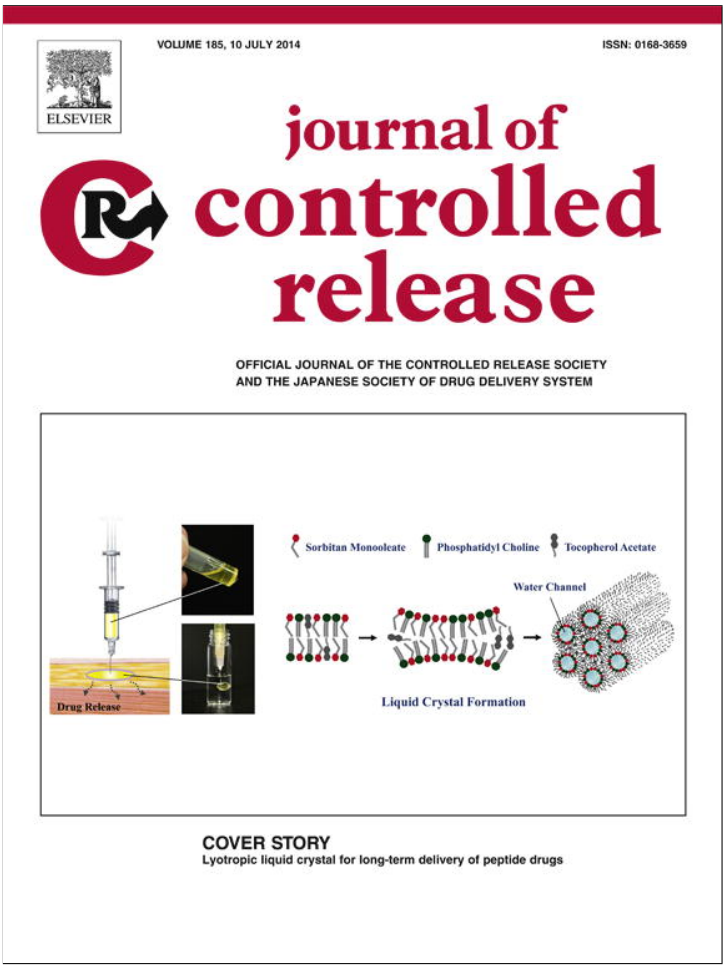

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Cover story

Lyotropic liquid crystal for long-term delivery of peptide drugs

Various injectable, sustained-release (SR) formulations have been developed for delivery of peptide drugs for extended periods of time, ranging from weeks to months. The current clinically used SR formulations are mostly based on poly(lactic-co-glycolic acid) (PLGA) microspheres. Since the first introduction of PLGA depot formulation of goserelin acetate in 1989, only less than 10 PLGA formulations have been clinically available for peptide delivery. Such a small number of PLGA depot formulations developed for peptide and protein deliveries over the last 25 years highlight various difficulties and significant challenges to overcome. Currently, PLGA is the only biodegradable polymer that has been used in products approved by the Food and Drug Administration of the United States (US FDA). It is time to explore other long-term peptide delivery systems beyond PLGA polymers.

Liquid crystal technology has gained increasing interest for developing *in situ* forming parenteral depot formulations [1,2]. Lyotropic liquid crystal systems, composed of amphiphiles, are usually classified into lamellar, hexagonal, and cubic phases based on their assembly shape. Among them, the reversed hexagonal phase (H_2) and the reversed cubic phase (Q_2) have been extensively investigated for their ability to control the release of diverse drugs, ranging from low-molecular-weight chemicals to macromolecular drugs (proteins, peptides and nucleic acids). Amphiphilic liquid crystal-forming materials (LCFMs) include glycerol monooleate, glycerol dioleate, glycerol oleyl ether, oleyl glycerate, phytanyl glycerate, and phytantriol [3]. A liquid crystal-forming system (LCFS) is formulated by mixing these with other hydrophobic materials, such as phospholipid, tocopherol, tocopherol acetate, and tricaprylin.

In this issue, the paper by Professor Dae-Duk Kim and his colleagues prepared a LCFS by mixing sorbitan monooleate (SMO, also known as Span 80), phosphatidyl choline, tocopherol acetate, Tween 80, and ethanol (33:45:10:2:10, w/w%) [4]. The SMO LCFS preparation contains 3.75 mg leuprolide acetate as a monthly dose in 90 μl of a liquid formulation. The semi-solid mesophase was formed upon contact with water. The mesophase showed typical characteristics of the liquid crystalline phase, which was classified as the hexagonal phase. The safety of the LCFS was studied by an *in vitro* extraction colony assay and by examining the injection site in rats and white rabbits after an autopsy. Both *in vitro* release test and *in vivo* pharmacokinetic and pharmacodynamic studies showed sustained release of leuprolide. When compared with the reference depot formulation of leuprolide acetate, the SMO LCFS showed a similar AUC_{last} value with a significantly reduced initial burst after subcutaneous injections in rats and dogs. Although the study by Professor Kim and his collaborators is focused on leuprolide in their current study, other peptide drugs can be certainly delivered.

It will take a while until a LCFS-based peptide depot formulation is approved by the FDA for clinical application. But a new opportunity for making an injectable depot formulation based on materials other than PLGA is encouraging. The new injectable SR formulations for clinical application need to improve a few shortcomings of the currently available formulations, mostly based on PLGA. First, the initial burst release has to be reduced dramatically. Most of the current formulations have significant initial burst release, reaching the drug concentration in the blood which is often two orders of magnitude higher than the steady state concentration. These formulations were still approved because such initial burst release was tolerable by patients. This, by no means, indicates that the huge initial burst release is acceptable. In addition, the drug loading needs to be increased. The higher drug loading usually results in a higher initial burst release. However, the high drug loading without initial burst release will allow longer release, *e.g.*, >6 months, without the side effects associated with large amounts of excipients. These are tall orders, but availability of injectable depot formulation materials different from PLGA will stimulate the development of various novel formulations. Clear understanding of the advantages and limitations of LCFMs as well as the problems associated with the current injectable depot formulations is essential in making the right step toward development of many clinically useful formulations.

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