Polymer-Based Delivery Strengthens Pharma Pipelines

FDA's approval in October of Risperdal Consta for the treatment of schizophrenia was not just a milestone for codevelopers Alkermes, Inc. (Cambridge, MA) and Johnson & Johnson Pharmaceutical Research and Development (La Jolla, CA). It was another link in the rapidly growing chain of polymer-based sustained-release systems.

A combination of Risperdal (risperidone) and Alkermes' "Medisorb" microsphere technology, Risperdal Consta is formulated for intramuscular injection. As such, it facilitates administration for patients unable or unwilling to take the drug by other means. However, unlike the drug's oral solution and quick-dissolving tablet forms, which have been available since the 1990s, the parenteral version requires only a once-per-two-week administration.

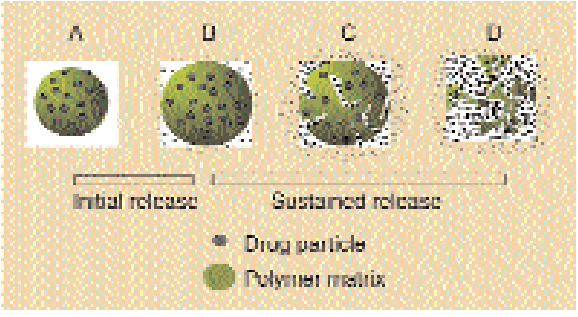

Figure 1: Hydrolysis of a Medisorb microsphere from initial swelling to final breakdown (Alkermes).

The Medisorb matrix system involves the encapsulation of risperidone in polylactide coglycolide (PLG), a biodegradable polymer. PLG consists of lactic acid linked with glycolic acid, the respective percentages of which play a major role in the rate of release. Microspheres are produced by first dissolving risperidone and PLG in an organic solvent mixture and then mixing it with a water solution to form an emulsion. The solvent is drawn out, and the polymer microspheres containing the drug are then dried into a free-flowing powder. Before dispensing, the appropriate quantity of powder is mixed with a water-based solution to create the suspension. Release of the drug occurs by means of a multistage hydrolysis process (see Figure 1) in which less than 1% of the active drug is released at the time of injection. The water-absorption activity leads to the gradual breakdown of the polymer, thereby releasing the drug.

Although the chemistry seems simple enough, the project was not without its challenges. Richard Opps, CEO of Alkermes, credits the project's success to the achievement of three major steps in formulation and manufacturing: molecular stabilization, achieving and maintaining the appropriate release rate consistently throughout the delivery period, and the development of a method and infrastructure to produce the drug at a commercial scale.

Says Opps, "We spent an enormous amount of time focusing on the kinetic aspect of the release profile. The interplay between molecular stability and appropriate release kinetics was the subject of a significant amount of experimentation before development of the right formula." The final hurdle, scale-up to commercial production, was also a major area of complexity. "Some people may think the work is done when you get a stable molecule that's released at the right period of time," says Opps. "Though this is necessary it's by no means sufficient. Unfortunately, the work done on a small scale such as for clinical trials isn't relevant, from a regulatory point of view, at a larger scale."

Moreover, because the drug–polymer microspheres would be destroyed under terminal sterilization, they must be produced under aseptic conditions. For this reason, the drug will be manufactured at Alkermes' CGMP polymer manufacturing facility in Wilmington, Ohio.

Treating diseases with sustained-release drugs is not solely a matter of convenience. Notes Opps, "It's a matter of patient compliance—that is the motivating factor in developing these dosage forms. Improved compliance leads to a better outcome." Citing a study by Johnson & Johnson showing that as many as 75% of schizophrenia patients don't adhere to a routine medication regiment, Opps points out that "It doesn't matter how miraculous the compound is if the patient doesn't take it."

Especially for proteins and peptides, the use of polymers allows drugs to exist long enough in the body to provide a therapeutic effect. Christopher J. Searcy, PhD, vice-president of corporate development at Nektar Therapeutics (San Carlos, CA) notes that the company's polyethylene glycol (PEG) technology often "enables" a drug compound. "The half life of these compounds in the body is so short," explains Searcy, "that a commercial product would not be possible without PEGylation." A recent example is Pfizer's Somavert, approved earlier this year for the treatment of acromegaly.

Unlike the Medisorb technology, PEGylation enables sustained release by modifying the drug at the molecular level (see Figure 2). The molecule is essentially made bigger so it circulates in the body for a longer period of time. In addition, because PEG is an inert polymer it doesn't interfere with the therapeutic effect of the drug. Although molecular engineering by PEGylation is not new, "The simple polymer that has been around for a long time is maturing into a very interesting drug delivery technol-

ogy as well," says Searcy. "It's like an old technology with a new birth."

The pipelines of both Nektar and Alkermes reveal that polymer-based drug delivery is indeed enjoying a renewed interest from industry and that new promising therapies may be on the horizon. For example, Nektar has 15 PEGylated products in clinical trials or already approved. Among these is a collaborative project with Eyetek (New York) and Pfizer called "Macugen" for the treatment of age-related macular degeneration. Results of pivotal Phase II/III trials were expected to be announced last month. Alkermes also has projects in clinical trials that incorporate its Medisorb technology—most notably its proprietary "Vivitrex" compound targeted for the treatment of alcoholism and opiate abuse, which will require only a once-per-month administration.

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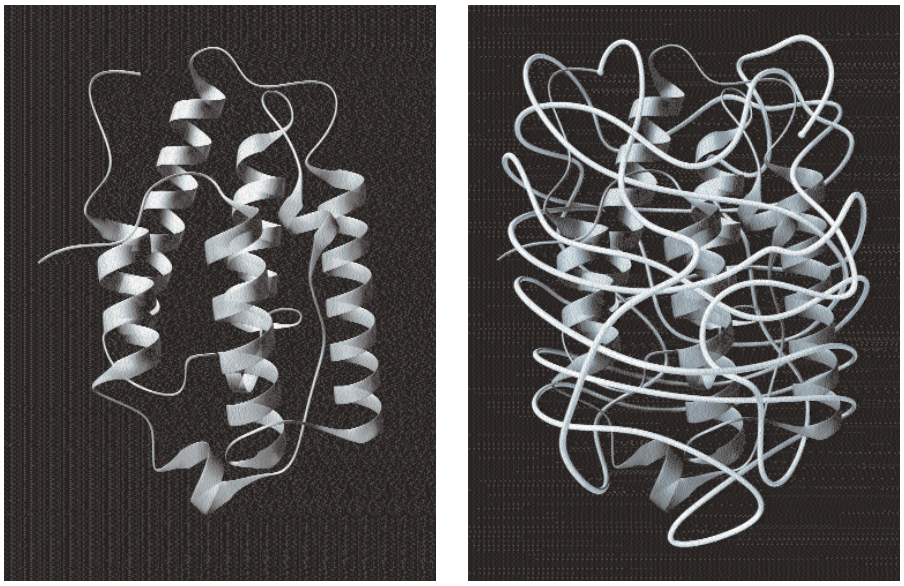

Figure 2: UnPEGylated (left) and PEGylated (right) interferon-alfa 2a (Nektar Therapeutics)