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Cover story

IVIVC of parenteral PLGA microspheres

There have been only a dozen parenteral extended release formulations that are designed to deliver drugs from a week up to 6 months since the first introduction of Lupron Depot® made of poly(lactic-co-glycolic acid) (PLGA) microspheres in 1989. All parenteral extended release formulations are made of PLGA in the form of microspheres, solid implants, and in situ forming implants. Over the past few decades, the development of in vitro–in vivo correlation (IVIVC) for parenteral products has increasingly gained more significance. A Level A IVIVC can open the possibility for an in vitro release method to be used as a surrogate for bioequivalence studies. This can minimize the need for human studies and reduce the regulation burden. Accordingly, establishing IVIVCs for parenteral products is expected to propel the development of both generic and innovator products. In the case of PLGA microspheres, due to their complex characteristics (e.g., long-term (weeks to months) release and multi-phasic release profiles), deconvolution of in vivo data and correlation with in vitro release data has been very challenging. In addition, the lack of compendial in vitro release testing methods has delayed the development of IVIVCs for PLGA microspheres and other extended release parenterals. The IVIVC study by Professor Burgess and her team in this issue is important as it presents the possibility that IVIVCs for parenteral polymeric microspheres can be established [1].

The study by Professor Burgess and her team shows that Level A IVIVCs can be established for parenteral PLGA microspheres. The Burgess group elected to work with compositionally equivalent risperidone-loaded PLGA microspheres prepared with different manufacturing processes. The physicochemical properties (e.g., porosity and particle size) of the risperidone-loaded PLGA microspheres were sensitive to minor manufacturing changes, such as different solvent systems and microsphere collection procedures, which subsequently resulted in changes in their in vitro and in vivo performance. The two most commonly used in vitro release methods for parenteral PLGA microspheres (e.g., sample-and-separate and USP apparatus 4) were investigated in this IVIVC study. Compared with the sample and separate method, the USP apparatus 4 method was superior in its ability to discriminate between the compositionally equivalent risperidone microspheres with manufacturing differences. The ability to distinguish drug release properties from microspheres made by different manufacturing processes is critical in evaluating different formulations that consist of the same drug and polymer. The developed IVIVCs can be very useful to guide formulation and/or process development changes in various stages of parenteral microsphere drug product development. Furthermore, the study was conducted using a compendial apparatus (USP apparatus 4), which makes inter-laboratory comparison feasible, thus helping to facilitate drug product development. The IVIVC constructed in the current study by the Burgess group was based on rabbit pharmacokinetic data [1]. Since there are known differences in drug release, absorption and metabolism between small animal models and humans, the results from this IVIVC study may not be fully extrapolated to humans. Thus, a similar study performed with human pharmacokinetic data would be necessary for an IVIVC to be fully applicable to human parenteral microsphere drug products.

It is not an easy task to establish robust IVIVCs for microsphere formulations designed to release drugs for months, and it will require collective efforts by many researchers in the field. This is one of the important problems facing the pharmaceutics and drug delivery field, and Professor Burgess has been a pioneer in this effort. Her earlier and current studies [1,2], taken together, show that IVIVCs for parenteral PLGA microspheres can be established and validated. The IVIVC study of parenteral microsphere formulations reported in this issue will certainly pave the way for more in depth studies of all parenteral extended release products based on PLGA. A suitable in vitro release testing method is critical in the development of IVIVC for extended-release parenterals, and the field collectively needs more input to tackle this important issue for rapid progress in producing many more clinical formulations.

References

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Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu

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