

# Targeted Therapeutics and Nanoparticles

A key objective of pharmaceutical and biopharmaceutical development is to increase product therapeutic specificity and safety. Some of the recent exciting developments have obviously been related to the development in new chemical entities for the treatment of underserved disease populations. However, increasingly, successful developments in this field involve new formulation technologies that use engineered physicochemical attributes to enable and improve the efficacy and safety of new and existing products. These formulation technologies can positively affect product specificity, bioavailability, biodistribution, pharmacokinetics and safety. Formulation technologies can not only impact the delivery of a single therapeutic molecule but combine pharmaceuticals and biopharmaceuticals to provide uniquely new and useful product attributes and clinical applications. Two major advances in recent years have been the development of monoclonal antibody-drug conjugates (ADC) and the many forms and applications of nanoparticles.

## Antibody-Drug Conjugates

The combining of pharmaceuticals and biopharmaceuticals in the form of ADC has been a goal of research since the advent of monoclonal antibody technologies forty years ago. This approach holds the promise of combining the beneficial attributes of drugs and the exquisite specificity of monoclonal antibodies. In oncology focused ADC for instance, cytotoxic drugs that could treat the desired disease are covalently bound to disease relevant antibodies via a chemical linker (Figure 1). Eight different human monoclonal antibodies have been approved for cancer therapy, several of which bind to cell surface tumor antigens<sup>1</sup>. From this portfolio of antibody specificities, two ADC products have recently been approved as commercial clinical therapies<sup>1</sup>.

Table 1

NANOPARTICLE TYPES AND MAJOR ATTRIBUTES				
Particle Types:	Solid-Lipid	Polymeric (PLGA)	Liposomes	LyoCell®
<b>Efficiency / Location of Formulated Drug:</b>				
<b>Hydrophobic Molecules</b>	++++ / interior of particle	+++ / interior of particle	+ / in lipid bilayer	+++ / in lipid phase
<b>Hydrophilic Molecules</b>	+ / on particle surface, & possibly entrapped in solid-lipids using proprietary technology	+ / on particle surface & possibly entrapped in polymer using some processes	++ / in aqueous core of liposomes	++ / in aqueous phase of LyoCells
<b>Amphiphilic Molecules</b>	++ / on particle surface	+ / on particle surfaces	+ / in lipid bilayer	++ / in lipid and aqueous phases
<b>Stability of Aqueous Suspensions</b>	++++	-	++	+++

ADC products must use antibodies with specificities that can bind to cell surface antigens and be subsequently internalized via endocytic vessels. The therapeutic success of ADC products depends upon the ADC construct being internalized by the tumor cells, and the linker associating the antibody to the drug being hydrolyzed by the acidic environment of the endosomes (approximately pH 5.0). Then the cytotoxic drug must maintain its ability to cross endocytic

membranes, possibly with linker remnants still attached, into the cytoplasm where it can function as a therapeutic. So development of ADC technology has depended heavily on these typically proprietary linkers. However, the utility of different combinations of antibodies, linkers and drugs has been difficult to predict, which has complicated the development of new ADC products.

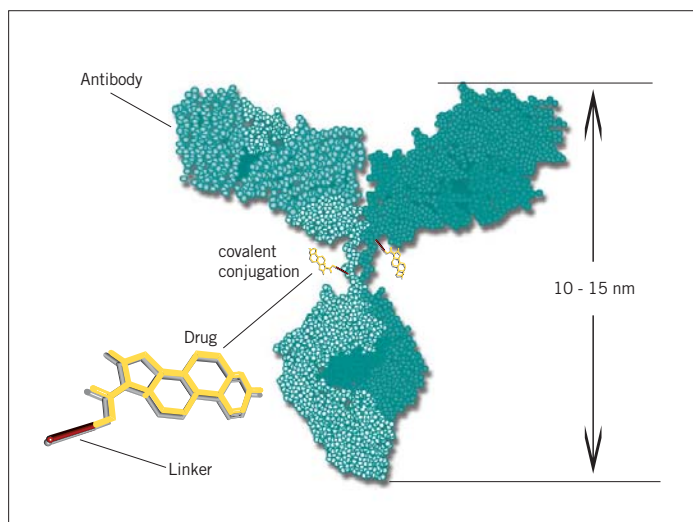
While the ADC pipeline is robust, there are technical limitations to what can be accom-

plished. Inability to significantly increase the ratio of the number of copies of cytotoxic drugs attached to targeting antibody creates dose boundaries for ADC development and limits its applicability. ADC products need a high copy number of targeted tumor antigens expressed on tumor cells to enable the needed cytotoxic dose of drug being internalized by cells, and the cytotoxic drugs used for these conjugates need to be of very high potency to minimize this necessary dose. These limitations result in only a small portion of the portfolio of therapeutic drugs being applicable to ADC.

## Nanoparticle Formulations

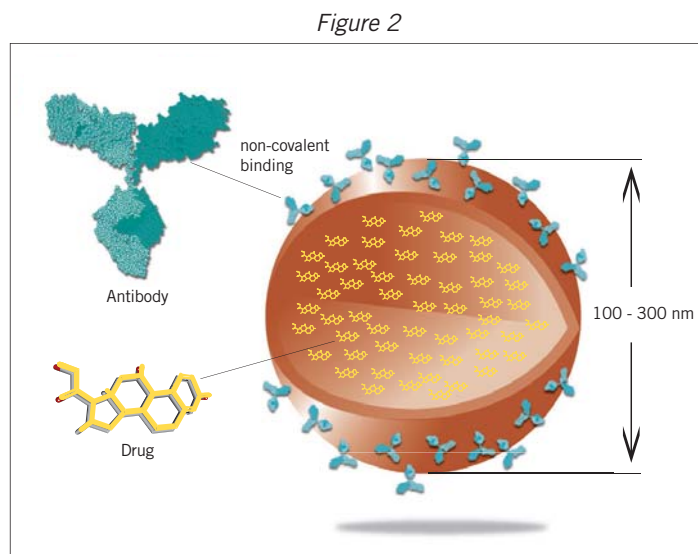
There are wide variety of nanoparticle technologies used in drug delivery and they have had a major impact on formulating pharmaceuticals. These nanoparticle technologies offer a number of attractive attributes for drug delivery including: improved bioavailability, delivery of high doses, protection of the drug from harsh environments, extending pharmacokinetics, targeted biodistribution of drug, sustained release of the therapeutics, and co-delivery/combinations of pharmaceuticals

Figure 1



and biopharmaceuticals. The underlying technologies behind the majority of nanoparticles include: liposomes, reverse cubic phase particles, and solid lipid particles. Ten different nanoparticle based drug products have been approved in oncology alone and many more are in pre-clinical and clinical development<sup>2</sup>.

Nanoparticle physicochemical attributes can be tailored including their size, hydrophobicity, charge, degradation rate, and payload<sup>2,3</sup>. This flexibility allows developers to optimally formulate and deliver drugs depending upon the drugs' attributes and clinical performance needs (Table 1). Nanoparticles composed of solid-lipids can be especially suitable for the formulation of hydrophobic small molecules, the loading of which can be maximized by blending various components to optimize solubility of the API in the particle<sup>2,3</sup>. These solid-lipid particles are routinely quite stable in aqueous suspensions, making them commercially attractive<sup>2,3</sup>. Polymeric nanoparticles (i.e. PLGA) have been used to formulate hydrophobic small molecule pharmaceuticals<sup>4</sup> but can be adapted to also entrap hydrophilic pharmaceuticals that can be released upon degradation of the polymer. Since most degradable polymer based nanoparticles hydrolyze gradually in aqueous suspension, these products need to be dry for storage and resuspended prior to administration. Liposomes are well adapted for the formulation of hydrophilic pharmaceuticals since the liposomal membranes encapsulate aqueous cores. Liposome formulations' most significant challenges typically are related to their limited payload and relatively unstable physical and chemical nature when in aqueous suspensions although these formulations have been successfully developed as commercial products. LyoCells<sup>®</sup> are also lipid nanoparticles but are in a very thermodynamically stable reverse cubic phase that, unlike liposomes, have continuous lipid and aqueous phases. It



is a formulation technology that is especially adapt to both lipophilic drugs and amphipathic molecules, like many biopharmaceutical proteins, since lipid and aqueous phases are never more than several nanometers apart.

When formulating chemotherapeutics for solid tumors, nanoparticles have been especially effective as a result of the enhanced permeability and retention (EPR) effect<sup>3</sup>. This EPR effect results in nanoparticles formulations efficiently distributing themselves within solid tumor tissues. Nanoparticles, once within targeted tumors, can be either internalized by the tumor cells where the formulated drug can kill the cells, or remain extracellular and provide sustained release of the drug within the tumor tissues which again affects the therapy.

Nanoparticle surface characteristics are critical determinants of behavior, impacting drug loading, drug release profile, circulating half-life, biodistribution, disease targeting and elimination<sup>2,3</sup>. The most common nanoparticle surface modifications are charge control, and the attachment of chemical moieties and targeting ligands. Charge can be customized on particles to enable their binding to other molecules including pharmaceuticals and biopharmaceuticals. The level of charge, zeta potential, can also affect how particles interact

non-specifically with biological systems and impact circulating half-life. Targeting of nanoparticles can be achieved through attaching ligand specific moieties to the particle's surface. For example, polysaccharides, including hyaluronic acid, have been covalently attached to nanoparticles, targeting them to cells expressing receptors for these polysaccharide ligands. Protein based targeting molecules have also been attached, typically by covalent linkers<sup>2</sup>.

### Targeted Nanoparticles

A number of different targeting molecules are being developed in combination with nanoparticle formulations, the most common of which is antibodies. Traditionally the binding of antibodies to particles is achieved covalently through various linker chemistries. Other options that have also been developed are solid-lipid nanoparticles formulated with surfactants that mediate non-covalent binding of antibodies and other biological molecules; a technology known as Surface Arrayed Therapeutics<sup>®</sup>(SATx<sup>™</sup>; Figure 2). The SATx<sup>™</sup> particles efficiently bind to biopharmaceutical molecules like vaccine components<sup>4</sup>, and monoclonal antibodies. SATx<sup>™</sup> can effectively link biopharmaceutical and pharmaceutical molecules, like that of ADC, but without the need for and limitations of conjugation chemistries.

Engineered nanoparticles, much like ADC, can “link” pharmaceutical drugs to targeting monoclonal antibodies generating highly specific therapeutics that also offers significant advantages that address the limitations and challenges faced by ADC products. Antibody targeted nanoparticles can dramatically improve the drug loading and delivery over ADC constructs. The delivery of these particles, with their high drug payloads, is no longer absolutely dependent on the target antigen copy number; as long as sufficient antibodies on the particles bind to the target antigen linking the particles to the cells, the drug contents of a particle will be delivered. This dramatic improvement in drug loading promises that drugs can be delivered to target cells with low copy number antigens. Furthermore, nanoparticle formulations, as compared to ADC formulations, can benefit from the EPR effect and do not depend on intracellular hydrolysis of a chemical linker, but rather provide therapeutic effect when either localized within tumor tissues or internalized by tumor cells.

Formulation technologies are a critical contributor to current and future improvements in pharmaceutical and biopharmaceutical development. Because of their compelling advantages, nanoparticles will see rapidly increasing adoption and use in both pharmaceutical and biopharmaceutical products. Lastly, as the biosimilar field expands and begins to improve existing biopharmaceutical products, creating “biobetters,” these formulation technologies are certain to play a leading role.

### References

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