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Nanoparticles in Medicine: Therapeutic Applications and Developments

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Abstract

Nanotechnology refers to the study and manipulation of materials on a molecular scale, typically between 1 and 100 nanometers in size. New therapeutic and diagnostic approaches may be developed with the use of nanotechnology, which is also known as nanomedicine. Unlike bulk materials of the same composition, nanomaterials exhibit distinct physicochemical features, such as extremely tiny size, enormous surface area to mass ratio, and high reactivity. Due to these characteristics, conventional medicinal and diagnostic agents may be utilized to circumvent some deficiencies.

Introduction

Solubility, diffusivity, blood circulation half-life, drug release characteristics, and immunogenicity are only few of the essential qualities that may be altered with unprecedented flexibility via the use of nanoscale materials. For the treatment of diseases including cancer, diabetes, pain, asthma, allergies, infections, and more, several nanoparticle-based therapeutic and diagnostic agents have been created in the recent two decades. 3,4 Potential benefits of these nanoscale compounds include reduced therapeutic toxicity, prolonged product life, and decreased overall healthcare expenditures. Nanoparticles have great potential as drug delivery systems because of their specificity and regulation of drug release. To detect anomalies such as virus fragments, precancerous cells, and disease indicators that cannot be recognized with conventional diagnostics, nanoparticles enable detection on the molecular scale. Improvements in the sensitivity and specificity of magnetic resonance imaging have also been shown for imaging contrast agents based on nanoparticles. Given the breadth of nanomedicine, we will zero emphasis on the therapeutic uses of nanoparticles, particularly in drug delivery.

Drug delivery using nanoparticles has been shown to have several benefits.

5,6 As a result, weakly soluble substances become more so. drugs that are insoluble in water, prolongs the half-life of consequence, the pharmaceutical industry has seen the introduction of a select number of medicinal treatments based on nanoparticles, with many more undergoing clinical testing or on the verge of entering the pipeline.

has steadily increased during the last two decades. More than 150 businesses across the world are working on nanoscale medicines, according to a 2006 study by the European Science and Technology Observatory. 7 Twentyfour medicinal treatments based on nanotechnology have been authorized for clinical use, with revenues of more than $5.4 billion to date. 7 More than 80% of the entire quantity is comprised of liposomal medicines and polymer-drug conjugates (Table 1).

Liposomes are bilayer membrane vesicles made of either natural or manufactured amphiphilic lipid molecules that are spherical in shape.

8,9 Liposomes have gained popularity as pharmaceutical carriers over the past decade due to their ability to (a) efficiently encapsulate hydrophilic and hydrophobic therapeutic agents, (b) protect the encapsulated drugs from undesired effects of external conditions, (c) be functionalized with specific ligands to target specific cells, tissues, and organs of interest, and (d) be coated with inert and biocompatible polymers.

5,6 As a result, weakly soluble substances become more so. drugs that are insoluble in water, prolongs the half-life of drug systemic circulation by reducing immunogenicity, releases drugs at a sustained rate or in an environmentally responsive manner and thus reduces the frequency of administration, delivers drugs in a targeted manner to minimize systemic side effects, and delivers two or more drugs simultaneously for combination therapy to generate a synergistic effect and suppress drug resistance. As a

Table 1 Clinically approved nanoparticle-based therapeutics

Composition	Trade name	Company	Indication	Administration
Liposomal platforms				
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections	i.v.
Liposomal amphotericin B	AmBisome	Gilead Sciences	Fungal and protozoal infections	i.v.
Liposomal cytarabine	DepoCyt	SkyePharma	Malignant lymphomatous meningitis	i.t.
Liposomal daunorubicin	DaunoXome	Gilead Sciences	HIV-related Kaposi's sarcoma	i.v.
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer	i.v.
Liposomal IRIV vaccine	Epaxal	Berna Biotech	Hepatitis A	i.m.
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza	i.m.
Liposomal morphine	DepoDur	SkyePharma, Endo	Postsurgical analgesia	Epidural
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis	i.v.
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech, Schering-Plough	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer	i.m.
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy	Topical
Polymeric platforms				
$_{L}$-Glutamic acid, $_{L}$-alanine, $_{L}$-lysine, and $_{L}$-tyrosine copolymer				
Methoxy-PEG-poly($_{D,L}$-lactide) taxol				

Abbreviations: ADA, granulocyte colony-stimulating factor, HGF, hepatocyte growth factor, HIV, human immunodeficiency virus, i.m., intramuscular, i.r., intravitreous, IRIV, immunopotentiating reconstituted influenza virosome, i.t., intrathecal, i.v., intravenous, PEG, polyethyleneglycol, s.c.

additives such polyethylene glycol (PEG), which increases the liposomes' circulation half-life in vivo, and (e) the formation of formulations with the required composition, size, surface charge, and other features.
9,10 Products containing liposomes that have been authorized during the last 15 years are listed in Table 1. FDA approved Doxil as the first liposomal medication formulation for theKaposi's sarcoma with HIV/AIDS therapy in 1995.
11 Doxil greatly increased doxorubicin drug deposition in tumor tissue and extended doxorubicin's circulatory half-life by encapsulating the drug inside stealth liposome carriers made of hydrogenated soy phosphatidylcholine, choles- terol, and PEGylated phosphoethanolamine. Other

AmBisome (amphotericin B liposomes), DaunoXome (dauno-rubicin liposomes), DepoCyt (cytarabine liposomes), and Visudyne (vismodegib liposomes) are all examples of liposomal medications now utilized in clinical practice (verteporfin liposomes).

Polymer-drug conjugates are another widely investigated nanoparticle drug delivery method with therapeutic use.
12 Particularly when used as anticancer chemotherapeutic agents, small-molecule therapeutic agents suffer from two drawbacks: a lack of site-specific targeting that necessitates many dosing sessions and a short circulation half-life that necessitates frequent dosing sessions. Improvements in adverse effects are possible by the conjugation of smallmolecule medicines to polymeric nanocarriers. The in vivo half-life of polymer-drug conjugates is increased from minutes to hours, while endocytic cellular absorption is decreased. This improves the passive transport of medications to tissues like tumors and atherosclerotic plaques, which have leaky blood arteries. 13,14 Drug delivery polymers are widely studied, but only a small subset of those with linear design have found their way into clinical use. Polymer toxicity, immunogenicity, nonspecific biodistribu- tion, in vivo circulation instability, limited drugcarrying capacity, fast drug release, and manufacturing are only a few of the many difficulties that must be overcome.

In the early 1990s, PEG was first used in a clinical setting. 15 The drug's stability and solubility in plasma may be improved, and its immunogenicity lowered, using this method. There are now six PEGylated medicines used in actual human medical procedures. Some of these drugs are Adagen (PEG-adenosine deaminase), Macugen (PEG-antivascu- lar endothelial growth factor aptamer), Pegasys (PEGa-interferon 2a), and Oncaspar (PEG-L-asparaginase), all of which are used to treat conditions such as hepatitis B and C, AMD, and ALL, respectively. Several additional linear polymers have also been used as polymeric drug delivery carriers, including polyglutamic acid, polysaccharide, and poly(allylamine hydrochloride).

Additional conjugates or adducts of macromolecules and drugs possess a hydrodynamic size between 5 and 200 nm and have been used as medication carriers. Abraxane, an albumin-bound paclitaxel medication with a 130-nm molecular weight, was given FDA approval in 2005 for use in advanced breast cancer patients. 16 Both transendothelial transport pathways mediated by the albumin-binding protein gp60 and the passive increased permeability and retention impact contribute to the localization of abraxane

Adding a medication like paclitaxel to an HPMA polymer greatly increases the drug's solubility in water. This facilitates the process of creating the medicine and giving it to patients. Not only is HPMA non-immunogenic and biodegradable, but it also does not trigger an immune response. Several HPMA compounds have been created and are under clinical trials because of their appealing properties. In phase II clinical trials, HPMA copolymerdiaminocyclohexane palatinate (ProLindac) is being used to treat recurrent ovarian cancer; in phase II, HMPA copolymerdoxorubicin-galactosamine (FCE28069) is being used to treat hepatocellular carcinoma; and in phase I clinical trials, HPMA copolymer-paclitaxel (PNU166945

Nanoemul- sions,22 dendrimers,23 and inorganic nanoparticles24, in addition to drug-encapsulated liposomes, have shown therapeutic promise. These systems have proven effective in the medical field by demonstrating new methods and considerably expanding the supply of therapeutic nanoparticles. In 2007, a topical therapy for genital herpes infection using a nanoemulsion-based medicinal product called NB-001 began its phase II study. Another example is the medicine VivaGel, which is in its phase I trial as a safe, convenient, and inexpensive therapy to prevent genital herpes and HIV infection in women and is based on the poly-L-lysine dendrimer technology. The Role of Nanoparticle-Based Therapeutics in Preclinical Research and Development

Researchers in academia and the private sector are increasingly interested in nanomedicine due to the recent triumphs of nanoparticle therapies. Over the last decade, the complexity of nanoparticle systems has increased in response to the accelerating rate of discovery. There are growing numbers of nanoscale vehicles with

in the tumor. Abraxane almost doubles the therapeutic response rate, delays disease progression, and improves overall survival for breast cancer patients, according to clinical research.

for a wide variety of medical uses requiring specific chemical, physical, or biological characteristics.

1,25 Polymeric nanoparticles, micelles, nanoshells, dendrimers, modified viral nanoparticles, albumin-based nanoparticles, polysaccharide-based nanopar- ticles, metallic nanoparticles, and ceramic nanoparticles are some of the most popular nanoparticle plat- forms now in use (Figure 1 and Table 3). There is therapeutic promise for these nanoparticles in almost every area of medicine, including cancer, cardiology, immunology, neurology, endocrinology, ophthalmology, pulmonary medicine, orthopedics, and dentistry. 1

Recently, there has been a lot of interest in biodegradable polymeric micelles between 10 and 200 nm in size as drug delivery nanocarriers due to their extraordinary therapeutic potential.

26–32 The self-assembly of block copolymers, which include two or more polymer chains with differing hydrophobicity, results in the formation of polymeric micelles. When placed in water, these copolymers spontaneously form a core-shell micellar structure, which lowers the overall free energy of the system. To reduce their interaction with water as much as possible, hydrophobic blocks cluster together in the center, while hydrophilic blocks surround the center like a corona to provide structural support. 33 The micellar structure is an excellent nanocarrier for administering drugs. Its hydrophobic core has a high loading capacity (5-25% weight) and can transport medications, even those that are poorly soluble. Its hydrophilic coating not only protects the micelle sterically, making it more stable in the circulation, but it also contains functional groups that may be used to alter the micelle in other ways. Each polymeric micelle is far bigger than polymer-drug conjugates, allowing it to transport more pharmaceuticals and allow for more controlled drug release. The capsules may then be used to

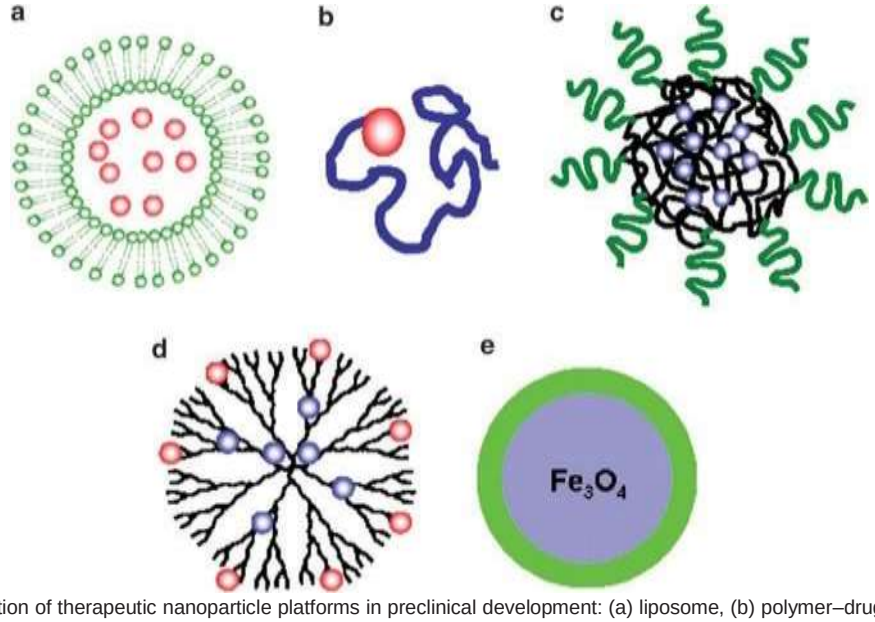

Figure 1 Schematic illustration of therapeutic nanoparticle platforms in preclinical development: (a) liposome, (b) polymer–drug conjugate, (c) polymeric nanoparticle, (d) dendrimer, and (e) iron oxide nanoparticle. The red dots represent hydrophilic drugs and the blue dots represent hydrophobic drugs.

numerical number representing the critical micelle concentration. These polymeric micelle systems may also be utilized to co-transport many medications at once, whether they have comparable or differing water solubilities, for combination treatment, or to administer multiple therapeutic modalities, such as radiation agents and pharmaceuticals. 34 In order to boost their specificity and effectiveness while decreasing their systemic toxicity, these micelles may have their surfaces modified with ligands including anti-bodies, peptides, nucleic acid aptamers, polysaccharides, and small compounds. 26,27,31 Common biodegradable polymers used to create micelles for drug administration and controlled release include poly(D,L) lactic acid, poly(D,L) glycolic acid, and poly(e) -caprolactone, as well as their copolymers at different molar ratios diblocked or multiblocked with poly(ethylene glycol). 28,31,33 Thanks to their distinct properties and well-defined design, dendrimers have recently gained attention as a promising new platform for drug delivery.

35–38 Dendrimers are a class of synthetic polymers characterized by their spherical shape, high degree of branching, and presence of an initiator core surrounded by several layers that terminate in active terminal groups. Every one of these tiers is a "generation," and it contains recurring units. Generation 0 describes the fundamental structure of a dendrimer. Dendrimers are able to transport a wide variety of medications because to their molecular design, which makes their multivalent surfaces amenable to covalent conjugation and electrostatic adsorption. Dendrimers' core cavities may also be used to load pharmaceuticals through hydrophobic contact, hydrogen bonding, or chemical coupling. Recent work in Michigan has resulted in the creation of a polyamidoamine-based G5 dendrimer with a diameter of around 5 nm and a surface covered with more than 100 functional primary amines. The G5 dendrimer was around 10 times more effective than methotrexate alone in preventing tumor development due to the attachment of folate as the targeted molecule and methotrexate as the therapeutic drug. Additionally, the systemic toxicity of the targeted, methotrexate-loaded dendrimer was lower than that of free methotrexate. 35 Since polyamidoa-mine dendrimers show great promise as a drug delivery method, researchers have been experimenting with different topologies and molecular weights to maximize accumulation in tumors and therapeutic effectiveness. Another category of nanoparticle platforms is made up of biopolymers and their self-assemblies, and this includes nanoparticles based on albumin, polysaccharides, and viruses. Because of their one-of-a-kind biological properties, these nanoparticles offer exciting therapeutic promise. Small-molecule medicines may have their stability and biodistribution greatly enhanced if they are conjugated with human serum albumin39,40 or a polysaccharide like chitosan41,42. The core-shell structure of viruses makes them similar to nanoparticles that may be considered alive. The infectious core may manipulate the host cell's transcription and translation processes. Different proteins or proteins encased in lipid membranes make up the shell. Due to their high gene transfection effectiveness, virus-based nanoparticles have been widely employed as gene delivery vehicles. 43,44 Considerable "hard" nanoparticles, such as metallic nanoparticles and ceramic nanoparticles, have also received

some attention and demonstrated some specific therapeutic potential, which makes for an intriguing contrast with the aforementioned nanopar- ticles, which normally belong to "soft" matter. When coated with dextran, surfactants, phospholipids, or other substances to increase their stability, metallic nanoparticles like iron oxide45,46 may be utilized as a passive or targeted agent. Thermotherapy with iron oxide nanoparticles coated with aminosilane has recently been used to treat malignant brain tumors. Survival in a rat model may be increased by a factor of 4.5 when thermotherapy is combined with magnetic field-induced excitation of iron oxide superparamagnetic nanoparticles. 45 Similar to silver nanoparticles, gold nanoparticles are a kind of metallic nanoparticle with promising infrared phototherapy applications because of their favorable optical and chemical characteristics. 47 Silica, titania, and alumina are just a few examples of ceramic nanoparticles that fit this description; their porous architecture and lack of biological activity make them ideal candidates for nanomedicine. 48,49 The use of these nanoparticles as drug delivery vehicles for a variety of cancer therapy is a relatively new concept.

CONCLUSION

The use of nanotechnology to the distribution of medicines has already had far-reaching effects on the medical field. It has been shown that nanoparticles may improve the efficacy of drugs, and more than twenty nanoparticle treatments are now being used in clinical practice. Along with nanoparticles that have previously been approved for use, several more are now the subject of preclinical and clinical study. These include liposomes, polymeric micelles, dendrimers, quantum dots, gold nanoparticles, and ceramic nanoparticles. If present research and development efforts in the field of nanotechnology are successful, it might dramatically alter the medical field during the next several decades.

techniques that produce properly designed nanoparticles, a growing number of multifunctional nanoparticles will find their way into clinical use in the near future.

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