Journal of Controlled Release 142 (2010) 2–7

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Breakout session summary from AAPS/CRS joint workshop on critical variables in the *in vitro* and *in vivo* performance of parenteral sustained release products

Marilyn N. Martinez [a,*,1], Michael J. Rathbone [b], Diane Burgess [c], Mai Huynh [a,1]

[a] US Food and Drug Administration, Center for Veterinary, Medicine, 7500 Standish Place, Rockville, MD 20855, United States
[b] School of Pharmacy, Gold Coast Campus, Griffith University, Queensland 4222, Australia
[c] University of Connecticut, 69 North Eagleville Road, Storrs, CT 06269, United States

ARTICLE INFO

Article history:
Received 21 May 2009
Accepted 29 September 2009
Available online 3 October 2009

Keywords:
Parenteral
Long acting
Sustained release
Modified release
In vitro drug release testing
Microsphere
Liposome
Implant
In situ forming implant
Lipophilic solution
In vivo-in vitro relationship
Quality by design

ABSTRACT

Parenteral drug delivery systems can be designed to provide the flexible delivery characteristics needed in an evolving therapeutic landscape. The goal of some parenteral formulations is to maintain effective drug concentrations over a period of months or years, thereby enhancing patient compliance. When functioning as intended, these formulations can be used to minimize undesirable effects that may occur in response to the fluctuating drug concentrations effected by immediate release products. In other cases, targeted parenteral delivery systems allow for the deposition of drug directly to its site of action, thereby minimizing systemic toxicity. While these novel formulations can be beneficial to both human and veterinary patients, disastrous effects can occur if there is an unanticipated change in product quality or performance. With these thoughts in mind, the Controlled Release Society (CRS) hosted a 2007 workshop entitled "In Vitro and In Vivo Considerations Associated with Parenteral Sustained Release Products". The objective of that workshop was to explore the physicochemical properties of parenteral products and the factors that could alter their in vitro and in vivo performance characteristics. The outcomes of that workshop were summarized in a Journal of Controlled Release article [1]. In response to questions raised during that workshop, the CRS and the American Association of Pharmaceutical Scientist (AAPS) co-hosted the follow-up 2008 workshop entitled "Critical Variables in the In Vitro and In Vivo Performance of Parenteral Sustained Release Products". This 2008 workshop provided a platform for exploring the application of design space concepts to these complex pharmaceuticals, and to consider the corresponding in vitro test methods that can be used to set batch release specifications. To foster discussion, the workshop provided two afternoon breakout sessions where critical questions were explored. This manuscript captures the results of those discussions.

Published by Elsevier B.V.

Contents

* Corresponding author.
E-mail address: marilyn.martinez@fda.hhs.gov (M.N. Martinez).

[1] The views expressed in this article are those of the authors and do not reflect the official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred.

0168-3659/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.jconrel.2009.09.028

1. Introduction

Understanding the factors influencing drug release, both from an *in vivo* and an *in vitro* perspective, is essential for the development of meaningful *in vitro* release tests and performance specifications. To provide an opportunity for experts to exchange their ideas and insights on these issues, the Controlled Release Society (CRS) hosted the 2007 Educational Workshop entitled: "*In Vitro* and *In Vivo* Considerations Associated with Parenteral Sustained Release Products". This workshop engaged pharmaceutical scientists and pharmacologists in discussions regarding the critical variables impacting the development of novel parenteral sustained or modified release (MR) formulations. The results of that workshop are summarized elsewhere [1].

One of the outcomes of that meeting was an appreciation of the need to identify the critical manufacturing variables that influence the *in vivo* performance of these products, *in vitro* methodologies that can be used to ensure product quality and performance, and some of the challenges that may arise when developing these *in vitro* tests and test specifications. In this regard, a number of critical questions were raised, including:

1. Is it possible to develop *in vitro* methods for complex targeted delivery systems?
2. What methods can be used to control for host responses to biomaterials?
3. What controls can be used in systems where the host system is an integral component of the targeted drug delivery?
4. Should *in vitro* release specifications be required for long acting lipophilic solutions?
5. Should there be a difference between manufacturing and batch release specifications versus those specifications needed to ensure *in vivo* bioequivalence?
6. What factors should be considered when evaluating whether or not it is feasible to grant biowaivers for sol-transition modified release products (i.e., where product is a true solution upon injection)?
7. Despite the possibility of unique formulations that will require variations in standard test methods, is it feasible to develop standardized *in vitro* test methods that can be applied to any specific type of modified release parenteral formulation?
8. When setting expiry for a long acting parenteral product intended to continue releasing for months upon administration, how does one ensure that the product will perform in a manner comparable to a fresh product if administered at expiry?
9. What unique challenges will be faced when attempting to develop generic versions of innovator products? Will it be feasible to have generic versions of parenteral modified release products?
10. What kinds of *in vivo* and *in vitro* data would be needed to support design specifications?

In an effort to address these questions, the CRS and the American Association of Pharmaceutical Scientists (AAPS) co-sponsored the 2008 workshop titled "Critical Variables in the *In Vitro* and *In Vivo* Performance of Parenteral Sustained Release Products". Notable features of this workshop were the presentations by leading experts in various parenteral formulation technologies and the breakout sessions where speakers and participants shared their experiences and perspectives on these ten challenging questions. Most of the speakers have agreed to summarize their perspectives on pivotal challenges and concerns in an upcoming theme issue of the AAPS Journal. With regard to the breakout discussions, this manuscript provides a compilation of the key points conveyed by meeting speakers and participants. Due to time constraints, discussions focused primarily on microspheres, lipophilic solutions, implants, targeted delivery systems, and *in situ* forming gels. Speakers and presentation titles are listed in the Appendix of this report.

The contents of this manuscript do not represent the views of any particular individual or organization. Rather, to ensure that the diversity of expressed opinions was adequately captured, a preliminary version of this manuscript was circulated for comment to meeting attendees. Therefore, this manuscript reflects the authors' efforts to convey the range of opinions expressed during the 2008 Workshop.

2. Day one break out session outcomes

2.1. Question 1: Is it possible to develop in vitro methods for complex targeted delivery systems?

The response to this question was mixed. Some participants concluded that currently available *in vitro* release test methods could not be adequately applied to these parenteral products while others considered it possible if the existing *in vitro* technologies were modified. However, even those individuals expressing a positive stand on this question concluded that product quality control tests would most likely necessitate the use of multiple testing procedures to ensure the quality and performance of these complex delivery systems.

Despite uncertainty regarding the *in vivo* relevance of these *in vitro* tests, there was general agreement that some methodology was needed to ensure that the product is functioning as intended prior to batch release. The nature of the test would be dictated by the specific targeting method. Examples given during the breakout discussion included:

- Particle size — Evaluated for exclusion-based delivery systems.
- Pegylation of proteins — Checked *in vitro* by adsorption chromatography (e.g., albumin; Immunoglobulin G).
- Spectroscopic methods — Used to check that parenteral delivery forms have the intended pegylation on particle surfaces.
- Column chromatography — Used to evaluate ligand binding to receptors for targeted delivery systems.
- Protein activity — Assessed through cell culture systems.

Because of disagreement on this topic, the issue of whether or not the quality control release test needs to be biorelevant remains a subject for future debate. Assuming that the release specification is intended to ensure therapeutic activity, participants generally agreed that it will be necessary to ascertain the biological relevance of the tests and release specifications through studies that establish *in vivo–in vitro* relationships (IVIVR). It was suggested that to accomplish this objective, cell culture and chromatographic systems need to be developed and validated. To date, this has not been done.