On Target

Nanoparticle-based carriers are gaining in popularity as a method of targeted drug delivery. The need to boost treatment efficacy and reduce side-effects makes this technology extremely attractive to researchers, but with little known about new risks posed to patients, a deeper understanding is crucial

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Targeted drug delivery – also referred to as smart drug delivery – is a method that aims to increase the drug concentration in the desired organ or tissues relative to others, thereby improving therapeutic efficacy and reducing adverse effects. A wide range of therapeutic indications, including oncology, autoimmune diseases, neurological disorders, cardiovascular diseases, pulmonary diseases and ocular conditions, require the safe, effective and specific targeting of certain receptors or direct drug delivery into the organ, making targeted drug delivery the need of the hour.

Delivery Vehicles

Drug delivery carriers are substances which act as vehicles carrying the actual drug, delivering it to the specified target organ within the body. Currently, liposomes and polymer-based carriers are the most widely used carriers, targeting insoluble drugs and sustained-release drugs respectively. Among liposomes, nanoliposomes, stimuli-responsive liposomes and conjugated liposomes are gaining increasing attention from researchers, while polymeric templates are being explored to develop artificial cells, such as platelets and biomimetic vehicles for targeted drug delivery.

Targeting peptides and nucleic acids for carrying drugs to the desired site has been a key area of research interest, as these particles are capable of delivering high drug payload. Although polyethylene glycol (PEG) has traditionally been in use for quite some time now, the development of polymeric nanomicelles and other co-polymers has witnessed increasing interest from researchers in recent years. Conjugates, including antibody conjugated liposomal carriers, multifunctional nanocarriers, and other particles that form conjugates with drugs, are also being extensively researched.

Nanoparticles

The concept of nanotechnology has become well-established in targeted drug delivery applications, particularly for cancer therapeutics, owing to the increased surface-to-mass ratio of nanoparticles, their quantum properties and ability to adsorb and carry a wide variety of compounds. Inorganic nanoparticles may be of chemical origin, such as particles made from silica, carbon, metal, metal hydroxides and so on, or those derived from biologic origin – for example phospholipids, lipids, dextran, lactic acid and chitosan.

The key benefits of nanoparticles that have led to its widespread use and research in drug delivery and diagnostics include the following:

- Nanosize of particles (> 100nm), which enables better and enhanced penetration of cells and various cellular components, including the nucleus
- Highly specific drug targeting and delivery without affecting the surrounding healthy tissues
- Reduced adverse effects, improved therapeutic benefits and better patient compliance
- Greater safety, biocompatibility and faster development of new, safe medicines

Currently, there are nearly 30 commercially available nano-based drug delivery systems on the market, spanning a wide range of therapeutic indications including cancer, hepatitis C, respiratory disorders and fungal infections. Nevertheless, a number of multi-functional, inorganic nanoparticles are being evaluated for targeted drug delivery and imaging applications. A few gold-based colloids and nanoshells are tested in clinical trials for cancer applications. Hybrid drug carriers combining stimuli-sensitive hydrogels and inorganic nanoparticles, as well as conjugation of biomolecules to nanoparticles, are important targets of research interest.

The following are some of the key areas of nanoparticle drug delivery systems being developed by universities and research institutions:

- Mesoporous nanoparticles conjugated with peptides, antibodies and other entities
- Stimuli-sensitive nanoparticles
- Surfactant-functionalised nanoparticles
- Aptamer-gated nanoparticles
- Multistage nanoparticles

Nanoparticle Applications

There are a number of nanoparticles that have been commercialised or used for research purposes:

Carbon-Based Nanoparticles

These particles are known to easily penetrate cell membranes and show good uptake by cells. The commonly employed carbon-based nanoparticles include nanorods, nanowires and nanoshells, alongside several others being developed for targeted drug delivery.

Gold-Based Nanoparticles

Gold-based nanoparticles can be directly conjugated to drugs or modified with targeting ligands as they are chemically inert and have tuneable physical/ optical properties.

Multifunctional gold particles are being widely explored for oncology applications.

Silica/Alumina Nanoparticles
Mesoporous silica particles are being commercially used to develop effective and sustained targeted drug delivery systems.

Metals/Oxides/Sulphides
These are an emerging class of nanoparticle carriers, which primarily include zinc, lead and other metals.

Quantum Dots
These are highly toxic and not a well-suited class of inorganic nanoparticles. However, they are shown to be promising for imaging applications.

Key Technology Innovations

The proprietary multi-stage mesoporous silica nanoparticle-based platform, developed by Leonardo Biosystems for spatio-temporally controlled drug release, has attracted the attention of several investors and pharmaceutical companies. This multi-stage nanocarrier-based delivery system allows targeting of drugs to specific tissues via active and passive methods. The custom-designed mesoporous silica nanoparticles can be fine-tuned to control drug release kinetics, and therefore, can easily cross the common biological barriers. These multi-stage nanoparticles have been shown to function much better than single-stage systems and focus on delivering small-interfering RNA, small molecules and imaging agents to tumour cells. Currently, the system is undergoing optimisation and enhancements.

Meanwhile, CytImmune Science's tumour-targeting technology is based on pegylated colloidal gold nanoparticles that can be used directly as drugs via tumour-targeting molecules, or as carriers for cancer drugs. The gold nanoparticles are known to harness the therapeutic potential of potent anti-cancer agents, limit bio-distribution primarily to tumour sites, and add to tumour necrosis factor's biological actions.

Furthermore, the platform is highly versatile and independent of tumour-specific biochemistry, and so, can be used to treat a wide variety of cancers. Early results from Phase 1 clinical trials demonstrated:

- The safe and systemic delivery of TNF in humans far beyond concentrations attained in previous human health studies
- The accumulation of gold nanoparticles only in and around the tumour sites, without affecting the surrounding healthy tissues and avoiding uptake by the liver

Table 1: Overview of nanoparticles and their applications in life sciences

Particle class	Nanoparticle	Application
Natural materials or derivatives	Chitosan Dextrane Gelatine Alginates Liposomes Starch	Drug/gene delivery
Dendrimers	Branched polymers	Drug delivery
Fullerenes	Carbon-based carriers	Photodynamics Drug delivery
Polymer carriers	Polylactic acid Polycyano acrylates Polyethyleinemine Block copolymers Polycaprolactone	Drug/gene delivery
Ferrofluids	Superparamagnetic iron oxide nanoparticles Ultra-small superparamagnetic iron oxide nanoparticles	Magnetic resonance imaging
Quantum dots	Cd/Zn-selenides	Imaging *In vitro* diagnostics
Others	Silica nanoparticles Mixtures of above	Drug/gene delivery

Source: International Journal of Nanomedicine and Frost & Sullivan analysis

Toxicological Hazards

Despite the fact that nanoparticle-based drug delivery carriers are intended to reduce toxicity and potential side-effects of drugs, it still remains a debatable issue whether the carrier systems themselves may impose risks to patients. While industry participants focus more on the reduction of toxicity of the incorporated drug, the possible toxicity of the nano-based carrier used in drug delivery tends to be overlooked.

Although a considerable amount of data is available on the toxicity of nanoparticles in general, not all hazards of nanoparticles in medical applications are known at the moment. As a result, it becomes crucial that parameters such as interactions with blood components, systemic distribution and kinetics are required to be evaluated when engineered nanoparticles are used as drug delivery vehicles to increase biological half-times, as well as for imaging purposes. Case-by-case hazard screening of each nanoparticle formulation based on their portal of entry is likely to be required. It is also important to be aware that very small (nano) particles can potentially be more toxic than larger particles with the same chemical composition.

Conclusion

Given the attributes of nanoparticle-based carriers in targeted drug delivery, the use of nanoparticles is likely to spread rapidly. The toxicological hazards posed by nanoparticles are quite different from the conventional ones imposed by chemicals used in drug delivery. Moreover, very little knowledge prevails pertaining to the scientific hypothesis for the possible adverse reactivity of nanoparticles, in terms of interaction with living cells, organs and organisms. It is therefore crucial that a sound understanding of the biological responses to nanoparticles, coupled with a close coordination of drug delivery mechanisms and particle toxicology, are necessary for the safe and effective use of nanoparticles in drug delivery.

About the author

Aiswariya Chidambaram is a Senior Research Analyst with the Healthcare Practice of Frost & Sullivan. She has authored syndicated and customised market research reports on key therapeutic and service areas for both the European and global pharma and biotech markets. Aiswariya has contributed several insightful articles for reputed journals, magazines and newsletters, awarded healthcare companies demonstrating excellence in specific market/product segments and technologies, delivered on-demand thought-leader interviews and presented at several reputed global conferences. She holds a BTech in Biotechnology from the Anna University.
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