Development of an In Vitro Release Testing Method for Porous PLGA Microspheres

J. Shen 1, W. Qu 2, S. Choi 2, Y. Wang 2, D. J. Burgess 1
1 University of Connecticut, 2 U.S. Food and Drug Administration

Purpose
The objective of the present study was to develop a reproducible in vitro release testing method for PLGA microspheres with a highly porous structure.

Methods
Risperidone was chosen as a model drug and PLGA with similar molecular weight to that of commercial Risperdal® Consta® was used to prepare the microspheres. Different preparation processes (e.g., emulsification, and solvent extraction) were investigated to produce porous risperidone microspheres. Critical physicochemical properties (e.g., drug loading, particle size distribution, porosity, and morphology) of the prepared microspheres were determined. In vitro release of the risperidone microspheres was investigated using the most commonly used in vitro release testing methods (such as sample-and-separate and flow through). Different release testing conditions (e.g., testing temperature and release media) were investigated.

Results
The obtained risperidone microsphere (drug loading (35%, w/w)) had a higher porosity (~70%) compared with the commercial product (40.7%). Morphology studies showed that some of these microspheres had irregular shapes and indentations. In the sample-and-separate method, a large amount of microspheres floated on the surface of the release media owing to their porous structure and this resulted in an inconsistent sampling process. More specifically, sample loss was observed and varied at each sampling time. Consequently, the in vitro release profiles obtained using the sample-and-separate method were not reproducible. In addition, it was shown that the addition of a suitable surfactant (e.g., Tween 20) to the release media was necessary to prevent microsphere aggregation and to facilitate risperidone release from the microspheres. Compared to the sample-and-separate method, the flow through method (USP apparatus 4 method) showed good reproducibility under both “real-time” (37°C) and accelerated (45°C) testing conditions.

Conclusion
The flow through method using USP apparatus 4 with well-defined geometry and hydrodynamics appeared to be an appropriate, reproducible in vitro release testing method for porous risperidone PLGA microspheres.

Acknowledgement: Support was provided by the Office of Generic Drugs, CDER FDA (1U01FD004931-01).