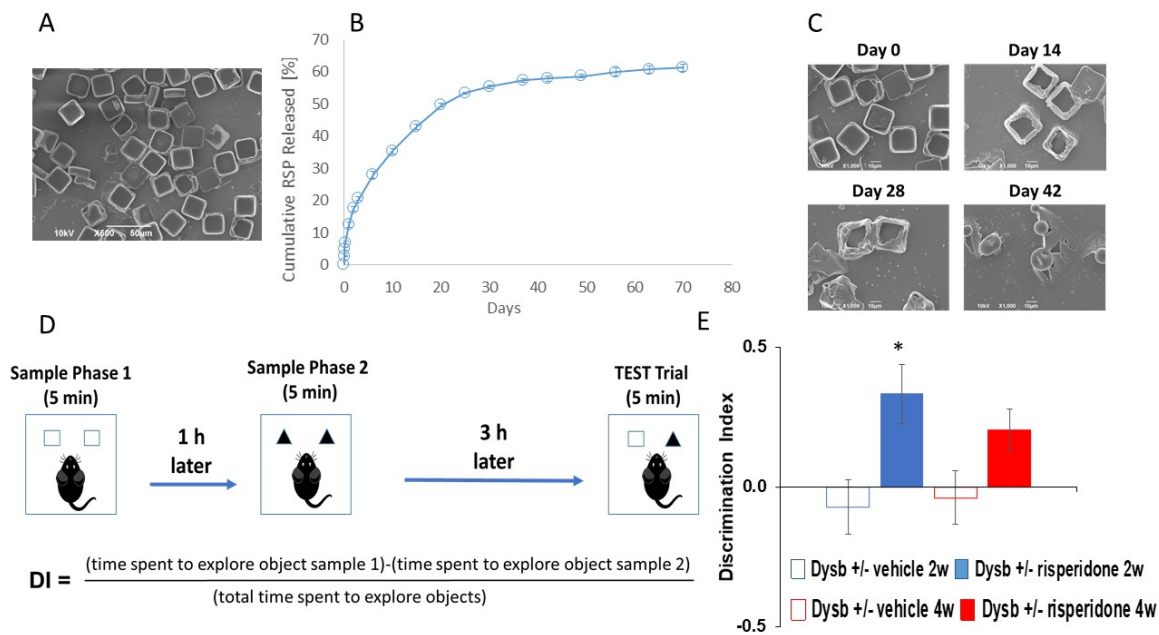
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## **Abstract**

**Introduction:** Schizophrenia is a serious psychiatric disorder characterized by psychotic symptoms, as well as impaired cognitive symptoms (1). Symptoms tend to fluctuate over time, with periodic relapses and remissions. The standard treatment for schizophrenia consists in the long-term administration of antipsychotics to reduce symptom severity. However, medication adherence is often poor leading to high rates of relapse and hospitalization (2). Here, we propose a long-term drug delivery system based on PLGA microparticles for the controlled release of risperidone, a second-generation antipsychotic prescribed to schizophrenic patients.

**Methods:** PLGA micron-sized particles were fabricated using a top-down approach to realize square hydrogel microplates ( $\mu$ PLs).  $\mu$ PLs were engineered in terms of geometry and polymer content to modulate the release of risperidone over a prolonged period of time (months).  $\mu$ PLs were characterized for properties relevant to drug delivery, including morphological, physico-chemical, and pharmacological features. Subsequently,  $\mu$ PLs were tested for their *in vivo* efficacy in a murine model of schizophrenia.  $\mu$ PLs were i.p. injected once at the beginning of the study, while free risperidone was injected every day as control. Subsequently, on day 14 and 28 post injection the temporal order recognition (TOR) test was carried out. Mice are still under treatment for TOR test at 2 and 3 months.

**Results:** The use of a top-down approach allowed for the precise control of particle geometrical features. Specifically, SEM and volume impedance analysis highlighted a square geometry for  $\mu$ PLs ( $20\ \mu\text{m} \times 20\ \mu\text{m} \times 10\ \mu\text{m}$ ), with an average dimension of  $20\ \mu\text{m}$ . Risperidone release from  $\mu$ PLs was analyzed via HPLC, and results showed a prolonged release up to 70 days. TOR test carried out 2 weeks after the injection showed a discrimination index (DI) for mice treated with risperidone-loaded  $\mu$ PLs significantly higher than the DI of the untreated ones and comparable to the DI of mice treated with free risperidone. Moreover, the DI of the treated mice was still higher than the one of the untreated group even after 4 weeks, suggesting that the prolonged and constant release of risperidone from  $\mu$ PLs helps restore the temporal order memory impairment.



**Figure 1:** A. SEM of PLGA  $\mu$ PLs. B. *In vitro* risperidone release assay. C. SEM micrographs representing  $\mu$ PL degradation over time. D. Schematic of the temporal order recognition (TOR) test and discrimination index (DI) formula. E. Discrimination index at 2 and 4 weeks after injection for mice treated with risperidone-loaded  $\mu$ PLs and mice treated with blank  $\mu$ PLs.

**Conclusion/Implications:** The precise control of  $\mu$ PL geometry and polymer content allowed us to precisely tailor the kinetics of risperidone release. The therapeutic efficacy of risperidone- $\mu$ PLs was demonstrated *in vivo* where they helped restore the impaired memory in a murine model of schizophrenia.

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**References:** (1) Mueser KT, Deavers F, Penn DL, Cassisi J. *Annu Rev Clin Psychol.* 2013;465-497 (2) Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. *J Clin Psychiatry.* 2006;453-460

**Keywords:** Route/target of delivery - Brain/Blood brain barrier/neurological, Delivery vehicle - Microparticle, Delivery vehicle - Biodegradable, Type of delivery agent - Small molecule

### Learning Objectives:

- Design polymeric particles with tuned geometrical features
- Design polymeric particles capable of long-term release
- Restore the impaired temporal order memory in an *in vivo* model of schizophrenia