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.
• 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.

Results

• Orbital agitation method produced reproducible results.
• Drug release kinetics are affected by the testing conditions, including vessel 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.

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: