Drug delivery trends for parenteral therapeutics

Drug delivery technologies for reformulation of parenteral therapeutics has received a lot of attention in recent years, due to significant advances in the field. There is a growing need for patient compliant dosage forms within the cancer therapeutics and biotechnology areas. Besides patient compliance, ease of administration, enhanced therapeutic efficacy, and reduced side effects, are additional factors that differentiate drug delivery products from conventional dosage forms, thus providing a competitive advantage.

This article reviews some salient trends in the parenteral drug delivery sector, within the realms of a changing regulatory environment. Drivers to growth as well as recent advances in this field have been reviewed. Finally, challenges associated with bringing parenteral drug delivery concepts to commercialization have also been discussed.

key words: parenteral drug delivery, protein delivery, lifecycle management, microspheres, nanoparticles

The global pharmaceutical industry has grown at an average rate of 7~12% over the past several years, with the global market estimated at approximately 550 billion dollars. In order to sustain this growth rate, pharmaceutical companies are constantly under pressure to maintain a rich pipeline of drugs. The drug development process, however, has become extremely expensive and time consuming. Currently it is estimated that the average cost of developing a new molecular entity exceeds one billion dollars. New molecular entities are being subject to higher regulatory scrutiny as is evident from recent recalls of high profile drugs such as Vioxx and Bextra. The biggest financial threat for the pharmaceutical industry is from the surge of generic drugs. When a drug patent expires, it is not unusual for sales to decline as much as 90%, due to the competition from lower priced generic drugs. The pharmaceutical industry is facing patent expiration of several blockbuster drugs, with close to $70 billion of sales being at risk in the next five years.

In this backdrop, pharmaceutical companies are facing the unique challenge of maintaining a healthy pipeline, while managing the drug development costs, and discouraging generic competition. This is often achieved by the innovator company via lifecycle management of drugs. Drug delivery technologies offer a viable option for pharmaceutical companies to maintain a healthy drug pipeline and effectively manage the lifecycle of a drug. Drug delivery products typically require lesser development time and costs. Such products may also extend the patent life of original drugs, and hence serve as a lifecycle management tool to counter generic competition. Additionally, as depicted in Fig. 1, drug delivery-based products can leverage existing safety profiles (when the active ingredient has an established safety profile), improve patient compliance and provide technology to reduce medication errors. Furthermore, drug delivery technologies can be used for new chemical entities, enabling them to be formulated in spite of challenging pharmaceutical properties.

Alza Corporation, founded in 1968, was perhaps
one of the earliest, true drug delivery company. The company started working on oral drug delivery concepts (OROS), as well as controlled release implants and transdermal systems (D-TRANS). A few additional companies such as Elan and R.P. Scherer (now part of Cardinal Healthcare) also focused, mainly on oral drug delivery. The commercial potential of drug delivery technologies however came to lime light with highly successful products approved in the late 1980s and 90s including Lupron depot and Cardizem. These products highlighted the power of drug delivery, in adopting an existing drug, and significantly expanding its appeal by enhanced patient compliance. For Lupron depot, this involved converting a once-daily injection to a monthly, sustained release formulation, and for Cardizem, multiple to once a day pill. As pharmaceutical companies took notice of this concept, a whole new segment of companies was formed, focusing primarily on novel drug delivery technologies. Drug delivery companies serve the advanced formulation needs of innovator pharmaceutical companies. At the same time, these drug delivery companies have now evolved to become specialty pharmaceutical companies, by taking generic drugs and reformulating them to enhance value (an example of this is Anesta, a drug delivery company that reformulated fentanyl into an oramucosal formula-
tion for pain management).

In the past twenty years, drug delivery technologies and the specialty companies developing such technologies have gone through significant changes. Drug delivery technologies have been attributed to the commercial success of a number of drugs. At the same time, a number of drug delivery companies have had to terminate programs at various stages of development due to failures or significant challenges. Oral drug delivery technologies can be considered to be at a matured phase, with such technologies now being used fairly routinely by pharmaceutical companies for lifecycle management. Drug delivery for parenteral drugs however has significant room for growth, although, the associated challenges are more pronounced. This article examines the current trends and future directions for drug delivery technologies.
delivery technologies, with a specific emphasis on parenteral therapeutics.

Current trends-drivers for parenteral drug delivery

Parenteral drug delivery technologies have roots in transdermal delivery patches that were first developed by Alza Corporation. The first commercial transdermal patch, Transderm Scop (scopolamine), was approved FDA in 1981. The same passive transdermal technology was also responsible for development of the most successful parenteral drug delivery product, Duragesic, which had peak sales of $2.1 billion in 2004. In recent years, parenteral therapeutics have experienced significant growth (Fig. 2). According to some estimates, the parenteral therapeutics market will outpace oral drug market. This growth has been primarily driven by biotechnology products and novel therapies for cancer, most of which are administered via the parenteral route.

1. Biotechnology products

The biotech industry has matured in recent years, leading to a number of breakthrough products. Several first-in-class biotechnology products have been approved in the last few years. For example, in 2006, the Food and Drug Administration approved the use of Rituxan (rituximab) for the treatment of rheumatoid arthritis. Rituxan has a unique mechanism of action, via targeting of B-Cells (as compared to the conventional tumor necrosis factor (TNF) antagonist therapies). In another example, in 2003, Xolair became the first humanized therapeutic antibody for the treatment of asthma and the first approved therapy designed to target the antibody IgE, a key underlying cause of the symptoms of asthma that has an allergic component. Similarly, in 2004, the FDA approved Erbitux, the first monoclonal antibody for the treatment of colorectal cancer. Erbitux is a chimeric antibody that works by specifically blocking epidermal growth factor receptor (EGFR) protein, which is overexpressed in cancer cells. Specific drugs such as these are capable of action without the side effects commonly associated with nonspecific small molecule treatments.

Currently, biotech products account for close to $50 billion in annual sales. As can be seen in Fig. 3, biotechnology-based products account for majority of parenteral drugs that are in clinical trials. Hence this number is expected to keep growing at a rate higher than the average pharmaceutical industry. Furthermore, till recently no generic pathway existed for biotech drugs.
Tab. 1 List of injectable products containing cyclodextrins
(Thompson DO et al., 2002)\textsuperscript{11}

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Route of administration</th>
<th>Cyclodextrin</th>
<th>Approa regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporanox</td>
<td>Itraconazole</td>
<td>Intravenous</td>
<td>Hydroxypropyl-β-cyclodextrin</td>
<td>Europe, USA</td>
</tr>
<tr>
<td>Vfend</td>
<td>Voriconazole</td>
<td>Intravenous</td>
<td>Sulfobutylether cyclodextrin</td>
<td>Europe, Japan, USA</td>
</tr>
<tr>
<td>Geodon</td>
<td>Ziprasidone</td>
<td>Intramuscular</td>
<td>Sulfobutylether cyclodextrin</td>
<td>Europe, USA</td>
</tr>
<tr>
<td>Prostain</td>
<td>PGE-Alprostadil</td>
<td>Intravenous</td>
<td>α-cyclodextrin</td>
<td>Europe, Japan, USA</td>
</tr>
</tbody>
</table>

Tab. 2 Examples of lipid-based products approved by FDA

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Drug</th>
<th>Technology</th>
<th>Targeting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxil</td>
<td>Johnson and Johnson</td>
<td>Doxorubicin</td>
<td>Stealth Liposomes</td>
<td>Passive tumor targeting</td>
</tr>
<tr>
<td>DaunoXome</td>
<td>Gilead</td>
<td>Daunorubicin</td>
<td>Liposomal</td>
<td>Macrophage uptake</td>
</tr>
<tr>
<td>DepoCyt</td>
<td>Skye Pharma</td>
<td>Cytarabine</td>
<td>Depofoam</td>
<td>None (Subcutaneous injection)</td>
</tr>
<tr>
<td>Myocet</td>
<td>Élan</td>
<td>Doxorubicin</td>
<td>Lipid complex</td>
<td>Macrophage uptake</td>
</tr>
<tr>
<td>Ambisome</td>
<td>Gilead</td>
<td>Amphotericin</td>
<td>Liposomal</td>
<td>Macrophage uptake</td>
</tr>
</tbody>
</table>

within the Food and Drug Administration. Hence the revenue stream generated by biotech drugs has sustained even beyond patent expiration. A number of marketed recombinant proteins, such as insulin and human growth hormone, continue to be successful even though their patents have long expired. This is expected to change, as biosimilar proteins are submitted to regulatory agencies for approval. Omnitrope, a biogeneric version of human growth hormone was approved for marketing in Australia, Europe and most recently in USA. Advent of such biogenerics will apply pose a challenge for biotech companies, driving a need for differentiated products.

At present most of biotech products are administered as injections. Due to the short half-life of proteins, a number of these molecules require injection on a frequent basis. These molecules hence serve as ideal candidates for drug delivery, where the frequency of injections could be reduced. Noninvasive routes of administration for systemic delivery of proteins have seen significant advances—the first inhaled insulin product, Exubera, was approved by FDA in 2006. A number of active transdermal technologies are also being explored for the systemic delivery of proteins.

2. Novel treatments for cancer

The second driver for parenteral sector is the novel treatments for treatment and management of cancer. These therapeutics include chemotherapeutic drugs as well as drugs to manage side effects of chemotherapy, including pain and nausea. Application of drug delivery technologies has been very successful for conventional drugs, as seen with transdermal delivery of fentanyl (Duragesic, for pain management), and sustained release formulations of leuprolide (Lupron depot, Eligard, for the treatment of prostate cancer). New molecules approved for chemotherapy in recent years include Alimta (pemetrexed), approved in 2004 for the treatment of non-small cell lung cancer, Vidaza, approved in 2004 for the treatment of myelodysplastic syndrome, and Velcade, approved
in 2003 for the treatment of refractory multiple myeloma. All these molecules are administered as injections and could significantly benefit from enhanced solubilization, stabilization and targeting technologies.

Drug delivery technologies for parenteral therapeutics can be sub-classified into two broad categories: (1) Formulation-based technologies; and (2) Device-based technologies.

**Formulation-based technologies**

As depicted in Fig. 1, drug delivery technologies can be exploited to reformulate existing molecules or enable formulation of difficult discovery molecules. Drug delivery technologies have also been used to impart targeting functionality to small molecule drugs. Advances in nanotechnology have opened additional opportunities to further exploit targeting opportunities. Technologies that address some of the most prevalent formulation challenges have been discussed below. The current trends in targeted drug delivery have also been reviewed in the section below.

1. **Formulation of poorly soluble drugs**
   
   Since early drug candidate screening does not differentiate compounds based on their solubility, there is an increasing bias towards lipophilic (and consequently poorly soluble) molecules entering/progressing through the drug development pipeline. Indeed, greater than 40% of drugs in recent years have been classified as poorly soluble. A number of drug delivery technologies have emerged to address this need within the pharmaceutical industry. Multiple oral drug delivery based products have reached the market in spite of their poor solubility. Within the parenteral space, cyclodextrins and nanoparticles represent two key approaches to formulate poorly soluble drugs. As seen in Tab. 1, a number of injectable formulations utilizing cyclodextrins for solubilization have been approved in US, Japan, and Europe.

   ![Table 3: Examples of polymer microsphere products approved by FDA](image)

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Drug</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupron Depot</td>
<td>TAP</td>
<td>Leuprolide</td>
<td>PLA</td>
</tr>
<tr>
<td>Zoladex</td>
<td>AstraZeneca</td>
<td>Goserelin</td>
<td>PLA</td>
</tr>
<tr>
<td>Trexima Depot</td>
<td>Debi RP</td>
<td>Triptolide</td>
<td>PLGA</td>
</tr>
<tr>
<td>Gliadel</td>
<td>MGI Pharma</td>
<td>BCNU</td>
<td>Polyanhydride</td>
</tr>
<tr>
<td>Sandostatin LAR</td>
<td>Novartis</td>
<td>Octreotide</td>
<td>PLGA-glucose</td>
</tr>
<tr>
<td>Eligard</td>
<td>QLT Therapeutics</td>
<td>Leuprolide</td>
<td>PLGA</td>
</tr>
</tbody>
</table>

If a drug is not suitable for complexation with cyclodextrins, other formulation approaches are sought. As listed in Tab. 2, liposomal technologies have resulted in more than five products that have been FDA approved. Advances in nanotechnology have led to several drug delivery platforms that are specifically designed for formulation of poorly soluble drugs, as injectable nanoparticles. A nanoparticulate technology was used in development of Abraxane, a novel formulation of paclitaxel that does not contain Cremophor EL, a toxic excipient known to cause hypersensitivity reactions. By using a nanoparticulate formulation, the drug could be infused at a higher rate, without any need for premedication, and with a higher maximum tolerated dose.

2. **Targeted drug delivery**

   Concepts in active and passive targeting have been explored for the past several years, with the aid of liposomal drug formulations. Conventional liposomes, when injected intravenously are taken up by the reticuloendothelial system. Such dosage forms can thus be used to target macrophage residing and propagating disorders. In recent years the concept of macrophage targeting has been further exploited using nanoparticles, which can provide a significantly higher drug payload as well as delivering the drug in its crystalline form, allowing sustained release at and from the macrophages.

   Tumor targeting for chemotherapeutic agents is desirable to enhance the efficacy of the drug.
while reducing systemic toxicity. An enhanced permeability and retention (EPR) effect was exploited for passive targeting of doxorubicin to tumors, in a product Doxil, marketed by Johnson and Johnson\(^{(15)}\). Passive targeting via the EPR effect has also been utilized by polymer–drug conjugates\(^{(14)}\). Styrene maleic acid-conjugated neocarzinostatin, or SMANCS is an example of an approved product based on the polymer–drug conjugation targeting approach\(^{(15)}\).

### 3. High concentration protein formulations

Recent advances in protein research has led to a large number of monoclonal antibodies that are now being tested in the clinic. These monoclonal antibodies have high plasma circulation half lives in the order of several days. Furthermore a number of monoclonal antibodies demonstrate stability to proteolytic enzymes present in subcutaneous space, providing an opportunity to administer such therapeutics via the subcutaneous route. Subcutaneous injections allow reduction of frequency of injections, and also the convenience of self-administration. However the volume that can be administered subcutaneously is typically limited to less than 1 mL, whereas the desired therapeutic dose may range from 100~800 mg. Hence in recent years there has been an interest in developing novel approaches to formulate monoclonal antibodies at high concentration (100 ~800 mg/mL). Challenges for high concentration protein formulations include lack of syringeability due to high viscosity, and self-association effects of the protein\(^{(16)}\). Monoclonal antibodies could be formulated with certain excipients (such as histidine) that in certain cases reduce viscosity of solutions\(^{(17)}\). Novel formulation concepts such as protein crystals and suspensions are also being explored to formulating high concentration monoclonal antibodies without compromising syringeability of the formulation\(^{(18)}\).

### 4. Sustained circulation/release (reduced frequency of injections)

Sustained release was the basis for some of the early breakthrough research and development in parenteral drug delivery. Use of biodegradable polymers has led to a number of highly successful products, some of which are listed in Tab. 3. Polymeric drug delivery has recently been revived by the needs in the medical device industry, for local delivery of medication to reduce restenosis (discussed in further detail in a subsequent section).

For protein drugs, PEGylation has been used to enhance circulation half-life and thereby reduce frequency of injections. In the case of interferon–alfa, the half-life of the protein increases from three to five hours for the native protein, to 30~50 hours for the protein conjugated with polyethylene glycol\(^{(19)}\). The technology has resulted in six FDA approved products. Early stage PEGylation involved non-specific conjugation of the protein...
with linear poly(ethylene glycol) chains. The product was typically heterogeneous with higher propensity towards activity loss. In recent years, a number of novel concepts have been introduced in the field of PEGylation. For instance, use of branched poly(ethylene glycol) was shown to increase circulation half-life as compared to the linear version. Site-specific PEGylation has been achieved via the use of mutagenesis techniques, resulting in homogeneous product with retention of bioactivity.$^{20}$

**Device-based technologies**

Medical devices and drug administration have come closer in recent years due to advances in drug delivery technologies. To address the growing demand of such highly specialized technologies, the Food and Drug Administration created an Office of Combination Products in December 2002. A number of products classified as combination products have been approved by this office (see Tab. 4), and several others are in development.

Device-based drug delivery technologies are generally developed for one of the following reasons:

1. To reduce invasiveness of the therapy (for e.g. switching from injections to inhalation)
2. To reduce potential for administration errors (for e.g. prefilled syringes)$^{21}$
3. To prevent needle–stick injuries (for e.g. needle-free devices)
4. To provide added therapeutic value (for e.g. drug eluting stents, where the drug reduces inflammation at site of implantation)

Device technologies offer significant promise in a number of areas for parenteral drugs. For instance injection devices can be used to accurately administer intradermal injections that may lead to enhanced vaccine performance. Injection devices are also useful for intramuscular administration of drugs in an emergency setting, and have found applications for biodefense and anaphylaxis treatments$^{20}$. Injection devices may also find applications to address formulation challenges such as for the delivery of highly concentrated protein solutions.

Inhaled insulin could change the paradigm of diabetes treatment by eliminating the need for daily injections. The first inhaled insulin product (Exubera) recently won FDA approval. This has paved the way for a number of other inhaled insulin products that promise even further convenience and product performance. Inhaled insulin products that are currently in the clinic include Novo Nordisk and Aradigm’s liquid formulation of insulin for inhalation, Eli Lilly and Alkermes’ porous dry powder formulation, and Baxter Healthcare’s uniform insulin microspheres (Promaxx—see Fig. 4)$^{20}$. Commercial success of inhaled insulin could also lead to systemic delivery of other therapeutic proteins.

Interaction between the drug and container is an important component of a combination product. Leachables from the container may cause unexpected side reactions or adverse stability concerns for the drug product. Hence drug–excipient–container compatibility considerations should be
addressed upfront during formulation development, and stability studies should be carefully designed to explore these factors. Drug-container interactions have received higher amount of attention in recent times, after the concerns observed for an erythropoietin product in prefilled syringe (Eprex), which resulted in increased occurrence of pure red cell aplasia (PRCA)\textsuperscript{[26]}. Another area of research has been the effect of silicone leachables from glass prefilled syringe in stability of protein formulations in such syringes\textsuperscript{[25,26]}. While both these examples refer to formulation concepts (as opposed to devices or combination products), it is anticipated that similar considerations should be explored for combination products.

For combination products, the biggest impact has been provided by drug eluting stents. Currently there are two FDA-approved drug eluting stents in the market-Cypher (Johnson and Johnson) and Taxus (Boston Scientific). These drug eluting stents release drugs locally at the implantation site, preventing inflammation and thereby reducing the occurrence of restenosis. This concept is expected to have applicability in other areas of medical devices as well. For example, clinical studies are already ongoing for use of drug eluting vascular grafts for use during coronary bypass surgeries\textsuperscript{[27]}.

A number of advanced technology concepts are being explored in the device area. One such concept is the use of combination coatings, where multiple polymers are combined to provide a tailored release profile for one or more drugs\textsuperscript{[28]}. Another concept is the use of biodegradable polymers as materials for medical devices or their coatings. An example of this is the use of lactide and caprolactone–based polymers as biodegradable stents\textsuperscript{[29]}. Other device concepts that have received attention in drug delivery include development of better, improved inhalation and nasal devices for effective delivery\textsuperscript{[30]}, use of microarray needles for intradermal delivery of drugs and vaccines\textsuperscript{[31]}, and development of single–use, prefilled needle–free injector devices\textsuperscript{[32]}.

**Use of formulation and device technologies for effective lifecycle management**

The above described formulation and device technologies can be used in tandem towards a very effective strategy for lifecycle management. An example of this concept is seen for Roche’s interferon–alfa product. As depicted in Fig. 5, Roferon was first introduced in the market in 1986 as a lyophilized powder of the protein, containing human serum albumin as a stabilizer\textsuperscript{[33]}. Subsequent generations of the product included a solution formulation without human serum albumin, use of prefilled syringe devices, and subsequently use of branched poly(ethylene glycol) for extension of circulatory half-life of the protein (PEGasys). Most recently, in 2004, the PEGylated protein was presented in a prefilled syringe format for enhanced convenience to the patient.

**Challenges for drug development**

The challenges faced in development of parenteral drugs formulated using drug delivery technologies can be broadly classified into manufacturing related, product performance related or regulatory related.

Manufacturing: Typically drug delivery technologies involve more complex manufacturing steps as compared to conventional dosage forms. This
increased complexity can lead to the following issues:

- Scale-up: A number of drug delivery technologies have been conceptualized in an academic setting. Scaling up the complex processes to pilot or production scales can provide challenges.
- Drug stability (for example, maintenance of protein activity during encapsulation into polymer microspheres)
- Producing consistent quality product
- Sterility (for example, protein microspheres cannot be terminal sterilized and have to be produced in an aseptic manner)

Product performance: Drug delivery products are designed to provide enhancement over existing products. Hence clinical studies are typically designed with a control arm of the existing product. This presents a challenge, especially when the drug delivery concept is intended for enhancement in quality of life, rather than efficacy. For such situations, designing a clinical trial that captures and quantifies such product features is important. In the device category, consistent performance of the device in terms of dose delivery is of paramount importance towards the success of the device.

Regulatory related: Novel parenteral dosage forms present regulatory challenges, since the dosage forms are unique, and hence testing methodologies may not be well developed. The safety profile of novel dosage forms may also be unique, requiring additional testing to convince the agency of the safety of the product.

The FDA is responding to this challenge by issuing guidance for testing of various novel dosage forms (for example, liposomes, as well as novel excipients used in formulations). Furthermore, the agency has facilitated discussions between FDA, USP, and the industry for testing of complex dosage forms, such as parenteral sustained release products.

Opportunities and future directions

As mentioned in this article, parenteral, and especially biotech drugs serve as ideally suitable candidates for drug delivery technologies. Success of next generation biotech molecules, such as DNA-based drugs as well as small interfering RNA molecules (siRNA), depends on the effectiveness by which such molecules are delivered to the desired site of action. In the protein delivery area, there is a need for novel technologies to deliver high dose monoclonal antibodies to the subcutaneous space. Noninvasive technologies (inhalation, transdermal) are also advancing rapidly towards reality. These technologies utilize breakthroughs in both the formulation and device areas to provide non-invasive routes of drug administration. The recent approval of Exubera for pulmonary delivery of insulin provides a showcase of how novel formulation and device technologies can be combined to produce a product that shifts the paradigm of conventional therapy.

It is important to understand that development of parenteral drug delivery products requires a detailed understanding and integration of experience in several core technical competencies associated with parenteral science. These include formulation science, manufacturing, and sterilization expertise as well as a clear understanding of regulatory requirements. These traditional concepts of parenteral science are required to be fully integrated in the development of novel drug delivery technologies. Since a number of drug delivery technologies employ complex processing steps, and/or novel dosage forms, product development becomes challenging. Having a product with consistent quality through the various stages of development is essential to avoid product delays in market introductions.

References

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