PharmTech.com
ESSENTIAL INSIGHTS FOR PHARMA MANUFACTURING

July 2, 2009

Down the Track: Different Speeds with Multiple APIs

By Maribel Rios,Erik Greb

Formulators and manufacturers have many options for modifying release profiles in multiple-API products.


ILLUSTRATION BY S. STEWART. IMAGES: DAVID MADISON, MEDICALRF/GETTY IMAGES

Dosage forms that contain more than one active pharmaceutical ingredient (API) can improve patient compliance and facilitate the treatment of certain diseases. Strategies to control the release of APIs in tablets and inhalable drugs include modifying the formulation, implementing specific coating technologies, and using techniques in particle-engineering.

Hydrogels

The formulation stage offers many opportunities for scientists to impart controlled release to multidrug dosage forms. Hydrogels, extremely hydrated polymer gels that hold many times their weight in trapped water, are a drug-delivery mechanism that can be manipulated to change the release profiles of APIs (1).

Rather than using commercially available materials, which is the traditional method, a team of researchers at the Massachusetts Institute of Technology (MIT) created designer peptides from scratch that had both hydrophobic and hydrophilic parts. When exposed to water, the peptides' hydrophobic parts assemble into a hydrogel scaffold, explains Shuguang Zhang, associate director of MIT's Center for Biomedical Engineering. The scaffold, a nanofiber that contains nanopores, can house small- and large-molecule drugs and carry more than one API at a time.

By modifying the hydrogel scaffold's peptides, scientists could provide different release profiles for separate APIs. The scaffold could include peptides with physical hooks that are specific to particular receptors in the body. An API associated with a hook would be released earlier than an API housed in the scaffold's micropores, says Zhang.

The nanopores in the scaffold are components or "harbors" that protect biological drugs from water ingress, Zhang says. Because the scaffold is stable at high temperatures, it also protects proteins from becoming denatured. The team's recent research shows that protein drugs are still functional when they emerge from the hydrogel scaffold, which could be used to deliver erythropoietin by injection, says Zhang (2).

Scientists could modify the hydrogel scaffold to alter the release profile of the drugs it carries. Zhang's team engineered specific enzymes to cut a particular site on the peptide chain to degrade the scaffold quickly, which increased the release rate. If the scaffold remained intact longer, it would release drugs slowly. Scientists can engineer the scaffold to resist enzymatic degradation, but this technique is difficult, says Zhang. Another way to modify the release profile would be to change the thickness of the nanopore enclosures that house an API.

The hydrogel scaffold is safer for patients than other natural and synthetic materials. In contrast with animal-derived

materials, MIT's hydrogel scaffold is entirely aseptic and has not provoked any immune response, Zhang says. The scaffold is easier for the body to process and reuse than synthetic polymeric materials, he adds. Innocuous polymers sometimes degrade into toxic monomers. In contrast, enzymes in the body break down the hydrogel scaffold's peptides into harmless amino acids. The team's isotope-labeling study found that the hydrogel scaffold breaks down at a rate of 10% every two weeks, an "almost perfect" rate for many drug-delivery applications, says Zhang. A conventional isotope takes two weeks to degrade by 10%.

Polymers

By including well-characterized polymers in a formulation, scientists can control the release of multidrug dosage forms. Chih-Chang Chu, professor of fiber science and biomedical engineering at Cornell University, and Ramaz Katsarava, head of the Center for Medical Polymers and Biomaterials at the Technical University of Tbilisi, Georgia, invented an architecture that generates families of synthetic, biodegradable polymers. Using the architecture, the scientists developed an amino-acid-based, synthetic, biodegradable polyester amide (PEA) (see Figures 1, 2). MediVas (San Diego, CA) licensed the technology from Cornell and is using it for its oncology vaccine, which contains two antigens.

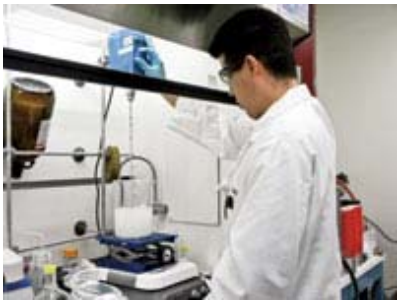

Figure 1: Engineering biopolymers as coatings, implants, or particles enables active ingredients to be delivered at various rates. (IMAGE IS COURTESY OF MEDIVAS)

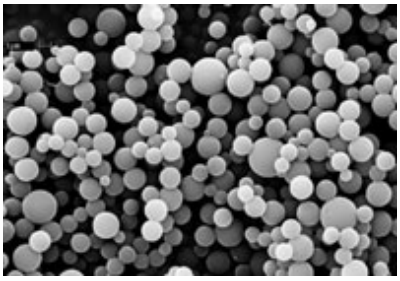

Figure 2: Scanning electron microscopic image of synthetic biodegradable saturated polyester amide fabricated at a homogenizer speed of 20k rpm. (IMAGE IS COURTESY OF C.C. CHU)

The family of PEAs and their biodegradation products (i.e., amino acids, diols, and diacids) are biocompatible with various cells and tissues, says William Turnell, senior vice-president and chief scientific officer of MediVas. The PEA is synthesized from scratch without animal materials that could carry pathogens. They cause no inflammation or immune response, regardless of whether they are engineered as a nanoparticle, hydrogel, fiber, or other form.

Scientists can change the PEA's physical and mechanical properties such as glass-transition temperature and hydrophobicity to suit the drug, says Turnell. The PEA can be engineered into forms such as hydrogels, gels, microspheres, and fibrous membranes, each of which provides a unique release profile.

The material can deliver small-molecule drugs, large-molecule drugs, and combinations of the two, says Turnell. Enzymes degrade PEA materials from the surface and work their way in, so PEAs maintain their structure better than commercial, absorbable materials such as polylactide or polyglycolide that undergo bulk degradation. PEA dissolves more like a jawbreaker than a sugarcube, which allows it to provide uniform, sustained release of drugs, says Kenneth Carpenter, the company's CEO. But scientists can engineer the PEA with separate layers of fibrous membrane or distinct types of nanospheres to carry various drugs with different release profiles.

Although this family of materials behaves like a protein in some respects and like a synthetic polyester in others, it is neither of those things, says Chu. The PEA consists of three building blocks—an amino acid, an alcohol, and carboxylic acid. By changing the building blocks, scientists can create various family members of PEA with properties adapted to specific clinical uses, including oral, transdermal, parenteral, and intranasal drugs.

To accommodate multiple APIs, scientists can engineer a PEA with several layers of fibrous membrane, and each layer can incorporate a separate drug. Another option would be to engineer the PEA into micro- or nanoparticles. A matrix could include several types of particles, each of which could carry a different drug.

Several members of the PEA family can be shaped into various forms in an aqueous environment, which eliminates the need for organic solvents that could cause toxic effects or denature protein-based drugs. MediVas developed the ability to add protein drugs to the PEA form in an aqueous environment, says Carpenter. This technique provides further protection to protein drugs' structure.

In addition, Turnell designed a system for adding proteins onto the PEA structure using a cation to create a self-forming nanoparticle for vaccines. The nanoparticles can then be lyophilized safely because the PEA protects the protein from becoming denatured. This process enables the production of vaccines that can be shipped and stored at ambient temperatures.

Although polymers typically do not interact with the drug, they may raise formulation concerns, depending on the administration route. "The biggest thing you have to worry about is the accumulation of a polymer," says Frank L.

Sorgi, vice-president of research and development at DPT Laboratories (San Antonio, TX). "The body must have some mechanism to eliminate it. When you take the drug orally, it's not a big deal, because it just flushes through. If you're inhaling the drug, then the body must have a natural mechanism that will clear the polymer from the lung, otherwise you run the risk of accumulation of the byproducts of your delivery system that remain in the lung. That is the big issue." For this reason, biodegradable polymers are of increasing interest.

Regulatory approval for multiple-API drugs may present its own concerns. "When you have multiple APIs and multiple polymers, you run into trouble sometimes because there are more variables," says Sorgi. "When you make combination API products, you have to look at it in pieces. Typically, you have to show superiority over just taking three tablets. And you run the risk that one drug may affect the stability of another drug. It may cause it to degrade or have multiple effects."

For suspensions, usually formulators will bind a drug to a resin, and the degradation of the matrix over time controls the release. Multivitamins in suspension are one example of formulations that include more than one active ingredient. Multiple APIs are created in the same way. "Again, however, it gets to be more challenging the more APIs you put in suspension," says Sorgi.

Tablets

Tablets, still the most common dosage form, are manufactured in various ways to deliver multiple APIs. For each tablet-method, companies have several options for controlling the release of the APIs. Although certain pairs of APIs could be incompatible, formulators generally can prevent adverse interactions by coating powder particles and adding excipients. But multidrug tablets do require a longer and more expensive formulation process than do traditional tablets.

Single-layer tablets. The simplest manufacturing method is to mix APIs together through high-shear or fluid-bed granulation into a single-layer tablet. By coating the tablet with one or more layers of polymers such as methyl acrylates, the release of multiple APIs can be controlled, says Nic Michel, vice-president of the process division at Oystar USA (Fairfield, NJ). The coating solution can ensure that the APIs dissolve over time, thus providing sustained release, or in a specific place in the intestinal tract.

Modifying the polymer coating on beads of APIs such as those used in capsules sustains the rate of release. Coatings tend to result in a drug "dumping," and release is controlled according to the thickness of the coating. In contrast, a polymer-matrix mixture creates tunnels through which a drug slowly travels out. The matrix option is useful for high drug-loading applications. Various triggers (e.g, pH sensitivity or enzymatic action) also can be incorporated to control the release (e.g., enteric-coated aspirin). For drug formulations containing multiple APIs, more than one polymer or more than one trigger may be used to control the release of each drug.

Multilayer tablets. Traditional multilayer tablets include one active layer sandwiched between two inactive layers. These tablets can be coated for controlled release. sanofi-aventis's (Paris) Ambien product is a bilayer tablet with two separate release profiles (i.e., immediate release and controlled release). Bilayer tablets such as Ambien could also incorporate a different API in each layer, each with its own release profile, says Doug Becker, senior director of process technology at Wyeth (Madison, NJ). A bilayer tablet could not, however, release drugs sequentially because the alimentary canal would affect each API immediately.

Although the compression technique is the same for single-layer and multilayer tablets, adding and controlling multiple tablet layers can present engineering challenges such as interfacial bonding problems. For example, formulators must ensure that the two API layers have similar expansion and contraction coefficients so that they do not separate. Some layers don't adhere to each other, so manufacturers may have to use a three-sided press to incorporate a boundary layer, says Becker. This method can improve the tablet's structural integrity during coating and handling.

Inhalation drug products

Treating lung ailments such as asthma and chronic obstructive pulmonary disease often involves doses containing a combination of APIs such as long-acting beta-2 agonists, short-acting derivatives, and steroids to open the airway and reduce inflammation. Examples of already marketed multiple-API inhalation products include AstraZeneca's (London) Symbicort (budesonide and formoterol fumarate dehydrate) and GlaxoSmithKline's (London) Seretide (fluticasone propionate and salmeterol xinafoate). Optimal efficacy of multiple-API inhalation products requires precise control of drug release, the correct drug ratio in each dose, and effective and reproducible delivery.

Nanoparticle structures may be desired for poorly water-soluble pulmonary formulations because they facilitate dissolution. Strategies to achieve the 1–5-µm particle size for aerosol formulations include jet milling, precipitation, and supercritical-fluid processes. These particles are then blended with several excipients to facilitate handling, filling containers, and aerosolization. To control dissolution, formulators may select low-solubility salt forms of the drug or different modifications of the drug that have low solubility. Excipients such as lecithin also can be used to modify dissolution rate and control release.

Nonetheless, when used in suspensions in nebulizers, solid nanoparticles may present problems such as agglomeration or Ostwald ripening. To help alleviate these problems, bottom-up approaches for producing combination API nanoparticles for inhalation have been developed (3).

Figure 3: A cluster of nanosized particles of two active pharmaceutical ingredients. (IMAGE IS COURTESY OF SAVARA PHARMACEUTICALS)

One novel strategy involves the assembly of nanoparticles of API into clusters for oral or nasal inhalation. Savara Pharmaceuticals [http://savara pharmaceuticals|~www.savarapharma.com/site_flash/technology.html] (Austin, TX) develops respiratory therapeutics using its NanoCluster dry powder aerosol technology. The dry powder is composed nearly entirely of API and comprises discrete nanostructured microparticles of low density and irregular shape (see Figure 3). According to Cory Berkland, cofounder and chief scientific officer of Savara and associate professor at the University of Kansas, the company uses existing methods to make the nanoparticles, but the new composition of matter is embodied in the assemblies or agglomerates. Under controlled conditions and at room temperature, a stable colloid nanosuspension is made and usually consists of the nanosized API particles in a water-based system. Small amounts of generally regarded as safe additives (e.g. lecithin or leucine) are then introduced that cause the particles to assemble into clusters. Driving forces to assemble the particles include charge interaction and hydrophobic interaction. The clusters are then filtered off and dried to obtain a fine powder.

"We have a lot of flexibility to make the agglomerates," says Berkland. "We've made several formulations of diverse active ingredients ranging from steroids to insulin that do not include any excipients. For example, insulin nanoparticles were obtained by changing the pH of insulin to render it less soluble in water. You can then assemble the nanoparticles in suspension. NanoCluster technology seems to be equally amenable to water-soluble and water-insoluble compounds."

"Instead of using 1- to 3-µm solid drug microparticles, the method uses drug nanoparticles to rebuild the microparticles. The result is drug microparticles with many spaces and cracks and with low density. When breathed in, the low-density particles are captured into the air flow field (aerosolized) and 'fly' better than solid particles, thereby enabling the particle to travel deeper in the lung," explains Berkland. "Poorly water-soluble drugs can be processed into nanoparticles using water as a continuous phase, and we can assemble the materials in water. When we work with water-soluble drugs, we tend to precipitate into another material to form the nanoparticle suspension," he adds.

Multiple-API drug products can be developed in various ways. One method is to have two discrete nanoparticles of the two different types of drugs created and then assembled together. Another way is to assemble a nanoparticle suspension of a poorly water-soluble drug (e.g., a steroid) into an agglomerate or cluster and have the other ingredient in solution with the NanoCluster. When the solution is dried, the water-soluble compound that was in solution deposits on the cluster.

The amount of each drug in each cluster can be controlled by modifying the relative amount or relative concentration of the two drugs in suspension. This approach allows assembly into various ratios, even high ratios such as 50:1 or 100:1 for high-potency drugs. "There are even cases where you might want to have two different NanoClusters, for example one that has drug A and deposits in the upper airways and another that contains drug B and deposits in the peripheral airways or the aveolar region of the lung," says Berkland. In such cases, the process would produce two different NanoClusters with different flight characteristics. The clusters would be blended together to get a homogenous mixture of the two for delivery.

Conclusion

Multidrug dosage forms will likely become more popular among patients, partly because they are convenient and facilitate compliance. Producing these drugs is challenging for formulators and manufacturers alike, even when controlled release is not a consideration. Yet, as drugmakers gain experience with these sophisticated therapies, they better understand how to surmount the particular difficulties they present. Patient demand and patent issues, among other factors, could prompt future improvements to the formulation and manufacturing methods—and production equipment—that these medicines require.

For information on this topic, see the online exclusive, "A Tale of Two Techniques [http://a tale of two techniques|~pharmtech.findpharma.com/pharmtech/articlestandard/article/detail/607461]"

References

1. Glossary, *Nature,* www.nature.com/nrmicro/journal/v2/n2/glossary/nrmicro821_glossary.html, accessed June 5, 2009.

2. S. Koutsopoulos et al., "Controlled Release of Functional Proteins through Designer Self-Assembling Peptide Nanofiber Hydrogel Scaffold," *Proc. Natl. Acad. Sci. USA* **106** (12), 4623–4628 (2009).

3. G. Ruecroft and D. Parikh, "Power Ultrasound and the Production of Mesoscopic Particles and Aqueous Dispersions," *Pharm. Technol.* **32** (9), s28–s35 (www.prosonix.co.uk/combination-therapy.html, accessed June 11, 2009.

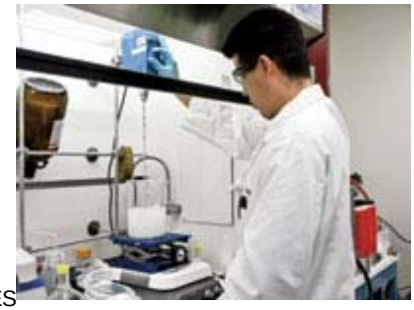

ILLUSTRATION BY S. STEWART. IMAGES: DAVID MADISON, MEDICALRF/GETTY IMAGES

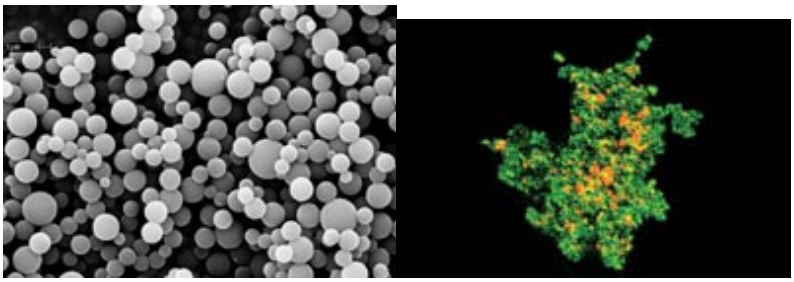

Figure 1: Engineering biopolymers as coatings, implants, or particles enables active ingredients to be delivered at various rates. (IMAGE IS COURTESY OF MEDIVAS)
Figure 2: Scanning electron microscopic image of synthetic biodegradable saturated polyester amide fabricated at a homogenizer speed of 20k rpm. (IMAGE IS COURTESY OF C.C. CHU)
Figure 3: A cluster of nanosized particles of two active pharmaceutical ingredients. (IMAGE IS COURTESY OF SAVARA PHARMACEUTICALS)