Drug Delivery Systems: Entering the Mainstream

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VIEWPOINT

Drug Delivery Systems: Entering the Mainstream

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Drug delivery systems (DDS) such as lipid- or polymer-based nanoparticles can be designed to improve the pharmacological and therapeutic properties of drugs administered parenterally. Many of the early problems that hindered the clinical applications of particulate DDS have been overcome, with several DDS formulations of anticancer and antifungal drugs now approved for clinical use. Furthermore, there is considerable interest in exploiting the advantages of DDS for in vivo delivery of new drugs derived from proteomics or genomics research and for their use in ligand-targeted therapeutics.

Many of the pharmacological properties of conventional ("free") drugs can be improved through the use of drug delivery systems (DDS), which include particulate carriers, composed primarily of lipids and/or polymers, and their associated therapeutics. DDS are designed to alter the pharmacokinetics (PK) and biodistribution (BD) of their associated drugs, or to function as drug reservoirs (i.e., as sustained release systems), or both. Table 1 gives examples of problems exhibited by free drugs that can be ameliorated by the use of DDS.

Here we analyze the opportunities and problems associated with the use of small-scale DDS (nanoparticles and microparticles with diameters of ~200 nm or less) for parenteral (primarily intravenous) applications. These include liposomes and other lipid-based carriers such as micelles, lipid emulsions, and lipid-drug complexes; also included are polymer-drug conjugates, polymer microspheres, and various ligand-targeted products such as immunoconjugates (*1*–*5*). We will not address the use of larger scale systems such as drug-releasing implants or systems used as vaccines or immunostimulants.

Several DDS have reached the market (Table 2). The majority of the DDS currently approved for parenteral administration fall into the category of liposomal or lipid-based formulations or therapeutic molecules linked to polyethylene glycol (PEG). One such product is a PEG-stabilized liposome, pegylated liposomal doxorubicin (Doxil/Caelyx). Several ligand-targeted therapeutics have also received approval (Table 2). Although most of the approvals are for DDS used as a monotherapy, approved DDS typically undergo additional clinical trials in which they substitute for the free drug in combination chemotherapy. Many more DDS are in early- to late-phase clinical trials (table S1).

How can we decide whether a particular therapeutic is suited to delivery in a DDS? Is one type of DDS more suited than another for particular classes of drugs? One of the more important drug properties to consider is potency. Additional properties such as stability, solubility, size (molecular weight), and charge are also important. As a general rule, the fewer molecules that a DDS can carry (i.e., the lower the drug:carrier ratio), then the more potent the drug must be. For some types of DDS that can carry only a few molecules of a drug (such as immunotoxins and immunoconjugates) or a few tens of molecules (such as polymer conjugates), drugs with higher potencies are needed in order to deliver therapeutically relevant amounts of drug (*5*).

The use of unreasonably high quantities of the carrier can lead to problems of carrier toxicity, metabolism and elimination, or biodegradability. Because each liposome can entrap up to tens of thousands of drug molecules (*6*), drug potency is less of an issue for this type of carrier. However, even the relatively high carrying capacity of liposomes becomes problematic for very large therapeutic molecules such as proteins, par-

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ticularly if small liposome diameters are desirable for reasons of biodistribution. Although drug solubility may not be a limiting factor for systems such as polymer-drug conjugates, in which the drug is chemically linked to the carrier, it can be an important consideration in liposomal DDS. Hydrophilic drugs can be readily entrapped with a high degree of latency within the liposome aqueous interior, but neutral hydrophobic drugs or those with intermediate solubilities tend to be rapidly released in the presence of plasma proteins or cell membranes (*7*). Fortunately, excellent retention of drugs that are hydrophobic weak bases (such as doxorubicin and vincristine) has been achieved through "remote loading" techniques that rely on pH or chemical gradients across the liposome bilayer to accumulate and retain the drug (*8*, *9*).

There are additional questions to consider when combining a drug with a DDS. Will the drug survive the procedures required for its incorporation into the DDS—for example, if the formation of chemical bonds is required? Can the carrier help to stabilize the drug or prevent premature metabolic breakdown? Will the drug stay associated with the carrier for appropriate lengths of time and be released at an appropriate rate? The regulatory status of the drug may also play a role in the decision to use a DDS. For example, if the free drug is already in clinical use, the advantages of the DDS compared to the free drug can be directly evaluated in well-established indications, potentially resulting in more rapid clinical development. In addition, although the DDS can result in new toxicities compared to the free drug, the toxicity profiles of DDS are usually similar to those of the free drug, the differences being in degree rather than in kind. As a result, procedures used to treat the side effects of the free drug can often be applied to the DDS. The mechanism of action of a drug may also dictate its suitability for delivery in a particular DDS. For example, schedule-dependent anticancer drugs, which require sustained levels of drug in the tumor in order to kill cells that enter and exit the sensitive phase of the cell cycle in an asynchronous manner, may be well suited to sustained release formulations.

Are there applications for which DDS are particularly suited? The particular strength of DDS is their ability to alter the PK and the BD of their associated therapeutics (assuming they stay associated with the carrier) (*10*, *11*). For example, the coupling of PEG or other inert polymers to a variety of therapeutic molecules (Table 2 and table S1) decreases drug clearance by the kidneys and by immune recognition (*12*). In general, when a drug is associated with a carrier, the drug clearance decreases (the half-life increases), the volume of distribution decreases, and the area under the time-versus-concentration curve increases (*13*). For larger particulate carriers, such as liposomes, polymer-drug conjugates, and microspheres, the size of the carrier (normally 50 to 200 nm in diameter) confines it mainly to the blood compartment, and the volume of distribution of the carrier-associated drug will approach that of the plasma volume if the rate of release of the drug is slow. In essence, the PK and BD of the drug is the same as that of the carrier itself when the drug is released slowly. By contrast, if the drug is released rapidly from the carrier, as has been seen for neutral hydrophobic drugs associated with liposomes or micelles, then the PK and BD of the carrier-associated drug will approach those of the free drugs, although improvements in solubility of the drug and reductions in excipient-mediated toxicities may be seen (*14*). Most polymer-drug conjugates and liposomes occupy an intermediate ground between these two extremes; the PK and BD are a composite of the PK and BD of the free drug and the PK and BD of the carrier, with the balance depending on the rate at which the drug is released from the carrier.

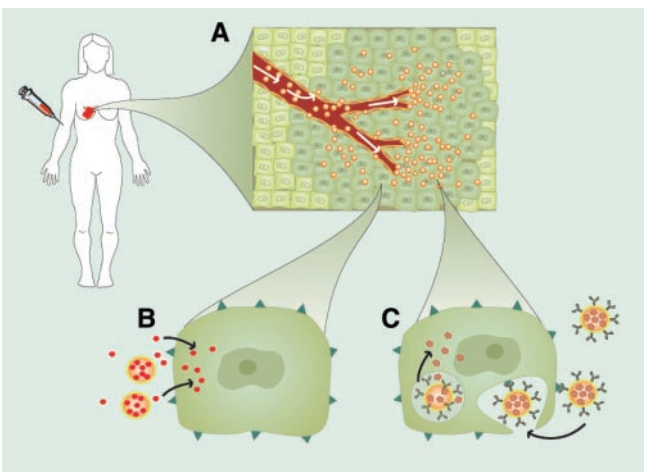

Fig. 1. A schematic diagram depicting the passive or ligand-targeted accumulation of liposomal DDS in breast cancer tumors through the EPR effect. (**A**) Liposomes containing an anticancer drug extravasate from the blood through gaps in vascular endothelial cells and accumulate in tumor tissue (dark green), but not in normal tissue (light green). (**B**) Drug is released from the liposomes in the vicinity of the tumor cells and taken up into the cells. (**C**) Ligand-targeted liposomes containing anticancer drugs, or nucleic acid–based therapeutics such as plasmid DNA or antisense oligonucleotides, bind to cell surface receptors (dark green triangles), which triggers internalization of the DDS into endosomes when a ligand against an internalizing receptor is chosen. Some proportion of the encapsulated material escapes the endosomes and traffics to its intracellular site of action.

Drug release rates can have implications for the therapeutic effects of DDS. In polymer-drug conjugates or liposome systems, the drug is inactive (not bioavailable) while associated with the carrier, and failure to release the drug from the carrier in a timely manner may result in a reduced therapeutic effect relative to the free drug (*15*). On the other hand, rapid release of the drug from the carrier may result in therapeutic effects that are similar to those seen for administration of the free drug (*14*). The maximum tolerated dose (MTD) of the drug may either increase, decrease, or stay the same, depending on the properties of the drug itself, the effect of the DDS on the PK and BD of the drug, and the drug release rate. Examples include liposomal amphotericin B, in which the increase in MTD reflects the higher achievable doses when the dose-limiting kidney toxicity of the free drug is controlled (*16*); liposomal vincristine, in which the MTD is similar but the potency of the drug is improved (*17*); and liposomal topotecan, in which the MTD decreases because the free drug is protected from degradation when liposome-associated (*18*). When a drug is inactive when associated with (or attached to) a carrier and the rate of release of the drug from the carrier is slow, then large increases in the MTD may be seen, as in the case of N-2-hydroxypropyl methacrylamide copolymer–linked doxorubicin (*11*).

Alterations in the BD of DDS can occur through a mechanism known as the enhanced permeability and retention (EPR) effect, sometimes called passive targeting (*19*). In certain pathological conditions, the permeability of the tissue vasculature increases to the point that particulate carriers, which are normally excluded from tissues, can extravasate and localize in the tissue intrastitial space (*20*). Examples include inflamed tissues and solid tumors (Fig. 1). Vascular remodeling to enable leukocyte extravasation, in response to signals released from infected or inflamed tissues, results in increases in vascular permeability and the localization of particulate carriers to these locations (*21*, *22*). As tumors grow and begin to outstrip the available supply of oxygen and nutrients, they release cytokines and other signaling molecules that recruit new blood vessels to the tumor, in a process called angiogenesis. Angiogenic blood vessels, unlike the tight blood vessels in most normal tissues, have gaps as large

as 600 to 800 nm between adjacent endothelial cells. Carriers can extravasate though these gaps into the tumor interstitial space, in a size-dependent manner (Fig. 1). Because tumors have impaired lymphatic drainage (*23*), the carriers concentrate in the tumor, and large increases in tumor drug concentrations (10-fold or more higher) can be achieved relative to administration of the same dose of free drug (*10*). However, the localization of the DDS is focal rather than homogeneous, and the factors that result in high concentrations of carrier in one part of a tumor but not another are not well understood yet (*24*). In general, the level of accumulation of DDS in tumors will depend on factors such as the size of the DDS, the circulation half-life of the DDS (longer half-lives lead to higher accumulation, because peak tumor levels of drug do not occur until 1 to 3 days post-injection), the degree of tumor vascularization (poorly vascularized tumors will accumulate less of the DDS), the degree of angiogenesis (small pre-angiogenic tumors or large necrotic tumors will accumulate DDS poorly, if at all), and the size of the pores.

Not all DDS are designed to use the EPR effect. Some applications take advantage of the sustained release of drugs from DDS, so that the DDS function in a manner similar to a drug infusion but with less patient inconvenience (*25*). Other applications take advantage of the natural tendency of particulate DDS to localize to the mononuclear phagocyte system (MPS), particularly to liver and spleen macrophages; the delivery of antileishmanial drugs against the parasite that is resident within macrophages (*26*) is one example. DDS do not normally cross the blood-brain barrier, although limited penetration may occur in certain pathological states, so applications of DDS in the central nervous system are usually restricted to intraspinal or intracerebral administration (*27*). DDS do not lead to clinically relevant systemic levels of drug when given by the oral route.

An important question concerning particulate DDS is whether they lead to appropriate rates and levels of drug bioavailability. For applications that take advantage of the EPR effect, long half-lives are required for optimal accumulation of the drug in diseased tissue, and the drug should stay with the carrier until this accumulation has occurred (*13*, *28*). Once the DDS has localized to its site of action, such as a solid tumor, then the drug must be released (become bioavailable) at a rate that maintains free drug levels in the therapeutic range for optimal periods of time. Measurements of the total tumor level of drug do not tell us how much of the drug is bioavailable—that depends on the rate of drug release. For example, for a schedule-dependent anticancer drug, bioavailable drug should be maintained at levels above the minimum therapeutic dose for at least several hours. Until recently, the design of particulate DDS has been somewhat empirical, and little attention has been paid to this requirement. For a schedule-independent anticancer drug, theory suggests that it is more important to have a large amount of drug become rapidly bioavailable, such as through a triggered-release mechanism, once the DDS has reached peak tumor concentrations. These types of systems can be difficult to design. Efforts to improve control over the rate and extent of drug bioavailability currently center around the design of triggered-release systems in which drug release from liposomes, environmentally responsive polymers, or hydrogels is triggered at the desired site of action by changes in pH, temperature, or magnetic fields or by engineered sensitivities to biocompatible chemicals and enzymes, light, or radiofrequency (*3*, *29*). An interesting variation on this is the site-targeted application of a drug-activating signal. For example, the liposomal photosensitizer verteporfin (Visudyne) contains a hydrophobic drug that is rapidly transferred to blood proteins in vivo. Activation of the drug by targeting laser light to blood flowing though the eye causes its site-specific activity in the treatment of wet macular degeneration (*30*).

Most DDS use nontoxic, biodegradable ingredients, so toxicities associated with the carrier molecules per se tend to be mild. Perhaps the most common side effect is a hypersensitivity reaction after intravenous administration (*31*), possibly due to complement activation (*32*). This can be ameliorated by slowing the rate of infusion of the product or by patient premedication (*33*). Hypersensitivity reactions often fail to appear on repeat administration of the DDS. Usually, side effects that accompany the administration of DDS are reduced, sometimes substantially, relative to the free drug; for instance, the cardiotoxicity of doxorubicin is reduced when a DDS is used, because of reductions in the peak cardiac levels of the drug. Associating a therapeutic molecule with a carrier may, however, result in the generation of immune reactions against the carrier or the therapeutic (*34*). In some cases, side effects may appear that are related to alterations in the PK and BD of the drug (*35*). For example, palmar plantar erythrodysesthesia (hand-foot syndrome), a documented side effect of free

Table 1. Non-ideal properties of drugs and their therapeutic implications.

Problem	Implication	Effect of DDS
Poor solubility	A convenient pharmaceutical format is difficult to achieve, as hydrophobic drugs may precipitate in aqueous media. Toxicities are associated with the use of excipients such as Cremphor (the solubilizer for paclitaxel in Taxol).	DDS such as lipid micelles or liposomes provide both hydrophilic and hydrophobic environments, enhancing drug solubility.
Tissue damage on extravasation	Inadvertent extravasation of cytotoxic drugs leads to tissue damage, e.g., tissue necrosis with free doxorubicin.	Regulated drug release from the DDS can reduce or eliminate tissue damage on accidental extravasation.
Rapid breakdown of the drug in vivo	Loss of activity of the drug follows administration, e.g., loss of activity of camptothecins at physiological pH.	DDS protects the drug from premature degradation and functions as a sustained release system. Lower doses of drug are required.
Unfavorable pharmacokinetics	Drug is cleared too rapidly, by the kidney, for example, requiring high doses or continuous infusion.	DDS can substantially alter the PK of the drug and reduce clearance. Rapid renal clearance of small molecules is avoided.
Poor biodistribution	Drugs that have widespread distribution in the body can affect normal tissues, resulting in dose-limiting side effects, such as the cardiac toxicity of doxorubicin.	The particulate nature of DDS lowers the volume of distribution and helps to reduce side effects in sensitive, nontarget tissues.
Lack of selectivity for target tissues	Distribution of the drug to normal tissues leads to side effects that restrict the amount of drug that can be administered. Low concentrations of drugs in target tissues will result in suboptimal therapeutic effects.	DDS can increase drug concentrations in diseased tissues such as tumors by the EPR effect. Ligand-mediated targeting of the DDS can further improve drug specificity.

doxorubicin given by prolonged infusion but not by bolus administration (*36*), can also appear in patients receiving pegylated liposomal doxorubicin (*37*). Because particulate DDS cause increased accumulation of drugs in MPS cells in the liver, spleen, and bone marrow, the possibility exists for increased toxicities to these tissues. However, this has not proven to be a problem in preclinical or clinical studies, possibly because of the ability of MPS cells in these organs, such as Kupffer cells, to rapidly renew themselves.

Attempts are being made to increase the site-specific actions of DDS by combining them with ligands targeted against cell surface antigens or receptors, a process called active or ligand-mediated targeting. Various radioimmunopharmaceuticals, immunotoxins, and immunoconjugates are already on the market (Table 2 and table S1), while immunoliposomes, immunopolymers, and antibody-directed enzyme prodrug therapies are in clinical development. One of the advantages of this approach (*5*) is the possibility of additive or synergistic activities between a signaling antibody used as a targeting moiety and a cytotoxic drug associated with the DDS.

Considerable efforts have been made to exploit DDS as carriers of nucleic acids, either as plasmid delivery systems for gene therapy applications or as agents to deliver antisense oligonucleotides or small interfering RNA to down-regulate target genes. DDS composed of cationic lipids or polymers, complexed with DNA, have been most commonly employed for these purposes. However, toxicities associated with the cationic molecules, the short circulation lifetimes associated with these positively charged particles, their limited intracellular delivery capabilities, and poor gene expression have resulted in limited progress, particularly for intravenous applications (*38*). Clinical experience has been largely confined to the use of "lipoplex" systems comprising liposomes that contain cationic lipid mixed with plasmid DNA. These have been used to deliver DNA directly to tumor tissue, to vascular endothelial cells by catheter-mediated delivery, and to lung tissue by nasal installation, as well as to elsewhere in the respiratory system and into the brain (*39*). Some recent progress has been made in the development of surface-neutral, long-circulating formulations of antisense oligonucleotides targeted against proliferative proto-oncogenes, which has resulted in substantial antitumor effects in animal models (*40*, *41*).

DDS have often been criticized on the basis of their pharmaceutical and commercial qualities such as complexity, cost, storage stability, and intellectual property (IP) issues. IP issues can be difficult to resolve, as control of the product requires an IP position on the drug, the carrier technology, and the characteristics of the drug and carrier together. In the case of liposomes and PEG-protein conjugates, these perceived difficulties have been largely overcome, as indicated by the regulatory and commercial acceptance of these products. Two-year or longer stability has also been achieved for these products, which can be in a wet or lyophilized form. Although the cost per treatment for DDS can be higher than the cost per treatment of the free drugs, cost analyses that take into account the total cost, including the cost of treating drug-related side effects, show that the DDS are cost-competitive with free drugs (*42*, *43*). The complexity of these systems does present new challenges in commercial manufacture and regulatory requirements. For example, an "in vitro release" assay may be required by regulatory agencies for liposomal products in order to establish equivalent batch-to-batch drug release characteristics.

DDS have a bright future as pharmaceuticals for several reasons. First, features such as the passive-targeting effect can substantially enhance the amount of drug at disease sites such as tumors and sites of infection and inflammation. Second, DDS technology allows the therapeutic index of already established drugs, with well-established therapeutic profiles, to be improved. This removes some of the considerable risks associated with the development of new pharmaceuticals. Third, many of the potential new pharmaceuticals aris-

Table 2. Examples of DDS that have received regulatory approval. Years given are for the United States, unless otherwise specified. Table S1 gives a more comprehensive listing for products in Phase II or later clinical trials.

Drug or therapeutic agent (trade name), manufacturer(s)	Indication	Year of approval	Reference
Liposomal amphotericin B (AmBisome), Gilead, Fujisawa	Fungal infections Leishmaniasis	1990 (Europe), 1997 2000	(*44*)
PEG-adenosine deaminase (Adagen), Enzon	Severe combined immunodeficiency disease	1990	(*45*)
Styrene maleic acid and neocarzinostatin copolymer in Ethiodol (SMANCS/Lipiodol, Zinostatin stimalamer), Yamanouchi	Hepatocellular carcinoma	1993 (Japan) 1996 (Japan)	(*46*, *47*)
Stealth (PEG-stabilized) liposomal doxorubicin (Doxil/Caelyx), ALZA, Schering Plough	Kaposi's sarcoma Refractory ovarian cancer Refractory breast cancer	1995 1999 2003 (Europe, Canada)	(*10*, *48*)
Liposomal cytosine arabinoside (DepoCyt), SkyePharma	Lymphomatous meningitis Neoplastic meningitis	1999 Phase IV	(*25*, *49*)
Denileukin diftitox or interleukin 2–diptheria toxin fusion protein (ONTAK), Seragen	Cutaneous T-cell lymphoma	1999	(*50*)
Liposomal doxorubicin (Myocet), Elan	Metastatic breast cancer in combination with cyclophosphamide	2000 (Europe)	(*51*)
Gemtuzumab ozogamicin or anti-CD33–linked calicheamicin (Mylotarg), Wyeth-Ayerst	$CD33^+$ relapsed acute myeloid leukemia	2000	(*52*)
Liposomal verteporfin (Visudyne), QLT, Novartis	Wet macular degeneration in conjunction with laser treatment	2000 2001 2003 (Japan)	(*30*)
PEG-interferon α-2b (PEG-Intron), Enzon, Schering-Plough	Hepatitis C	2001	(*53*)
PEG–granulocyte colony stimulating factor or pegfilgrastim, (Neulasta), Amgen	Reduction of febrile neutropenia associated with chemotherapy	2002	(*54*)
^{90}Y-ibritumomab tiuxetan or ^{90}Y anti-CD20 (Zevalin), IDEC	Relapsed or refractory non-Hodgkin's lymphoma	2002	(*55*)
^{131}I-tositumomab (anti-CD20) (Bexxar), Corixa, GlaxoSmithKline	$CD20^+$ relapsed non-Hodgkin's lymphoma	2003	(*56*)

ing from advances in biotechnology are macromolecules such as proteins, peptides, oligonucleotides, and plasmids. Clinical development of these types of pharmaceuticals may not be possible without some type of carrier system that allows these new entities to access target tissues and cells.

The future challenges for DDS are substantial but not insurmountable. These include the development of methods to appropriately regulate the bioavailability of associated drug once the DDS has reached the target tissue, methods to enhance the specificity of DDS for target cells, and methods to enhance the ability of DDS to deliver macromolecules more efficiently to their sites of action in the interior of target cells. Recognition of these challenges is leading to new approaches that will help to make these goals increasingly realizable.

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Table S1
References and Notes

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