Biopharmaceutical Application of in situ Polymer Gel

Yong-Hee Kim, Ph.D.

Department of Bioengineering, School of Chemical and Biomolecular Engineering, Hanyang University, 17 Haengdang-Dong, Seongdong-Gu, Seoul 133-791, Korea
Tel: +82-2-2220-2345, Fax: +82-2-2220-1998, E-mail: yhkim4427@yahoo.com

During the past two decades, recombinant DNA technology has led to a significant increase in the number of approved and developing biotechnology medicines. In 2004, the global pharmaceutical, biotechnology and generic markets were reported to be worth US$550, US$55 and US$62 billion, respectively. There are 197 approved biotechnology products, 100 products waiting for regulatory approvals, and 800 in clinical trials. The top ten blockbuster products account for 69% of global biotechnology product sales. The lipid lowering, antiulcer, anticancer, antihypertensive, antidepressant, antipsychotic and antirheumatic drugs are the best-selling therapy classes and by 2008, cardiovascular and central nervous system drugs are expected to be the dominant classes. According to a report, the US patents on blockbusters with global sales totalling more than US$52 billion will expire in the next four years, starting in 2004. This means that biogenerics will provide an challenging opportunity for established generic, pharmaceutical and bioventure companies in the near future.

The successful formulation and development of recombinantly expressed therapeutic proteins depend on a thorough understanding of their physico-chemical and biological characteristics, including chemical and physical stability, immunogenicity, site and rate of administration, pharmacokinetic and pharmacodynamic properties. The pharmaceutical and pharmacokinetic properties of proteins can be optimized by different approaches — for example by mutagenesis, chemical modification, additives such as stabilizers and enhancers or by designing specific drug-delivery systems. The encapsulation technologies are the most widely used formulation principles adopted for protein-delivery systems. Polymeric drug delivery systems, such as hydrogels, nanocapsules and microspheres, polymeric micelles and lipid-based drug-delivery systems such as liposomes and solid lipid nanoparticles, are typical examples of protein-delivery systems.

In recent years, a large number of literatures have disclosed in situ forming biodegradable drug delivery systems that solidify or gel in the tissue, organ or body cavity from injectable

fluids, control the release rate of drug for a certain period of time and are progressively degraded and eliminated after a certain period of application times. These systems have been also applied to tissue regeneration and cell encapsulation.

In situ gels are formed by physical or chemical changes of the system and classified into four categories depending on their mechanisms: (1) thermoplastic pastes, (2) in situ cross-linked polymer systems, (3) in situ polymer precipitation and (4) internal stimuli (e.g., temperature, pH or ion) induced gelling systems. Among these categories, the in situ polymer precipitation and thermo-reversible gelling methods are the most advanced and practical technologies.

In situ polymer precipitation methods are using water-miscible and biocompatible organic solvents to dissolve water-insoluble and biodegradable polymers, to which drugs were mixed. When these systems are injected into the body, the organic solvents move out to water phase and water penetrates into the system allowing depot formations by polymer precipitations. This system consisted of water soluble biodegradable polymers, such as poly(DL-lactide), poly(DL-lactide-co-glycolide) and poly(DL-lactide-co-caprolactone), dissolved in water miscible organic solvents such as N-methyl-2-pyrrolidone (NMP), benzyl benzoate, benzyl alcohol, ethanol, triacetin and glycofurol. This method has been developed by ARTIX Laboratories and named as the Atrigel® technology. The most advanced product using Atrigel® as a drug carrier, Eligard®, contains the LHRH agonist leuprolide acetate and PLGA 75/25 dissolved in NMP. This system is indicated for the palliative treatment of advanced prostate cancer. The SABER Delivery System of DUREC Corp. is a three or four component technology consisting of sucrose acetate isobutyrate (SAIB), solvent, and release modifier. SAIB is a very hydrophobic, fully esterified sucrose derivative with a nominal ratio of six isobutyrates to two acetates, which exists as a very viscous liquid and was approved as a food additive in many countries. If SABER is formulated with a water-soluble solvent such as ethanol, the solvent will diffuse rapidly out of the injected volume leaving a high viscosity. On the other hand, a more hydrophobic solvent, such as benzyl benzoate, results in a less viscous depot. A SABER-bupivacaine system for the treatment of post surgical pain is under a Phase II clinical study.

The MacroMed co0mpany developed thermosensitive biodegradable polymers based on ABA and BAB triblock co-polymers, in which A denotes the hydrophobic polyester block and B represents the hydrophilic poly(ethylene glycol) block. Low molecular weight polymers of this polymer class are water-soluble and yield a temperature-dependent reversible gel–sol transition. The carrier formulation of MacroMed, ReGel®, 23% (w/w) ABA-triblock copolymer (PLGA–PEG–PLGA) in phosphate-buffered saline (pH7.4), has entered the market. OncoGel®

containing paclitaxel in ReGel is under a phase II study for local treatment of solid tumors by releasing drug for 6 weeks. As an aqueous hydrogel, ReGel® provides a protein-friendly environment that has demonstrated the ability to minimize protein aggregation and release proteins in their active form from periods of days to weeks.

In situ polymer gel systems are easy to form desired shape or depot by injecting flowing fluids and safe and less invasive as the surgical intervention is not needed to place and remove the system, which improve patient compliance and comfort. In situ gels can solve the problems associated with most widely used biodegradable microsphere formulations, such as the drug loss caused by low encapsulation efficiencies of microspheres, the use of harsh organic solvent and manufacturing costs increases by several processes.

Definitely, the parenteral delivery including in-situ polymer gels is currently most demanding and suitable for the successful development of recombinant therapeutic proteins by stabilizing and controlling the release rate of sensitive proteins. Much work still remains, but when it works, it is blockbuster!!!