Delivery Systems

For over a decade, the search has been on to find ways of intervening in disease processes by delivering drugs to the body at a sustained rate, directly to the site of action, with low toxicity and in a disease-specific manner. Effective drugs have been made available and, in some cases, are being used extensively – but only with attendant toxicity and side effects, particularly in the area of cancer. Systems for targeting drugs – that is, for guiding molecules such as antibodies to their required site of action – have been developed over the past two decades, and the missing component to date has been the optimum carrier of the therapeutic reagent. This is the role for the nanoparticle – or, to be more accurate, the myriad of nanoparticle and nanoshell types that are being developed for a wide range of applications.

NANOTECHNOLOGY AND NANOPARTICLES

The definition of ‘nanotechnology’ which is most commonly adhered to is ‘materials considered to have dimensions of between 1 and 100 nanometers, with those materials having unique or unusual properties different from those of bulk materials of the same composition because of their size and surface phenomena.’ However, in many cases, nanoparticles are considered to be any sub-micron sized particles. Let us first consider the key advantages that we wish nanotechnology in general and nanoparticles in particular to bring to drug delivery. Of course, these must include the holy grails of, i) improving drug bioavailability through enhancing aqueous solubility, ii) increasing the residence time in the body (increasing the half-life for clearance/increasing specificity for its cognate receptor), and iii) targeting the drug to a specific location in the body (its site of action). This results in a concomitant reduction in the quantity of drug required and dosage toxicity, enabling the safe delivery of toxic therapeutic drugs, and protection of non-target tissues and cells from severe side effects.

NANOCRYSTALS

Nanoparticles in their simplest form are made by milling the drug, followed by delivery via the traditional routes of administration. If a drug is poorly water soluble, then this correlates with a slow dissolution rate; by decreasing particle size, the surface area is increased, leading to an increase in dissolution rate. An example of this is Elan’s NanoCrystal® technology. NanoCrystal® particles are small particles of drug substance produced by milling the drug substance using a proprietary, wet-milling technique. The particles are then stabilised against agglomeration by surface adsorption of selected ‘generally regarded as safe’ (GRAS) stabilisers. The result is an aqueous dispersion of the drug that behaves like a solution – a NanoCrystal Colloidal Dispersion™ – which can then be processed into finished dosage forms for all routes of administration.

The first product incorporating NanoCrystal technology to receive US FDA approval was Wyeth’s solid-dose formulation of the immunosuppressant Rapamune® (sirolimus), approved in August 2000; previously, the product was only available as an oral solution in bottles or sachets. Other examples include: Merck’s Emend® (aprepitant, MK 869), approved by the FDA in March 2003 and developed as an NCE in a NanoCrystal formulation; Abbott’s TriCor® (fenofibrate) launched in the US in December 2004 and providing the benefits of
a simplified, flexible dosing regime; and Par Pharmaceutical’s Megace® ES (megestrol) which enabled the dosage of drug to be reduced to one-quarter of the volume of the original product.

**NANOPARTICLE ENCAPSULATED DRUGS**

For toxic or easily degradable drugs, encapsulation provides an advantage and – in some cases – an absolutely obligatory barrier. A recent example is Abraxane (Abraxis Bioscience, Inc) – an albumin nanoparticle conjugate of paclitaxel for the treatment of breast cancer that takes advantage of albumin – a protein that acts as the body’s key transporter of nutrients and other water-insoluble molecules, and selectively accumulates in tumour tissues. Abraxane is the first FDA-approved anticancer agent in this emerging class of drug formulations.

Coatings which dissolve under specific physiological conditions can also facilitate the uptake of materials that would otherwise have poor bioavailability. There are relatively few commercial products which use this technology at the present time, although enteric or pH-sensitive coatings are used for the delayed release of drugs – usually within the alkaline environment of the colon. Liposome and micelle-based encapsulation techniques are frequently described in the literature for intracellular drug delivery and cancer therapeutics; these have not yet, however, been successfully commercialised. The Australian-based company SIRT eX is developing a Selective Internal Radiation Therapy product, SIR-Spheres, based on this type of system; yttrium-90 loaded microspheres are passively targeted to liver tumours where, due to their size, they become lodged in the tumour vasculature, leaking into the interstitial space and thereby entering the bulk of the tumour tissue.

The inherent size of nanoparticles facilitates their intracellular uptake, enabling drug delivery in situations where technology at the micro scale is challenging. Ongoing research activities in this area include the work of Professor Frank Caruso at the University of Melbourne, which involves the loading of mesoporous silica beads with biological compounds such as enzymes and other macromolecules; these are then released as a result of either the biodegradation or rupture of the polymeric shells.

Nanoparticle-based drug delivery approaches also have the potential for rendering hydrophobic compounds dispersible in aqueous media, close to or at the site of action, thus circumventing the pitfalls of poor solubility. For example, an encapsulated formulation of the medical agent curcumin – nanocurcumin – utilises the micellar aggregates of cross-linked and random copolymers, giving a narrow size distribution in the 50nm range. Unlike free curcumin, the encapsulated form is readily dispersed in aqueous media, while maintaining comparable activity against a panel of human pancreatic cancer cell lines.

**NANOSHELLS AS DELIVERY VEHICLES**

Metallic nanoshells are a new class of nanoparticles with tunable optical resonances that strongly absorb light in the near infrared (NIR), where optical transmission through tissue is optimal. The nanoshells are used to deliver a therapeutic dose of heat by using moderately low exposures of externally applied NIR light. This has been demonstrated in human breast carcinoma cells incubated with nanoshells *in vitro* on exposure to NIR light. Likewise, *in vivo* studies using magnetic resonance guidance revealed that exposure to low doses of NIR light in solid tumours treated with metal nanoshells reached average maximum temperatures capable of inducing irreversible tissue damage within four to six minutes.

The systemic administration of chemotherapeutic agents results in indiscriminate drug distribution and severe toxicity. Nanoshells derived from 400nm bacterial minicells encapsulate the chemotherapeutic agent, thereby overcoming their side effects; cancer cell-specific targeting of minicells via antibodies to receptors on cancer cell membranes results in their uptake into only
these cells, followed by intracellular degradation of the nanoshell and drug release into the target cell. Animal studies have shown that only minute amounts of the chemotherapeutic agent are required to achieve an effect.

**DELIVERY OF siRNA**

By using targeted nanoparticles, researchers have demonstrated that systemically delivered small interfering RNA (siRNA) can slow the growth of tumours in mice without eliciting the toxicities often associated with cancer therapies. Researchers at the California Institute of Technology (Caltech) have incorporated siRNA into nanoparticles that are formed completely by self-assembly; the behaviour of these nanoparticles has been characterised and their safety and efficacy has been studied in mice. siRNA delivery via such nanoparticles was expected to enter Phase I clinical trials in late 2007. At the same time, the researchers discovered that, by attaching polymeric nanoparticles to the surface of red blood cells, the in vivo lifetime of the nanoparticles could be dramatically increased.

**BIOSILICA AS A DELIVERY MATERIAL**

Biosilica is gaining popularity as a delivery material with both academics and companies in the US (University of California, Los Angeles, UCLA) and Australia (pSivida Ltd). Researchers at UCLA have successfully manipulated nanomaterials to create a new drug delivery system that promises to solve the challenge of the poor water solubility of today’s most promising anticancer drugs, and thereby increase their effectiveness. The California NanoSystems Institute at UCLA in collaboration with the Jonsson Cancer Center have reported the use of mesoporous silica nanoparticles as a delivery system for hydrophobic cancer drugs such as camptothecin into human cancer cells. The results suggest that mesoporous silica nanoparticles might be used as a vehicle to overcome the insolubility problem of many anticancer drugs.

pSivida (Perth, Australia) has developed a nanostructured form of elemental silicon, known as BioSilicon™, which has been engineered to create a ‘honeycomb’ structure of pores. This structure allows silicon to biodegrade whilst also allowing the retention of various drugs and vaccines within the honeycomb matrix. In preclinical studies, BioSilicon™ has been shown to be both biocompatible and biodegradable, dissolving in body fluids into silicic acid, commonly found in everyday foods. pSivida’s core focus is the development of applications for controlled release drug delivery; other potential applications include diagnostics, orthopaedics, tissue engineering, ophthalmology and targeted cancer therapies. Its most advanced BioSilicon™ product, BrachySil™, delivers a therapeutic P32 directly to solid tumours and is currently in Phase II clinical trials for the treatment of pancreatic cancer.

**THE BLOOD BRAIN BARRIER – A SPECIAL CASE**

Significant effort worldwide is being focused on the delivery of therapeutic compounds across the blood brain barrier (BBB), looking in particular at whether nanotechnology and nanoparticles can facilitate this somewhat elusive process. Doxorubicin is a drug that is effective in the treatment of aggressive tumours; however, it has serious side effects and cannot effectively cross the blood brain barrier. NanoDel Technologies (Magdeburg, Germany) has developed a drug-loaded and coated nanoparticle process whereby doxorubicin is bound to the surface of polycyanacrylate nanoparticles and coated with a surfactant (polysorbate 80). Here, the nanoparticle is used to provide local high concentrations of the drug at a targeted site, as confirmed in studies in rats, which showed that intravenous injection of these particles resulted in enhanced (60x) concentrations of doxorubicin in the brain.

**MAGNETIC NANOPARTICLES**

The main advantages of magnetic nanoparticles are that they can be visualised by magnetic resonance imaging (MRI) due to their paramagnetic properties; they can be targeted in a location by use of a magnetic field and heated by the magnetic field to trigger drug release. Although magnetic nanoparticles can be used therapeutically as hyperthermia reagents, here we will only look at their function as magnetic vectors – directed to carry their payloads to a certain location by means of a magnetic field gradient.

Chemicell GmbH (Berlin, Germany) has achieved successful results in animal models using 50nm nanoparticles with a multi-domain magnetite core and a starch matrix coated in the anticancer drug doxorubicin. The limitation of penetration of the magnetic field to only 10-15cms into the body is overcome by implants of magnets. Para-magnetic nanoparticles are preferred in order to stop aggregation of the nanoparticles when the...
magnetic field is removed, and therefore need to be less than 50nm in diameter. Coating of the magnetic nanoparticles is important in increasing the half-life of clearance from blood; and this is usually done with biocompatible materials such as polyethylene glycol or biosilicone, which is also used to host the drug to be delivered.

After binding DNA segments to iron-containing nanoparticles, a magnetic field is used to direct the nanoparticles into arterial muscle cells, where the DNA could have a therapeutic effect. This may represent a new method for delivering gene therapies for the treatment of blood vessels damaged by arterial disease. The magnetically driven delivery system may also find broader use as a vehicle for delivering drugs, genes or cells to a target organ. The technology represents a novel delivery system, and the first to use a biodegradable, magnetically-driven polymer to achieve clinically relevant effects. Impregnated with iron oxide, the nanoparticles carry a surface coating of DNA bound to an organic compound called polyethylenimine (PEI). The PEI protects the DNA and prevents it from being broken down by enzymes present in the cell cultures and occurring naturally in the bloodstream.

**TRANSDERMAL DELIVERY**

The delivery of drugs across the outer layers of the skin via transdermal patches has been achievable for some time, the main commercial successes being products such as nicotine, and hormones for contraception and hormone replacement therapy. The limitations of these devices are, however, generally related to the size of the molecules that can be delivered. Only small molecules can traverse the outer layer of the skin, or stratum corneum, which comprises a 30-40 micron thick layer of dead skin cells acting as a natural protective barrier.

A number of approaches are being developed to deliver large biomolecules in a pain-free way. At NanoVic and Monash University Pharmacy College, polymeric patches are being developed which are structured on the skin side with microprotusions which hold the drugs to be delivered. When the patch is applied to the skin, these microprotusions cross the outer surface layer, reaching only as far as the interstitial space and thus avoiding nerves and blood vessels. In this interstitial space, the nanostructured drugs are released from the surface of the protrusions, and as the biocompatible polymer biodegrades, the drugs are released continuously from the body of the protrusions.

The nanostructured drugs are either taken up by the cells of the immune system (for vaccination applications) or flow through the interstitial fluid to other compartments in the body. The patches are intended for applications in human and animal health for delivering vaccines, proteins and peptides, peptide hormones and other drugs.

**PULMONARY DELIVERY**

The administration of medication by inhalation has been successfully exploited for a number of applications – primarily, for the delivery of anti-asthmatic drugs and hormones such as insulin. A number of systems have already been commercialised using this type of delivery system: companies looking to exploit this technology, in particular for insulin delivery, include Baxter Healthcare MannKind Corporation and Aradigm Corporation.

For the delivery of therapeutics to specific regions of the lung, it is crucial that the particle size is tightly controlled. At present, most commercial systems can deliver particles produced from dry powder in the micron-range to specific regions of the lungs; however, bioavailability can be limited due to the size, and hence surface area, of the particles. The use of nano-sized particles enables delivery to specific regions, and also increases bioavailability due to the increased surface area, enabling lower doses to be administered. Such a device is in development at Monash University (Melbourne, Australia), based on the production of particles by ‘surface acoustic wave’ or SAW technology. This will offer advantages such as dose-to-dose reproducibility, efficient delivery and flexible dosing.

**CONCLUSION**

There is a wide range of nanoparticulate materials and structures being developed for the delivery of therapeutic compounds. Each has its own particular advantages – but as these nanoparticles become optimised for their specific applications, the outcome will be better-controlled therapy as a result of targeted delivery of smaller amounts of effective drugs to the required sites in the body. This is being made possible through the use of advanced materials, improved control of particle size, and better understanding of the interface between the biological and material surfaces, and their effects in vivo.

The author can be contacted at bob.irving@nanovic.com.au