Biopharmaceutical Drug Delivery

Published on: August 1, 2004
BioPharm International
BioPharm International, BioPharm International-08-15-2004, Volume 2004 Supplement, Issue 2

Entire biopharmaceutical development projects can succeed or fail based on the feasibility of an acceptable dosage form. Therapeutic proteins range in size from a few hundred to over 100,000 Daltons. The biological manufacturing process leads to complex, unstable, and potentially variable products that frequently require novel dosage forms and new patterns of process validation.

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By far the most common delivery method used in the biopharmaceutical industry is parenteral dosing; that is, liquid formulations for subcutaneous or intramuscular injection or intravenous drip. "An assured bioavailability will make this route the first development objective," explained D. Ganderton from the Chelsea Department of Pharmacy at King's College in London in *Polypeptide and Protein Drugs: Production, Characterization, and Formulation.* "Until a consistent bioavailability, which may be acceptable even if low, has been achieved, formulations derived for the oral route should not be included." Bioavailability measures how much of the drug molecule arrives at its site of action compared with how much is in the formulation delivered to the body.

"In exploiting routes other than parenteral administration," Ganderton cautioned, "one encounters barriers for which there is little or no intrinsic permeation of the peptide. Breaching these barriers raises important questions of toxicity and, until massive research is carried out on the mode of action of penetration enhancers and the reversibility of their effects, a major regulatory hurdle will be raised against their use. In the meantime, much can be done to refine parenteral dosage forms, both in terms of the time course of their action and the ease with which they are used."

Ganderton wrote those words over a decade ago, but they still apply to most development projects today.

Parental Drugs

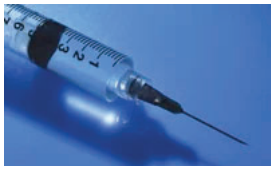
Scientists are refining injectable delivery forms for better patient comfort, convenience, and compliance with dosage regimens. Three main technologies are under development: high-concentration formulations, needle-free injection devices, and controlled — sustained or targeted — delivery.

High-concentration formulations. Comfort and efficiency of delivery limits the volume of subcutaneous injections to less than one milliliter per injection. The less volume a patient must receive in a single injection, the better. Many biopharmaceutical companies are exploring high-concentration formulations (>100 mg/mL) for protein drugs that require large doses, such as some monoclonal antibodies.

The improper selection of filling equipment for high-concentration proteins will result in sheared, precipitated, aggregated, or adulterated solutions during the actual filling step. Traditional vial-filling methods (see Chapter 4) must be replaced by gentler technologies. For high-concentration formulations, lyophilization may be used to concentrate rather than preserve the formulation. The freeze-drying process removes water, and the formulation may be reconstituted by adding back into it a smaller quantity of water-for-injection.

Questions yet to be answered about high-concentration formulations include the details of loading concentrations and fill volumes. The company's marketing department has a say here: Do end users want to see a vial with hardly anything in it? More technical questions arise over the higher concentrations of excipients in the product. Will stabilizing-excipients impede tonicity at high concentrations?

forces tiny droplets of a formulation through the skin. These technically are transdermal delivery devices.



Another emerging technology is iontophoretic (electrically assisted) delivery. The skin is not naturally permeable to peptides and proteins; its main job (besides acting as the body's largest sensory organ) is precisely this kind of protection: keeping what's outside from getting inside. However, it can be induced to take a certain amount of very specific material — a formulation on the skin, held in place by an adhesive that keeps other substances away from the delivery site — by an electric field that temporarily changes the chemical and physical properties of the skin cells. As soon as that electrical field is switched off, the skin returns to its normal state.

Controlled delivery. Both the drug's duration (for sustained delivery) and its site (targeted delivery) of action and bioavailability can be controlled. Targeted delivery has been practiced for some time using monoclonal antibodies and surgical implantation, among other methods (see the "Blood-Brain Barrier" box on Page 22). Sustained delivery is gaining much interest in the biopharmaceutical arena.

According to Nandini Katre of SkyePharma, "The major challenges in formulating therapeutic proteins and peptides for sustained delivery are as follows: maintaining the structural integrity of the therapeutic molecule to preserve its bioactivity and stability; obtaining high loading in the delivery vehicle to ensure sufficient bioavailability for the duration of therapy; providing sustained therapeutic levels for the desired duration without a 'burst' effect, controlling the duration of drug release to accommodate a range of dosing regimens that match therapeutic needs; and providing in vivo biological effects that can be sustained over the required period of time."

For sustained delivery, a depot (reservoir) of drug is created in the body (at the injection site, for example), from which the drug is released over a specified time. Biodegradable polymers open the possibility of implants that deliver a drug over days or months. Like any other method, sustained delivery presents certain challenges. In time, a protein may interact with its surrounding matrix, or the implant could be attacked by the immune system. If proteins stick (adsorb) to the delivery matrix, they may not be released at all. Even before implantation, creation of a delivery matrix often involves steps that can harm proteins. Four methods of creating a delivery matrix for sustained delivery can be used with biopharmaceuticals: emulsification, coacervation, extrusion, and polymerization.

Emulsification. When the drug is water-soluble but the delivery matrix is not, they are dissolved into two different media and then mixed to create a water-in-oil emulsion. Usually, for better protein distribution, that emulsion is dispersed and mixed with a second aqueous solution to create a water-in-oil-in-water emulsion. The interfaces created by the droplets can denature proteins, especially when a series of emulsions are used to create the delivery matrix. Additionally, energy is required to combine the two (mechanical or ultrasonic mixing), which also can denature proteins.

Coacervation. In coacervation, formulators add a competing molecule that is more soluble to a solution of the protein in liquid. The resulting chemical reactions create microspheres of the drug. This method is gentler than emulsification, but some loss of bioactivity can happen through pH changes and chemical reactions.

Extrusion. A solution or particulate formulation is forced through holes to form microdroplets. High shear forces may damage proteins. Combining this technique with lyophilization may be a better choice because the cold, dry form is more stable, and the protein receives some protection from shear forces.

Polymerization. Hydrogels, polymers that swell when they come into contact with water or an aqueous solvent, are mixed with the drug. Electromagnetic radiation forces chemical reactions that create a gel matrix to carry the drug.

Inhaled Biopharmaceuticals

Offering an almost direct line to the circulatory system, alveoli in the lungs would be a good place to deliver proteins. However, because the lungs are a pathway for infections, the body's defense mechanisms make the alveoli hard to reach. Pulmonary delivery of polypeptides requires a device such as a nebulizer that makes an aerosol of the formulation (a liquid or a lyophilized powder) for inhalation. Only very tiny particles can reach far enough into the lungs for efficient drug delivery. The portion of the particle size spectrum generally considered able to penetrate farthest and deposit well into the lungs (<2-3 Âµm) is called the fine particle fraction (FPF). For biopharmaceutical drugs, a large portion of the device output should be 1-6 Âµm. Particle size distribution and weight determine how far into the progressively smaller lung pathways the drug will go. Heavier particles are deposited sooner, sometimes just at the back of the throat. If swallowed, the drug is wasted (see "The Oral Route" on Page 29).

Delivery by way of the respiratory system creates new stability issues. We know that protein structure determines bioactivity, and the generation of an aerosol for inhalation can subject a molecule to new modes of structural degradation. Metered-dose inhalers, familiar to asthmatics, don't work with biopharmaceuticals because of the harsh conditions they present to a formulation in the form of propellants and their mechanism of action. Some stabilizing excipients cannot be used for inhaled biopharmaceuticals because they may cause cough or bronchitis side effects, which may be dangerous as well as unpleasant for some patients. Formulation components cannot be allowed to interfere with aerosol generation, but the protein must be stabilized to survive the delivery process. Nebulizers expose a lot of the product's surface area for possible interactions, which must be minimized. If the delivery device is too customized, it may need to be approved through FDA's Center for Devices and Radiological Health as a medical device before the product's Biologics License Application can be approved. Patient factors (such as lung anatomy, breathing patterns, and possible pulmonary obstructions) can also affect the efficiency of delivery.

Four key questions are on the mind of a formulator developing a biopharmaceutical for inhalation:

(1) How much drug will exit the device as an aerosol?

(2) What is the size distribution of particles in the aerosol?

(3) How reproducible is the aerosol generation process?

(4) How do the device and its aerosolization process affect the quality and efficacy of the drug formulation?

The first three questions will be addressed by laser diffraction for nebulizer clouds. For the last question, characterization techniques (as used in preformulation) should be performed on the product that exits the device as well.

Like parenteral drugs, inhaled biopharmaceuticals come in liquid and lyophilized forms. No matter which form the basic formulation takes, it will go through three main steps toward incorporation into the delivery device:

- Choose the device
- Choose excipients
- Determine related manufacturing issues.

Step 1: Choosing the device. Various types of nebulizers use compressed gas (usually nitrogen because oxygen can degrade proteins) or sound waves to create droplets and force them out of the device. Potential degradation pathways include high concentrations and heat build-up with the ultrasonic method and product recirculation with the gas. Mechanical methods of extrusion through tiny holes can cause shear stress.

Few multidose powder formulations are in development because of humidity and crystallization problems over time with the micronized (a process that reduces the particles to FPF size) particles. Unit-dose foil blister packs or "multidose" disks and tapes (really unit-dose multipacks) provide patient convenience. Unit-dose packaging (in blister packs) is usually preferred in liquid formulations because multidose products require preservatives. Complete sterility is not required for such products by US or EU regulatory authorities. Instead, inhaled biopharmaceuticals must conform to microbial limits measured in colony-forming units (cfu).

Patients prefer hand-held nebulizers to larger, more complex devices. Most devices are patient-driven, but some companies are working on powered nebulizers. In this case, the choice depends more on delivery requirements than molecular characteristics. Because the digestive system is very adept at disassembling proteins, accidental swallowing of the product is avoided more for cost than safety.

Step 2: Choosing the excipients. The drug indication matters — most asthmatics are sensitive to a range of excipients. Most buffers are known to cause coughing, an adverse reaction that can expel the drug, so no buffer can be used in an inhaled biopharmaceutical even though pH control is needed because degradation is often pH-dependent (>5 is best). At 1-6 Âµm, the dry particles of powdered formulations often act against each other, requiring excipients or carriers for the larger ones. Formulators must weigh flow and dispersal rates against each other to determine the optimal conditions for a given formulation.

Multidose liquid formulations require preservatives that can interact with proteins to denature, aggregate, precipitate, or change their efficacy. Europe is stricter than the US on preservative use, citing that some preservatives can cause bronchoconstriction. Salt included as an isotonicifier can interact with stainless steel storage of bulk formulations to cause metal-chelated oxidation. It may be helpful to add sugars, but some can cause bronchoconstriction.

Step 3: Determining manufacturing issues. Small doses are better than large doses, so high concentrations (>50 mg/mL) are desirable for inhaled biopharmaceuticals if they don't lead to solubility or aggregation problems. Whereas asthma drugs are typically given by the microgram

devices in a fill and finish operation. Preservatives or different stabilizers may be required, and sterility is always a concern for liquid formulations. Liquid formulations for pulmonary delivery are stored frozen (requiring freeze-thaw testing) or at a controlled temperature (typically 2-8Â° C). Powder formulations are spray-dried or lyophilized and then micronized.

The Oral Route

Pills are sort of a **Holy** Grail for drug formulators, especially those involved with biopharmaceuticals. Many successful therapeutics are delivered to patients by way of a tablet, capsule, or pill. Oral delivery is preferable for several reasons, and patient compliance is near the top of the list. Patients are much happier swallowing a pill than getting an injection, using an inhaler, or spending time hooked up to an IV unit. Pills are also highly stable and typically have long shelf lives.

So why are protein pills so difficult to develop? Our digestive systems evolved to do one thing well — break down food into usable raw materials. Proteins are some of the main nutrients we eat, so our gastrointestinal tract is pretty good at breaking them down.

Built-in barriers to protein and peptide uptake by the oral route include enzymatic membrane mechanisms, protein biocompatibility, chemical breakdown, and physical clearance. Transport of the large molecules is controlled by enzymatic breakdown, particularly in the stomach and small intestines.

Many research laboratories are working on oral delivery systems, specifically protection against degradation and other approaches to oral delivery. For peptide or protein drugs to make it through the digestive system intact, they must be protected from enzymatic degradation and get into the bloodstream. They must be maintained at maximum solubility until they get to the intestines, where proteins are best absorbed into the bloodstream. Recall Ganderton's comment that even low bioavailability might be acceptable if it is reliable.

Buccal delivery. Other companies are developing buccal delivery formulations for biopharmaceuticals. The drug is delivered to the body by way of the mucosal membranes, in this case those inside the mouth. Biopharmaceuticals may be incorporated into patches that stick to the roof of the mouth or underneath the tongue. Buccal delivery requires absorption enhancers.

Other Delivery Methods

Transmucosal drug delivery (including suppositories, which suffer from a poor reputation with patients) usually falls into the "miscellaneous" category of drug delivery technologies for therapeutic proteins, and only a few are in development. Several biopharmaceutical companies and companies that specialize in drug delivery are trying to create new methods of delivering large protein molecules to the body.

Sometimes the method of delivery depends on the indication, as with intraocular drugs (those delivered through the mucosal membranes surrounding the eye) and topical formulations, such as Regranex Gel for treating diabetics' skin wounds.

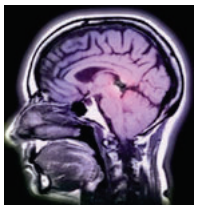
Nasal delivery. Doctors and patients want methods of drug delivery that are more convenient than parenterals. Nasal delivery is transmucosal delivery through the nose, which has good protective mechanisms for keeping proteins and infectious agents from crossing its mucosal barriers. For nasal delivery of biopharmaceuticals to be a viable therapeutic option, therefore, such mechanisms must be overcome, which may involve adding absorption enhancers. Even so, the nose offers low bioavailability (<5%) for proteins, but its mucosa are permeable to many peptides. Several peptide drugs are currently on the market as nasal drops or sprays. Sprays work best, but as with certain inhaled formulations, device development and manufacturing may become an issue. For patient compliance, sprays are preferable because nasal drops require special directions (to move the head in a particular way, for example), and the tickle causes many patients to sneeze.

Nasal delivery requires larger particles than pulmonary delivery. Droplets <10 Âµm are so light they go right past the nose and into the respiratory tract. Also nasal dosages must be high to make up for the low bioavailability. Absorption enhancers are being studied to address this problem.

Cellular implants. What if you could dispense with all the intermediate steps between cell-culture production of a therapeutic molecule and its delivery to the patient? In a process similar to creating drug microspheres for sustained parenteral or pulmonary delivery, genetically engineered cells (often human skin or epithelial cells) can be encapsulated in cellulose sulfate or another biopolymer. The encapsulated cells are then implanted under a patient's skin to form "neo-organs," which the body automatically provides with vascularization like it often does with tumors. But this tiny invader helps the body rather than harms it.

The biopolymer encapsulation provides an immunoprotective barrier for the cells, allowing in only nutrients from the bloodstream and allowing out only pure cell-secreted protein with the typical cellular waste products the body handles all the time. The patient's body will not reject this "neo-organ" as foreign because there is no contact between its immune-response cells (such as T-cells) and the encapsulated cells.

To protect the brain from infection and from damage that could be caused by foreign chemicals, the endothelial cell linings of its capillaries are tightly packed together. Nothing but water can diffuse freely from the blood to the brain. Nutrients are actively transported by cellular mechanisms across the blood-brain barrier (BBB). Most drugs are treated as foreign material to be excluded from entering brain fluids. Only a few drugs can enter the brain at all. Much of the time this is beneficial; many powerful drugs could cause trouble if they got past the BBB. But, what if the brain is already in trouble (it has a tumor, for example), and the drugs need to get into its fluids to do their job?



The Blood-Brain Barrier

Some drugs are chemically similar enough to brain nutrients (or can be made enough like them) that they can be moved into the brain by the nutrient back door. Water-soluble substances are almost universally excluded from the brain. But fat-soluble substances can dissolve across the membranes of endothelial cells and pass through them into the brain. So another method of getting a drug across the BBB is to make it lipid soluble. With a protein, that can be a tall order. And if those chemical methods won't work, there is currently only one other choice, and it can be risky.

Highly concentrated sugar solutions, when injected into the arteries that supply the brain, will force the endothelial cells to shrink temporarily. That opens up gaps between them through which drugs injected immediately following can diffuse. Of course, anything else that happens to be going by in the bloodstream at that time may get across the BBB as well, and that makes this a risky approach. But sometimes — as in the treatment of brain tumors — the cure is worth the risk.

Biopharmaceutical developers are used to thinking in such terms. The field of risk assessment is about weighing the possible benefits of a therapy or process step against its drawbacks. Meanwhile, product developers continue to work toward breaching the BBB. Some methods under study include facilitated diffusion; receptor- or carrier-mediated transport using glycoproteins, nucleosides, certain vitamins, iodine, or amino acids; and oligoglycerols.

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