

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"

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

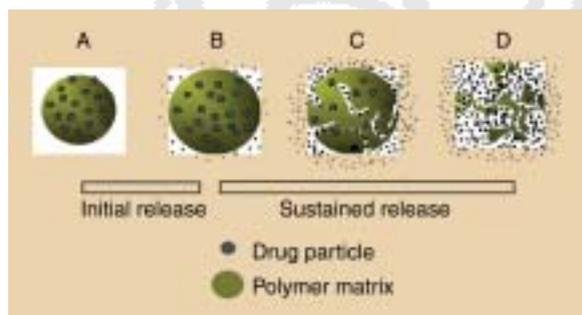


Figure 1: Hydrolysis of a Medisorb microsphere from initial swelling to final breakdown (Alkermes).

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.

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

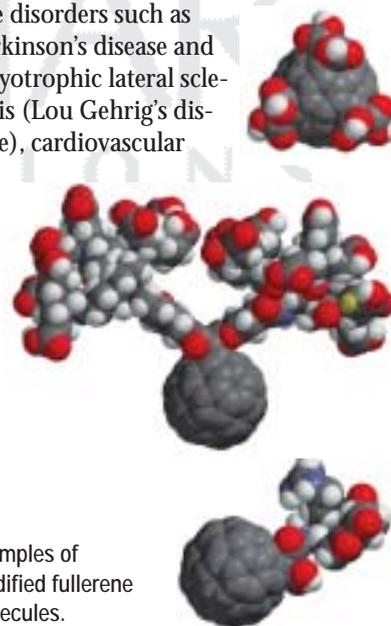
period, and the development of a method and infrastructure to produce the drug at a commercial scale.

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."

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Merck and C Sixty to Pursue Fullerene Antioxidant Technology

Merck and Co. (Whitehouse Station, NJ) has entered into an agreement with the biotechnology company C Sixty (Houston, TX) for the development and commercialization of C Sixty's fullerene antioxidant technology. Although the two therapeutic areas covered by the agreement have not been released, fullerenes have shown therapeutic antioxidant potential in several areas, including neurogenerative disorders such as Parkinson's disease and amyotrophic lateral sclerosis (Lou Gehrig's disease), cardiovascular



Examples of modified fullerene molecules.

diseases, skin conditions, and the aging process.

A fullerene is a natural hollow sphere composed of 60 carbon atoms. Discovered in 1985, these molecules were named after Buckminster Fuller because their shape resembles the geodesic dome that Fuller invented. "Fullerenes have interesting and unique electrochemical properties that make them very useful," notes Russ Liebovitz, vice-president of research and development at C Sixty.

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Those properties include an external electron cloud that makes it easy for the fullerene to pick up electrons and stabilize free radicals. "That means fullerenes have the potential to serve as very powerful antioxidants, by interacting with a

accommodate the small quantities of free radicals produced in normal biological processes. In certain disease states, however, free radicals are overproduced. These unstable molecules, which have an unpaired electron, react with other molecules and can start a chain reaction of damage. For example, one free radical may react with a molecule in a cell membrane, damaging it and generating another free radical in the process. The new free radical can react with other cell structures, causing more damage, and so on.

Antioxidants can stop the damage by taking up those free electrons and stabilizing them. "Fullerenes do this more effectively than almost anything else looked at," Liebovitz says.

Formulating the molecules

The fullerenes are highly insoluble, a characteristic that must be addressed before their power can be harnessed. This has been the primary focus of C Sixty's development work. "We can attach groups to the surface of fullerenes that make them more soluble in water, blood, and many biological membranes. This allows them to get to the site where antioxidant activity occurs," says Liebovitz.

If targeted to the right sites, fullerenes can stop the production of free radicals at their source.

"Since one free radical can damage hundreds or thousands of molecules," notes Liebovitz, "it's a hundred or a thousand times more effective to inactivate the free radical where it's produced rather than at one of the thousand sites it's damaging downstream."

So far, C Sixty hasn't faced any serious issues regarding the stability of the adapted molecules. "We might have three or four formulations that go to a specific organ or target within those organs," Liebovitz says, "so obviously we'll pick the ones that have the best profile with respect to pharmacokinetics."

The Merck-C Sixty partnership

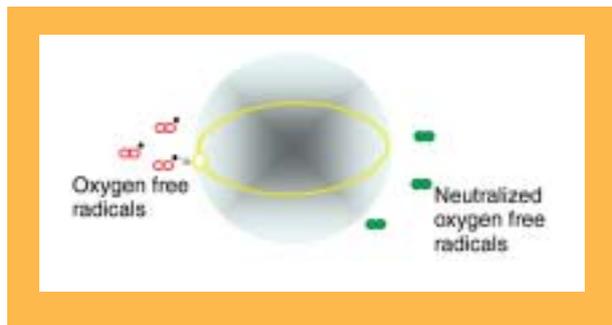
Under the terms of the agreement between Merck and C Sixty, Merck has the exclusive right to conduct research on fullerenes in two undisclosed therapeutic areas. If Merck decides to move forward with the technology, Merck can exercise its commercial license option to market the drugs, which can be supplied by C Sixty.

"Getting a new class of molecules, no matter how powerful, through the regulatory process and through the barriers associated with marketing is a formidable task," comments Liebovitz. "We think we can be more effective by partnering with a company like Merck that has experience doing this."

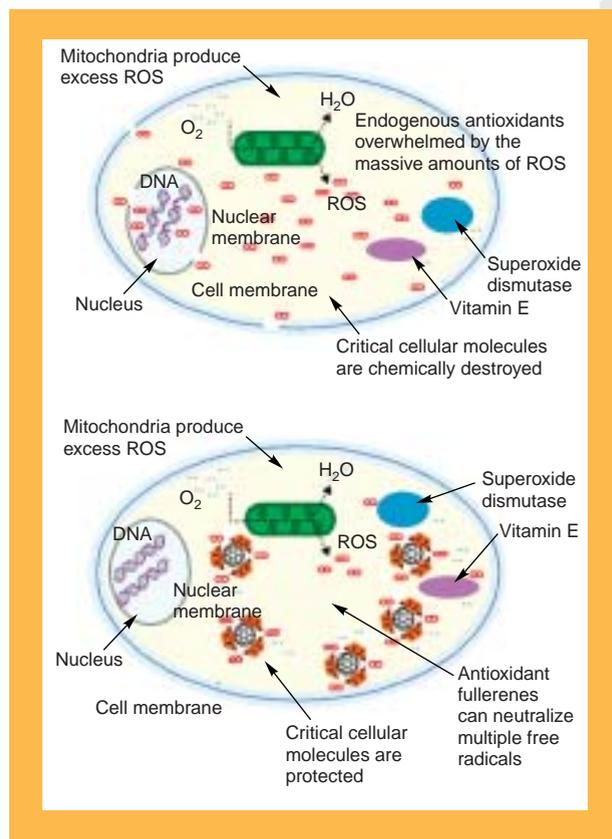
Scale-up

Currently, C Sixty is producing small quantities of the modified fullerenes at its facilities in Houston, Texas, using core fullerenes produced by various suppliers in North America, Japan, and other parts of the world. Liebovitz is confident that fullerene production capacity is sufficient to meet future demand as well. "Three years ago, the world's capacity to produce fullerenes would not have been sufficient to produce the quantities of drug needed for any single indication," Liebovitz points out. "But the fullerene suppliers of the world have been one step ahead of us and have expanded their capacity exponentially." As for the ultimate production of the final drug products in commercial quantities, Liebovitz says that C Sixty and Merck will determine the most efficient and cost effective way to produce them, whether that means building new production facilities or outsourcing.

Laura Bush



Fullerenes are surrounded by an electron cloud that can neutralize oxygen free radicals.



In oxidative injury or disease (above), cells are damaged by oxygen free radicals (ROS). Fullerene antioxidants (below) can neutralize multiple free radicals, protecting critical cell structures.

wide variety of oxygen free radicals that cause extensive damage and are responsible for a number of diseases and the aging process," he continues.

Under normal circumstances, the body's endogenous antioxidants can

Nasal Powder Form Resurrects Dihydroergotamine for Migraines

Those who remember dihydroergotamine (DHE) may soon see this once-popular treatment for migraine headaches back on shelves in a new delivery form. In nasal powder form, DHE may exhibit increased speed of onset and duration of action, and absorb more effectively than competing nasal sprays and tablets.

Because DHE was initially available only in a suppository or injectable form, the drug lost its popularity when triptan, another migraine medication, became available in tablet form. Patients liked it better because of its ease of use, and physicians preferred it because it allowed them to avoid needles.

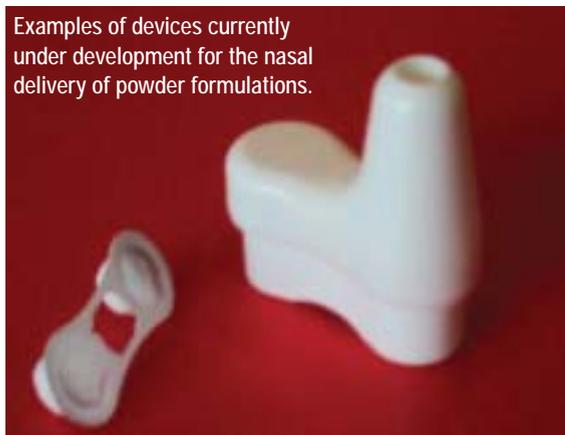
Britannia Pharmaceuticals Limited (Surrey, UK) is working to develop DHE in a nasal powder formulation. DHE was selected because of its long duration of action. "A large number of U.S. physicians would give DHE equal or better quality marks than triptan," says Alex Duckworth, director at Britannia Pharmaceuticals. "One-third of all patients who take triptan may have a recurrence when the medication starts to wear off, whereas with DHE, it's only one-in-six, or one-in-seven. The only problem with DHE has always been getting it into the bloodstream."

Britannia collaborated with Novartis to develop the powder treatment. According to Duckworth, Novartis tried to develop a nasal spray form of DHE after triptan became available in an oral form. However, in solution form DHE can be a very unstable molecule. A specific device had to be created that addressed this problem, but because the device was so complicated for patients to assemble, Novartis had trouble selling it once it hit the market.

That's when the idea to create a DHE powder became a goal for Britannia. Tablets may take up to 30–60 minutes to absorb, while powders require only 5–10 minutes or less to start relieving pain. Likewise, nasal sprays have become a popular treatment for migraines



PHOTOS: BRITANNIA PHARMACEUTICALS / PFEIFFER.



Examples of devices currently under development for the nasal delivery of powder formulations.

because their onset of action is quicker than tablets. However, liquid nasal sprays can release too much liquid into the nasal cavity, which is unable to absorb it all. In this case, the excess liquid drips to the back of the nose, down the throat, and into the stomach. As a result, the liquid must be orally absorbed just as a tablet. "Quite often, liquid nasal sprays have a very similar pharmacokinetic profile to an oral tablet," says Duckworth. "DHE in powder form can be virtually 100% nasally absorbed, which is how a proper nasal product should be."

The company has been developing the powder product since 2001 and envisions the final version to be packaged in a blister that will sit within the well of a small plastic device. A cone on the upper part of the plastic device includes a bayonet that will pierce the foil of the blister. The medication will then be administered by lightly inserting the cone into one of the nostrils and sniffing.

According to the National Institute of Neurological Disorders and Stroke and the National Headache Foundation, migraine headaches affect nearly 30 million Americans, disturbing 1 in 4 households, causing 157 million missed days of work, and costing American taxpayers \$13 billion in reduced productivity each year. Also, migraine headaches have been identified as the most common neurological condition in the world, and it is estimated that as much as 20% of the world's population suffer from them.

"Depending on the progress of clinical trials, we're hoping to have the product on the market in perhaps two years in the UK and three years in the US," says Duckworth.

Doreen R. Coppola

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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

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



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

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 regimen, 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.

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 technology 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.

Maribel Rios

Biomimetic Plants Offer Rich Vaccine Harvest

Many vaccines in use today aren't suited to the needs of developing countries. Not only are traditional injectable vaccines expensive to produce, they must also be kept refrigerated from point-of-manufacture to point-of-use. In regions where electricity is not readily available, it's challenging to transport and deliver vaccines before they expire. A research team from the Center for Infectious Diseases and Vaccinology at Arizona State University (ASU, Tempe, AZ) is developing a novel manufacturing technology that could provide solutions for these problems.



Powder from freeze-dried, genetically-altered tomatoes can be used to make oral vaccines against bacterial and viral illnesses.

The key to ASU's unique approach is the use of genetically-altered plant material as the basis for vaccine formulations. Basing their technology on biomimetics, a technique that imitates natural mechanisms and processes, ASU's team of 25 research scientists changes a plant's genetic code to produce fruits that induce certain immune responses when consumed. Much like traditional vaccines that use yeast or eggs as surrogate hosts for viral pathogens, biomimetics transforms fruit-bearing plants into production lines for subunit vaccines by inserting genes for non-infectious viral protein segments into the plants cells. The genetically altered plant cells mature into cuttings that are planted and grown in soil to full-size plants.

After harvest, ASU's team freeze-dries the fruit, grinds it into a powder, and

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inserts it into a capsule. "At this point, the capsule is a vaccine, formulated in a freeze-dried state in plant cells. With this powder we can treat it like any other pharmaceutical," says Charles Arntzen, director of ASU's Center for Infectious Diseases and Vaccinology. The entire process takes about 4-5 months to complete, making possible oral, heat stable vaccines for the third world.

"Breaking the 'cold chain' is the key to this availability and is the group's primary focus," says Arntzen. "We're saving enormous costs because the freeze-dried material doesn't need to be refrigerated." For the same reasons that plant seeds can lie dormant for long periods of time without losing their vitality, the plant-derived vaccines also don't need to be kept cold. "In a dehydrated state, plant cells' enzymes, nucleic acids, and proteins are stable because they're not subject to any sort of degradative activity. We're mimicking a natural biopreservation system," points out Arntzen.

In addition to saving money on refrigeration, ASU researchers will be able to manufacture an oral plant-derived vaccine for a fraction of the cost of traditional vaccines. "Our target is to make unit doses of oral vaccines at five cents per dose or less," says Arntzen.

Since plants are also suitable sources of organic matter for excipients, scientists won't need to spend time formulating the vaccine once the fruit is produced. Both the excipient and active ingredient would be "packaged" together within the genetically-altered fruit. "We're skipping a step," says Arntzen. "By using just the starches, proteins, and sugars that are naturally present in plant cells, the entire formulation will be inside the freeze-dried plant cells."

Researchers are also addressing concerns that genetically-altered pharmaceutical plants could intermix with other plants in the food chain. For example, they are using tomatoes as the host of their vaccines. Tomatoes don't easily transfer their genetically altered genes to other plants. Additionally, all work on the genetically-altered plants is performed in greenhouses to prevent cross-breeding with other crops.

To validate the technology, scientists from the Center for Infectious Diseases and Vaccinology have conducted three human clinical trials on the oral plant vaccines. In all tests, the appropriate immune response was produced. The researchers also recently received approval from the National Institute of Health to perform a human clinical trial with a vaccine against diarrheal diseases. The study is expected to commence early in 2004.

Because millions of children living in developing countries die from diarrheal diseases each year, the research team chose to begin their studies with vaccines to treat Norwalk virus, cholera, and *Escherichia coli*. However, the oral, plant-derived vaccines have the potential to treat other types of bacterial and viral illness as well. "We're continuing to work on an oral vaccine to treat hepatitis B and human papilloma virus. After this is achieved, measles may also be a suitable target for freeze-dried vaccines," says Arntzen. Additionally, the Center is confident that their vaccine technology will be easily adapted to the production of veterinary vaccines for poultry, swine, and even household pets.

Kaylynn Chiarello