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Drug Delivery: What the Future Holds

William J. Lambert

ABSTRACT

Drug delivery technologies have the potential to enable drug candidates with poor pharmaceutical or biopharmaceutical properties, both for macromolecule and traditional compounds. While there have been many success stories to date, the future offers even more promise. In this article, the author surveys the top ten areas in drug delivery looking forward.

"Those who talk about the future are scoundrels. It is the present that matters."
–Louis Ferdinand Celine, 1894–1961

With all due respect to Dr. Celine, it is appropriate for businesses to consider what the future may hold. New technologies have the potential to impact business, and therefore cannot be ignored. Drug delivery technology, for example, is attracting a high level of interest. This may be attributed to normal life cycle management for drugs, the need to enhance the physicochemical or biopharmaceutical properties of drug candidates, and pharmaceutical and biotech companies' search for new opportunities in response to less-than-robust pipelines. Between 2004 and 2008, an estimated $70 billion in pharmaceutical sales will be at risk worldwide due to patent expiration.[1] One might ask if drug delivery technologies are being effectively employed to minimize this potential loss.

To be successful, a drug delivery technology must bring a real advantage to the patient (e.g., improved efficacy, safety, compliance), the caregiver (e.g., convenience), the care payer (e.g., a pharmacoeconomic advantage), and the company itself (e.g., increased sales, decreased cost of goods, extended patent life). This article will attempt to assess new drug delivery technologies likely to affect the market. In making this assessment, the author identified areas where improvements in delivery are most needed to create a "top ten list" of opportunities in drug delivery

ORAL DELIVERY OF PROTEINS

The biopharmaceutical market was valued at more than $70 billion in 2005.[2] Most of these proteins are being administered by injection. Given patient preferences for less invasive routes of administration, one can only imagine what the sales for therapeutic proteins would be if they could be given orally. It is easy to see why many consider the oral delivery of proteins to be the holy grail of drug delivery.

Despite decades of work toward oral delivery of therapeutic proteins, progress has been fairly limited. This can be attributed to the multiple challenges faced in this area. First, the protein must survive the low pH of the stomach, which is typically pH 1.5–2 in fasting adults.[3] Next the protein is exposed to numerous enzymes present in the gastrointestinal (GI) tract, many of which are designed to hydrolyze proteins.[4]

William J. Lambert, PhD, is the senior vice president of pharmaceutical development at Pacira Pharmaceuticals, Inc. (previously SkyePharma Inc.), San Diego, CA, 858.625.2424, BillL@pacira.com

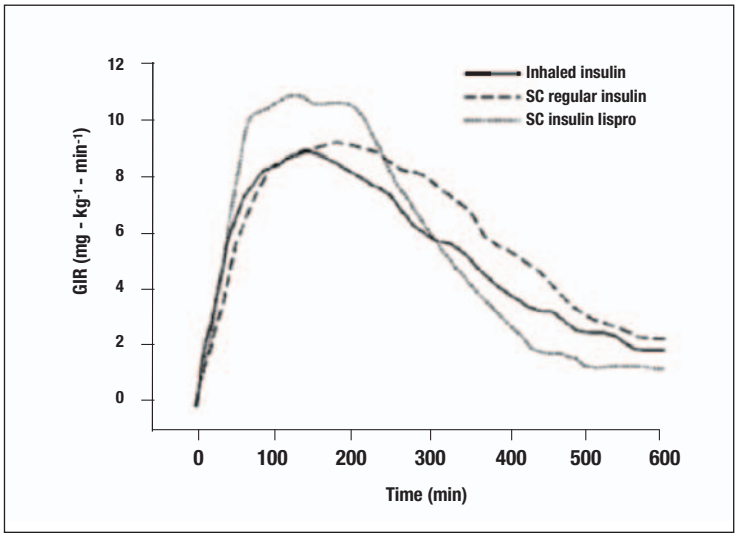

Figure 1. Pharmacokinetic profiles, shown as glucose infusion rates, following 6 mg of inhaled insulin and 18 units of subcutaneous insulin.[6]

If one is able to overcome these obstacles, the protein still must be absorbed through the intestinal mucosa. Permeability of proteins through cell membranes is extremely low. Their large molecular weights and high hydrogen-bonding capacity,[5] makes significant transcellular passive diffusion through membranes unlikely. Although the intercellular space between adjacent epithelial cells offers an aqueous pathway for protein diffusion,[5] this space is limited by the presence of tight junctions, and provides a small surface area relative to the total epithelial surface. Finally, once absorbed, the protein must survive first-pass metabolism.

The therapeutic index and cost of goods of the protein will also be factors in determining the feasibility of oral protein delivery. Due to the hurdles described above, it is reasonable to expect low, variable bioavailability. Thus, proteins with a narrow therapeutic index or high cost of goods will not be ideal candidates.

PULMONARY DELIVERY OF PROTEINS AND PEPTIDES

On September 8, 2005, an FDA advisory committee panel recommended the approval of Exubera, which delivers insulin by the pulmonary route using Nektar Therapeutics' dry powder inhaler. This approval is impressive given the many hurdles it had to pass, including the narrow therapeutic index of insulin and the need for strict particle size control to reach the alveolar surface.

The pulmonary route of administration offers a large surface area for absorption, and as a result, achieves rapid systemic levels.[6] Figure 1 shows the pharmacokinetic profile of inhaled versus subcutaneously delivered regular insulin and insulin lispro (a rapidly absorbed lys-pro-insulin analog). If Exubera is successful, it is likely that a number of other protein and peptide products delivered by this route will follow.

ORAL CONTROLLED RELEASE

Controlled release (CR) oral formulations for small-molecule drugs have existed for decades and thus, may come as a surprise in a list looking to the future. However, the need for oral CR will remain strong in the future for two reasons. First, as new drug candidates are identified, many will not have the pharmacokinetic profiles needed for once-a-day dosing. Using drug delivery technology to enable once-a-day dosing is generally a much less expensive and more successful approach than an analog approach aimed at maintaining activity while modifying the pharmacokinetics.

This approach has been extremely successful in the past. Take Pfizer's CR nifedipine product Procardia XL, as an example. It should be noted that this was Pfizer's first billion-dollar product. The original, immediate-release Procardia product had only a one- to two-hour plasma half-life leading to three-times-a-day dosing for angina.[7] Sales in the US reached approximately $200 million annually at peak levels.[8] Procardia XL was able to achieve $1.4 billion in US sales four years after launch, due to the convenience of once-a-day dosing and the addition of an indication for hypertension. The addition of this new indication was facilitated by the decreased plasma maximum concentration in the CR formulation relative to the immediate-release tablet.[7] By leveraging Alza's OROS technology, Pfizer was able to prolong its Procardia franchise well beyond the end of the nifedipine patent, and at sales levels significantly higher than could have been achieved with an immediate-release tablet.

New technologies are likely to impact oral CR in the future. One shortcoming of systems like OROS is that the drug must be readily absorbed throughout the gastrointestinal (GI) tract. However, many drugs are

poorly absorbed in the lower GI tract.[9] One solution to this problem is to use gastroretentive systems which remain in the stomach for prolonged times, slowly delivering drug to the upper GI tract.[10] Various approaches to gastroretentive formulations have been used, including dosage-form density, adhesion, swelling, and magnetic fields.

Pulsatile or chronotherapeutic delivery will provide improved treatment paradigms for various drugs. A delayed-release propranolol formulation, for example, intended to provide therapeutic morning blood levels following bedtime administration, has been shown to be effective in preventing acute cardiovascular events, which occur more commonly in the morning.[11] Another recent example is Ambien CR for the treatment of insomnia. This formulation of zolpidem tartrate is a bilayered tablet, with one layer designed to dissolve immediately to induce sleep and the other layer dissolving slowly to help maintain sleep.

IMPROVED ORAL BIOAVAILABILITY FOR TRADITIONAL DRUGS

Poor oral bioavailability of most drugs can be attributed to low solubility, slow dissolution, low membrane permeability, or rapid metabolism prior to reaching the systemic circulation.[12,13] Solubility- and dissolution-limited absorption has long been a challenge to oral absorption, and has become more problematic in recent years due to the tendency of many high-throughput screens to select larger and more lipophilic drugs.[14] Technologies that can solubilize drugs such as lipid-based formulations are one approach to this issue.[15] Alternatively, one can eliminate the energy barrier related to melting the crystal lattice by producing and keeping the active in an amorphous state in the dosage form.[16]

For many drugs, metabolism and efflux by p-glycoprotein may be important factors in bioavailability.[17] Metabolism may be the most significant factor in the absorption fate of small peptides.[13] Competitive enzyme inhibitors may be administered along with the drug in order to minimize efflux and metabolism in order to improve bioavailability.

PARENTERAL (INJECTABLE) FORMULATION TECHNOLOGIES

According to Kalorama Information, the implantable and injectable drug delivery market had revenues of $9.8 billion worldwide in 2006.[18] The parenteral route of administration will continue to play an important role in drug delivery, particularly for proteins, for a number of reasons. First, an obvious case is for drugs with poor oral bioavailability. While alternative routes of administration such as pulmonary are evolving, parenteral administration has a significant history with well understood development times. Second, injections can allow a drug to be delivered right at the site of action, as in the case of local anesthesia. Third, most targeted delivery systems will be based on injectable formulations (e.g., immunoliposomes). Fourth, oral delivery is limited to 24-hour durations due to the normal transit time of the GI tract. Injectable controlled-release formulations will continue to play a major role for delivery over a period of days, weeks, or even months. Fifth, injections are often the only practical route of delivery in many animal health applications. Finally, there are a number of conditions where oral administration is contraindicated (e.g., presurgery, patients with nausea, unconscious patients, etc.).

Of the above factors, the need for controlled release is clearly of greatest significance when looking toward the future. The market potential for proteins alone is exemplified by PEGylation, the covalent attachment of polyethylene glycol to a protein drug. The worldwide sales of the top three

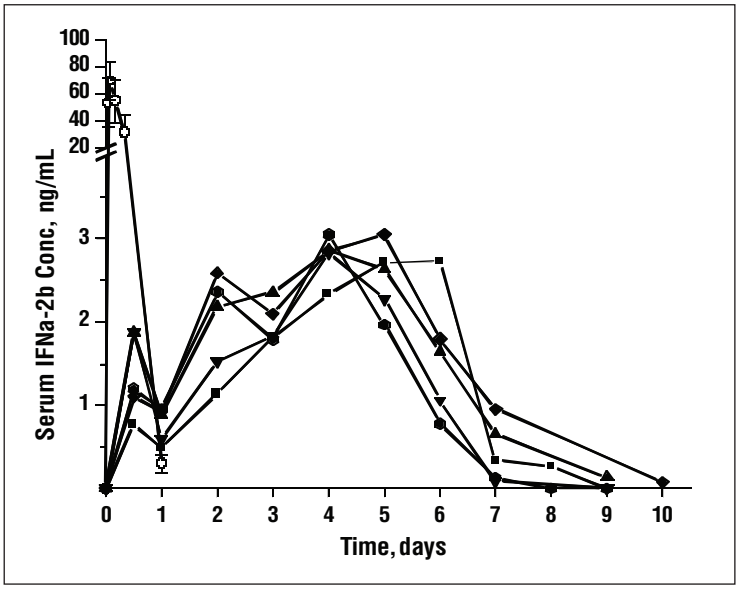

Figure 2. Plasma pharmacokinetics of IFNα–2B in rats following subcutaneous administration of DepoFoam-encapsulated IFNα–2B (160 mcg dose, closed symbols) and unencapsulated IFNα–2B (100 mcg dose, open circles).[21]

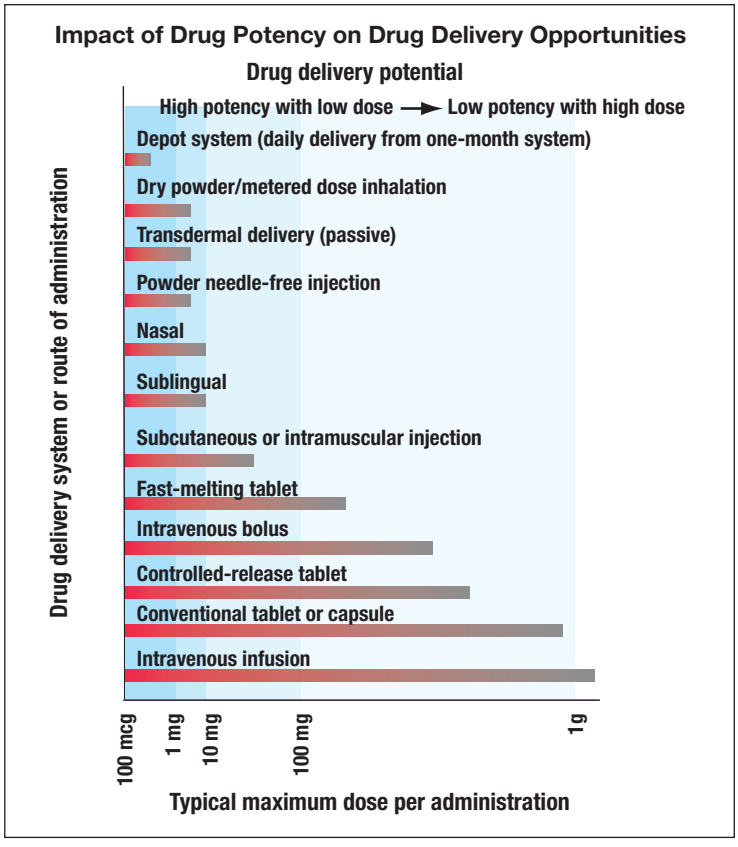

Figure 3. Typical doses which can be administered by various routes of administration.[23]

PEGylated products (Neulasta, Pegasys, and Peg-Intron) was over $3 billion in 2004.

While PEGylation and related technologies provide prolonged circulation time for a protein, there are a number of drawbacks: Manufacturing yields can be low, affecting the cost of goods; bioactivity can be significantly reduced; distribution in the body can be adversely affected; and of course the protein itself is modified, complicating safety and regulatory assessment.[19,20] For these reasons, there is much activity in injectable controlled-release formulation technologies that deliver a protein without covalent modification. Such controlled-release approaches include biodegradable microspheres, in-situ gelling systems, and multivesicular liposomes, all of which have been used in marketed products. An example of prolonged delivery of interferon-alpha using DepoFoam multivesicular liposomes is shown in Figure 2.[21] These technologies hold significant promise for the future.

For self-administration by patients, injections have three major drawbacks. First, many patients fear needles. Previous advances in needle technology have produced narrow gauge needles which significantly reduce the sensation of the injection. Pens that hide the needle, needle-less jet injectors such as the Biojector, and micro-needle systems[22] that deliver solutions through a platform of miniature needles will further help address this issue. Second, patient administration will continue to be limited to subcutaneous injections in order to avoid inadvertent intravenous administration. This leads to the third limitation, the limited volume which can be delivered by the subcutaneous route (typically 0.5–1 mL).

Horspool and Lipinski have reviewed the various routes of administration and the doses that can be delivered by each.[23] With the exception of intravenous and oral delivery, subcutaneous delivery has the potential to administer more drug than nearly any other route of administration. Nonetheless, the limited volume which can be given by the subcutaneous route can be problematic. Halozyme Therapeutics, Inc., has introduced a recombinant hyaluronidase that temporarily hydrolyzes the connective tissue in the subcutaneous space, thereby increasing the practical subcutaneous injection volume.[24] Once further established, this approach has the potential to significantly increase the number of drugs that can be self-administered by injection.

NANO- AND MICRO-TECHNOLOGY

Much has been written regarding miniaturized devices that will impact the future of medicine. Smart nanotubes have been envisioned that encapsulate drug and then open up to deliver a drug in a particular location in response to a stimulus.[25] Microprocessors will be able to deliver drug at predetermined times from tiny devices with multiple reservoirs.[26] The possibilities seem endless.

It can be argued that nanotechnology has already affected drug delivery. Submicron particles of poorly soluble drugs are currently being used to "solubilize" drugs to enhance oral bioavailability. Three products using such technology are on the market with sales of over $1 billion: Tricor (fenofibrate) tablets, Rapamune (sirolimus) tablets, and Emend (aprepitant) capsules. The approach will likely be used for injectable suspensions as well.

NONVIRAL GENE DELIVERY

The number of gene-therapy clinical trials that have been conducted is now over 1,000.[27] However, success to date is fairly limited. Significant challenges exist for gene delivery systems, including avoiding the immune system and efficiently transferring the gene to the nucleus of the target cell. If an efficient delivery system for gene delivery can be developed, it has the potential to revolutionize treatment paradigms, particularly for inherited, malignant, and infectious diseases.

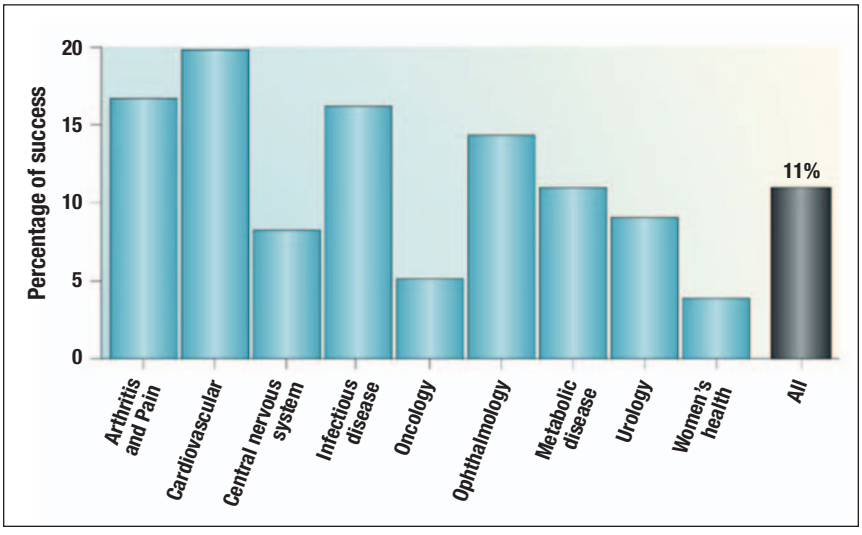

Figure 4. Success rates for drugs in various therapeutic areas.[33]

VACCINE ADJUVANT/DELIVERY SYSTEMS

The visibility of vaccines has significantly increased due to efforts to combat bioterrorism, drug-resistant bacteria, cancer, and viral diseases. Advances in today's vaccines include the use of recombinant proteins, DNA, and genetically-modified toxins.While aluminum hydroxide remains one of the most-used adjuvants for injectable vaccines, new adjuvant systems such as the saponin QS-21, and MF-59, a squalene-based emulsion, are now available.

Better adjuvants coupled with efficient delivery systems have the potential to enhance the effectiveness of vaccines.[28–30] This is particularly critical in the case of cancer vaccines. Not only are patients often immunocompromised, but tumor antigens are often poorly immunogenic, and tumor escape mechanisms exist (e.g., secretion of suppressive cytokines).[31,32] Thus, adjuvants for cancer vaccines may need to be more toxic than prophylactic adjuvants. The ideal vaccine delivery system would not only intensify the immune response, but would also provide an optimized exposure profile (e.g., prolonged or pulsatile release).

DRUG TARGETING

Kola and Landis reviewed success rates over the last decade for various classes of compounds gaining approval after having reached initial clinical trials.[33] Drugs for oncology and central nervous system (CNS) diseases have two of the lower success rates (less than 10%, as shown in Figure 4). While there are a number of factors involved, the failures in drug delivery to tumors and the CNS can be attributed at least partly to the drugs not reaching the target efficiently.

Treating cancer has long been aimed at selectively targeting the tumor while sparing normal tissue. Two approaches to cancer targeting are physical methods and specific binding. Enhanced permeability and retention is an example of physical targeting. Tumor vasculature is generally leakier than normal vasculature, allowing particles such as liposomes and macromolecules to extravasate and reach the tumor in higher concentrations than in normal tissue.[34,35] Accumulation at the desired site is further enhanced because lymphatic vessels do not form in tumors, so that the extracellular material is not drained as in normal tissue.

Antibody-based therapeutics, such as Herceptin and antibody-conjugated delivery systems, are examples of specific binding targeting. Recent advances in humanized antibodies have facilitated advances in this area.[36] The use of specific antibodies to treat patient subpopulations is a key area in personalized medicine.[37] By attaching nanoparticles or liposomes to antibodies, it is possible to specifically target the dose to the appropriate site of action.[38, 39]

DELIVERY ACROSS THE BLOOD BRAIN BARRIER

It seems appropriate to end by discussing drug delivery to that most complex of organs, the brain. As noted above, success rates for CNS

drugs have been low. In contrast to tumor vasculature, the capillaries of the the blood-brain barrier (BBB) are characterized by tightly packed endothelial cells held firm by tight junctions.[40] In general, this limits passive diffusion to small, highly lipophilic molecules. Even if a drug can permeate the membrane, the BBB has effective efflux mechanisms. Due to these restrictions, nearly 100% of large-molecule and greater than 98% of small-molecule drugs do not cross the BBB.[41]

Approaches to BBB delivery include using lipophilic pro-drugs, carrier-mediated transport, inhibition of efflux transporters, and receptor-mediated transport.[41] Given the importance of the CNS area, advances in BBB delivery should have significant impacts on the practice of medicine. ◆

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