The impact of *in vitro* test methods on drug release from PLGA microparticles

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Introduction

- Generic injectable long-acting (LA) formulations are required to qualitatively (Q1) and quantitatively (Q2) match the reference listed drug (RLD) product in terms of inactive ingredients. One of the most important tests for comparing a generic formulation with the RLD product is the *in vitro* release test.
- For injectable long-acting microparticle formulations, there are no compendial methods for *in vitro* drug release testing.
- The *in vitro* release tests described in the literature include USP Apparatus II, USP Apparatus IV (flow-through method), and orbital agitation methods.
- USP Apparatus II and IV have standardized protocols, but they require large volumes of release media.
- Orbital agitation methods, while simple, have no standard protocol and the results vary widely depending on the testing conditions, such as volume, agitation rates, container type, etc.
- The **purpose** of this study is to investigate the impact of testing conditions on the *in vitro* drug release of risperidone containing PLGA microparticles.

Methods

- Risperdal Consta® 25 mg was purchased and in-house risperidone-containing PLGA microparticles were prepared using an oil in water (o/w) emulsion method.
- Drug release testing was performed in 40 mL of phosphate buffered saline with 0.05% Tween 20, pH 7.4 (PBST).
- Orbital agitation was provided by shaking incubator (Southwest Science, Mini IncuShaker) set to 100 rpm (**Fig. 1**).
- Accelerated (45 °C) drug release testing using an orbital agitation method was performed in various shaped containers **(Fig. 2**) with risperidone containing PLGA microparticles to test the effect of container shape on drug release.
- Accelerated (45 °C) drug release testing using an orbital agitation method was performed in two containers (**Fig. 2-A & -C**) with Risperdal Consta® microparticles to test the effect of container shape on drug release.
- Drug release tests using orbital agitation methods with a small or a large sampling volume were performed to test the effect of sampling volume on drug release.
- Accelerated (45 °C) drug release testing was performed with Risperdal Consta® microparticles with and without orbital agitation.

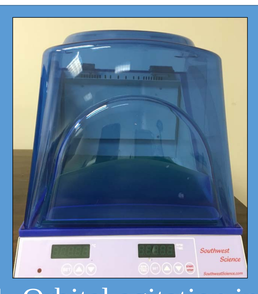

Figure 1. Orbital agitation incubator.

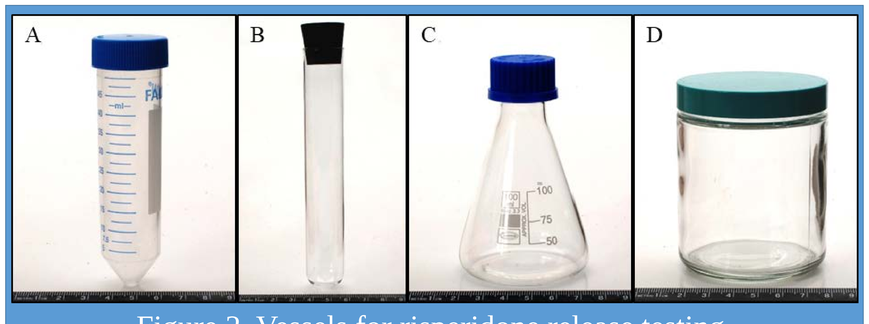

Figure 2. Vessels for risperidone release testing. Centrifuge tube (A), test tube (B), glass flask (C) and glass jar (D).

Results

- Orbital agitation method produced reproducible results.
- Drug release kinetics are affected by the testing conditions, including essel type (**Figs. 3 & 4**), sampling volume (**Fig. 5**), and agitation (**Fig. 6**).
- Orbital agitation method can be used to compare PLGA microparticle formulations with manufacturing differences when tested under the same experimental conditions.

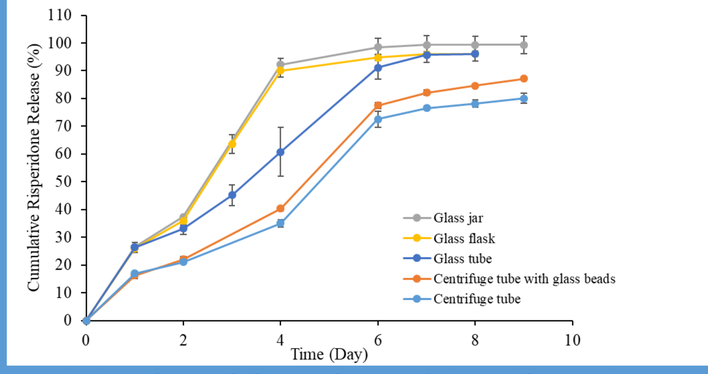

Figure 3. Accelerated drug release of risperidone microparticles in various vessels.

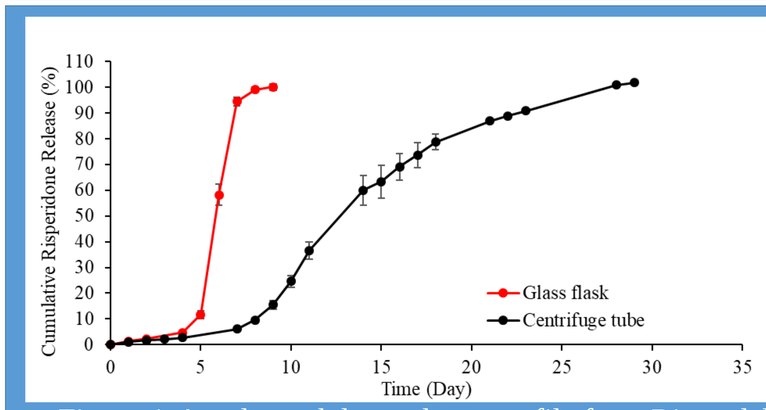

Figure 4. Accelerated drug release profile from Risperdal Consta® in flasks (n=3) and centrifuge tubes (n=2).

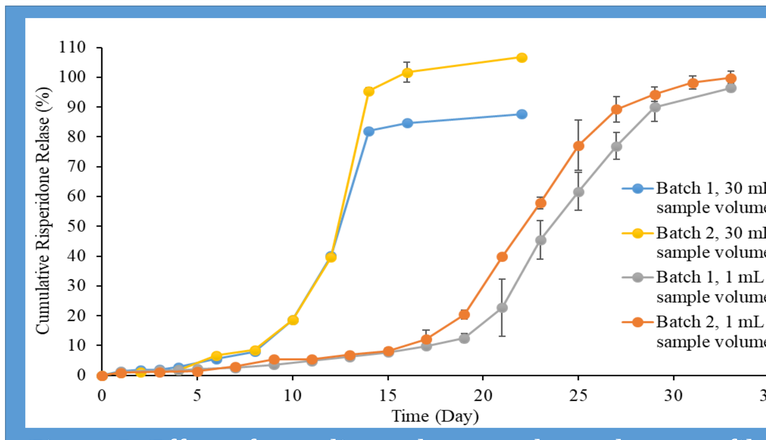

Figure 5. Effect of sampling volume on drug release profile of risperidone microparticles at 37 °C.

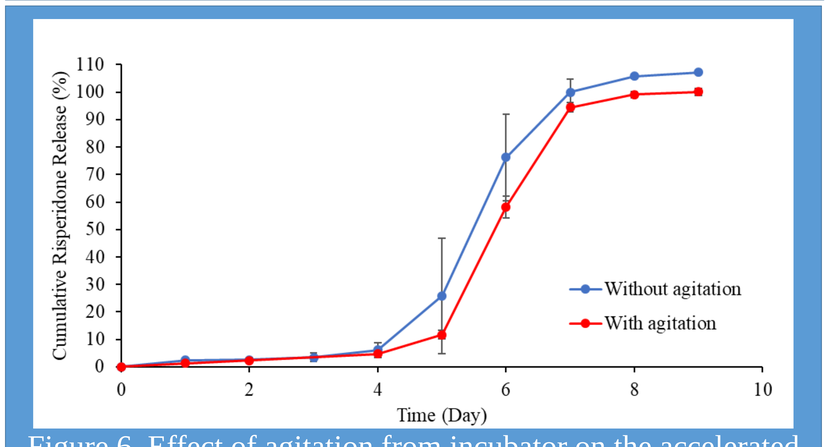

Figure 6. Effect of agitation from incubator on the accelerated drug release profile of Risperdal Consta®.

Conclusions

- Significant microparticle aggregation was observed in release vessels with small diameters, e.g., centrifuge tubes and glass tubes.

  The aggregation, occurring when tested in centrifuge or glass tubes, led to slower risperidone release from PLGA microparticles (**Fig. 3**) and Risperdal Consta® (**Fig. 4**).
- Minimal microparticle aggregation was observed in vessels with large diameters, e.g., glass jars and flasks.
- The release tests with a 30 mL sampling volume (**Fig. 5**) released risperidone faster than the tests with a 1 mL sampling volume**.**

  The microparticles with 30 mL sampling volume underwent additional agitation at every sampling point when the sample was removed and media was replaced. The microparticles with 1 mL sampling volume did not undergo this agitation and did not cause major turbulence in the vessel.

  It is also likely that sink conditions may not have been maintained with 1 mL media changes.
- The release of risperidone from Risperdal Consta® was slightly faster when agitation was not applied to the release vessels (**Fig. 6**).

  As the PLGA molecules in the microparticles degrade, the pH in the microparticles decreases with the build-up of lactic acid and glycolic acid. Risperidone is more soluble at a low pH, leading to faster release. The improved media flow around the microparticles by agitation may have diluted acids and increased the local pH, resulting in less risperidone molecules for release.
- The experimental condition of the orbital agitation test can greatly influence the drug release rate. As long as the same experimental conditions are used, however, the results are highly reproducible.
- Release methods using orbital agitation show promise as a simple, cost-effective way to perform *in vitro* release testing.
- Orbital agitation methods can be used to identify PLGA microparticles having manufacturing differences affecting the drug release kinetics, if the two formulations are tested under the same conditions.
- For long-term testing, e.g., >1 month, development of harmonized accelerated testing conditions will be highly useful.

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References:

1. Garner, John, Sarah Skidmore, Haesun Park, Kinam Park, Stephanie Choi, and Yan Wang. “Beyond Q1/Q2: The impact of manufacturing conditions and test methods on drug release from PLGA-based microparticle depot formulations.” Submitted to Journal of Pharmaceutical Sciences.

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