Scientific Gap Analysis of Polymeric In Situ Forming Depot Products for the Development of GDUFA Research Projects

Qiangnan Zhang, Bin Qin, Yan Wang, Qi Li, and Darby Kozak
Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland 20993

Abstract

Purpose: Long-acting parenteral in-situ forming depot formulations based on an active pharmaceutical ingredient (API) and a biodegradable polymer (e.g., poly (lactic acid) (PLA) or poly (lactide-co-glycolide) (PLGA)) solubilized in an organic solvent are a simpler, more cost-effective formulation compared to other PLA/PLGA-based long-acting drug delivery systems (i.e., microparticles or solid implants). Upon injection, the organic solvent diffuses out, leading to the precipitation of water-insoluble polymer giving rise to the formation of a depot implant. To date, FDA has approved four New Drug Applications (NDAs) for in-situ forming products but has no approved generics. The difficulties in formulation characterization and in vitro drug release testing, and high variability associated with in vivo pharmacokinetics (PK) profiles make the generic product development challenging. Although these difficulties are generally attributed to the unique in-situ phase inversion process, a complete understanding has not yet been obtained. Therefore, this work focused on identifying remaining scientific gaps for in-situ forming depot products via a search of current literature and internal FDA drug submission information. Findings will be used to develop future Generic Drug User Fee Amendment (GDUFA)-funded research projects to promote generic product development.

Methods: An in-depth analysis of the scientific literature and regulatory submissions on the in situ forming depot products was performed. Special attention was paid to data on the impact of polymer on product performance, factors affecting the phase inversion process, IVRT, and methodologies used to characterize the phase inversion kinetics.

Results: It has been demonstrated that the formulation parameters play a crucial role on the phase inversion kinetics, which ultimately controls the physiochemical properties of the depot. PK data of these products indicate a high intra- and inter-subject variability that are generally attributed to uncontrolled phase inversion process. However, it appears that information on the IVRT and methodologies for characterizing phase inversion process in vitro and in vivo is still lacking. In addition, no systematic studies have been conducted to understand the impact of polymer characteristics (e.g., molecular weight, ratio of monomer species, end-group functionality, branching, etc.) on product performance. These identified scientific gaps are critical for developing more detailed guidance on the in vivo bioequivalence (BE) study design and in vitro studies to support BE determination.

Conclusion: Scientific gaps for in situ forming depot product development have been identified. Based on these findings, we have initiated several GDUFA research projects aimed to 1) improve understanding on the impact of polymer characteristics and polymer sources on product performance; 2) develop reproducible and discriminatory in vitro drug release testing methods; and 3) explore novel tools for characterizing in situ phase inversion process in vitro and in vivo.

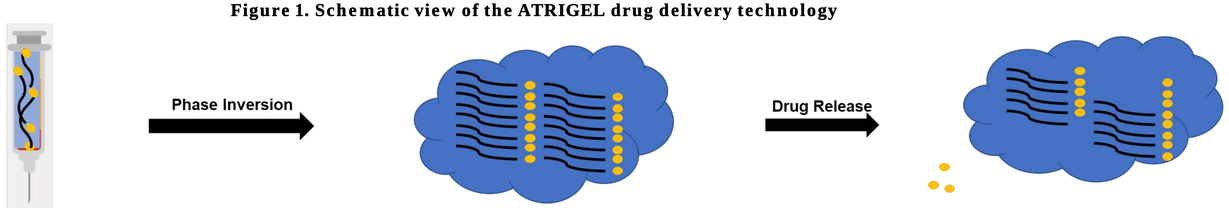
Materials and Methods

An in-depth analysis of the scientific literature and regulatory submissions on the in-situ forming depot products was performed. Special attention was paid to data on the impact of polymer sources on product performance, factors affecting the phase inversion process, in vitro drug release testing, and methodologies used to characterize the phase inversion kinetics.

Results and Discussion

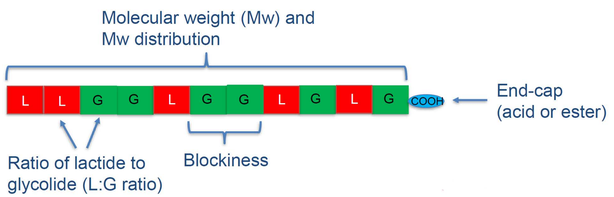
Upon injection of a drug product using ATRIGEL technology in human, a depot solidifies over a few days. The resulting depot consists of the biodegradable PLA or PLGA copolymer and the drug. The drug is then released in a controlled manner and the plasma levels are maintained in the therapeutic window for more than one month.

Figure 1. Schematic view of the ATRIGEL drug delivery technology



PLGAs are biodegradable random copolymers available with various characteristics. Differences in PLGA characteristics (e.g., molecular weight, molecular weight distribution, end cap, blockiness and monomer ratio) can alter the drug release mechanism and drug release rate. Varying the ratio of the repeat units, the end groups, and the molecular weight could affect not only the rate of degradation but also the rate of drug release during initial depot formation and throughout the release. However, there is no systemic investigation for the impact of polymer characteristics and polymer sources on product performance.

Figure 2. Schematics of PLGA with different characteristics [1]



Upon injection, the polymer drug solution or suspension undergoes a phase inversion process. Factors that may affect phase inversion process have not been fully investigated. In general, it is recognized that the phase transition process is critical for the shape of the formed depot, which subsequently affects drug release and polymer degradation. Current methodologies to characterize the phase inversion kinetics include hyperfine splitting change using Electron Paramagnetic Resonance (EPR), mechanical properties changes measured by Texture Analyzer, organic solvent peak intensity change using Nuclear Magnetic Resonance (NMR), precipitation front propagation via UV Imaging System, and NMP release rate using in vitro release test. But no systematic study has been done to investigate what methodologies are most suitable for characterizing PLGA-based drug delivery systems.

Figure 3. In vitro release for ATRIGEL product prepared with different MW PLGAs (n = 3, mean ±standard deviation.)

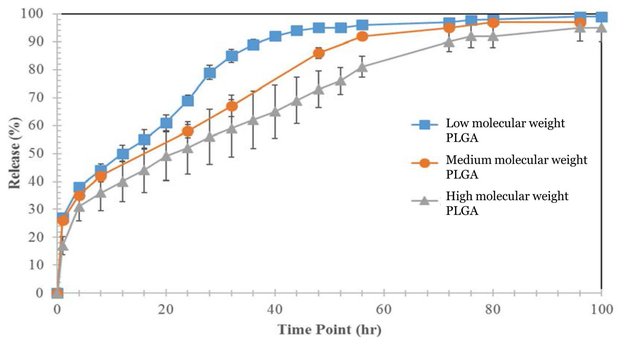
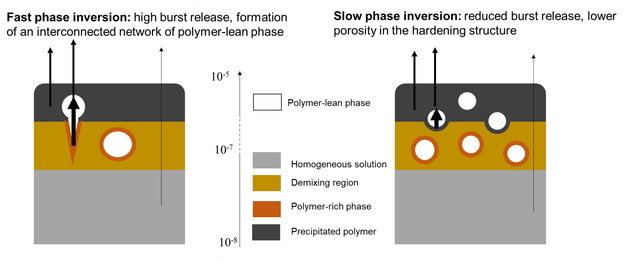


Figure 4. Release of drugs in ATRIGEL with different phase inversion kinetic [2]



Due to difficulties in controlling the phase inversion process, in vitro release profiles of in-situ forming products can be highly variable. The most widely used in vitro release test methodologies is flow through cell (USP Apparatus IV). Currently, there is no effective control to provide a consistent product shape due to the phase inversion process during in vitro release tests. More efforts are needed to develop reproducible and discriminatory in vitro drug release testing methods for in-situ forming gel/implant products.

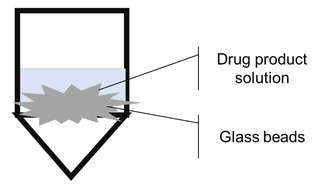


Figure 5. Schematic view of a USP IV in vitro release method

Conclusion

Scientific gaps for in-situ forming depot product development have been identified through searching literature and regulatory submissions. Based on these findings, we have initiated several Generic Drug User Fee Amendments (GDUFA)-funded research projects aimed to:

1) improve understanding on the impact of polymer characteristics and polymer sources on product performance;
2) develop reproducible and discriminatory in vitro drug release testing methods;
3) explore novel tools for characterizing in-situ phase inversion process in vitro and in vivo.

Reference

1. Bin Qin. Strategies to Demonstrate Complex Excipient Sameness. SBIA Complex Generic Drug Product Development Workshop. Sept 2019
2. Parent, M. PLGA In Situ Implants Formed by Phase Inversion: Critical Physicochemical Parameters to Modulate Drug Release. Journal of Controlled Release. 172, no. 1 (2013): 292-304.

Disclaimer

The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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