8 Pharmacokinetics and Pharmacodynamics of Liposomal Nanoparticles

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Contents

Abstract

In the past few years, some major advancements in liposome technology have induced the rapid development of new pharmaceutical liposomal applications. For the purpose of optimizing the delivery of factors for maximum efficacy, novel methods have been proposed to increase the permeation rate of drugs temporarily and deliver the desired target compound in a time-regulated and locally restricted manner to the target site.

Lipid-based nanoparticles (LNPs) are promising delivery vectors in the treatment of cancer, inflammation, and infections and are already used in clinical practice. Numerous strategies based on LNPs are being developed to carry drugs into specific target sites. The common purpose for all of these LNP-based platforms is to improve the payload's pharmacokinetics, biodistribution, stability, and therapeutic benefits and also to reduce adverse effects to a minimum. In addition, the delivery

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system must be biocompatible and nontoxic and should avoid undesirable interactions with the immune system. The rapid advancement in nanotechnology has allowed the emergence of theranostic NPs, which have shown advantages of diagnosis and drug delivery as well as targeting the biomarkers of the disease at the molecular level.

Keyword

Liposomes · Theranostic nanoparticles · Pharmacokinetics · Pharmacodynamics

1 Introduction

Liposomes were the first nanoscale drug to be approved for clinical use in 1995. Since then, the technology has grown considerably, and pioneering recent work in liposome-based delivery systems has brought about remarkable developments with significant clinical implications. This includes long-circulating liposomes; stimuli-responsive liposomes; nebulized liposomes; elastic liposomes for topical, oral, and transdermal delivery; and covalent lipid-drug complexes for improved drug plasma membrane crossing and targeting to specific organelles.

Liposomes are composite structures made of bilayered phospholipid vesicles (uni- or multilamellar) with a hydrophilic and/or aqueous inner compartment. The properties of liposomes are highly attributable to their physicochemical properties such as size, surface charge, composition, rigidity of bilayer, and preparation methods. These integrated liposome features enable the encapsulation, embedding, or association with a wide range of molecules (i.e., drugs, antigens, proteins, and nucleotides) as well as enhance the delivery of therapeutic payloads into specific tissues and cells. Liposomes also improve in vitro and in vivo stability and reduce adverse effects. The successful combination of protection of its payload molecules from one hand and its potential to be cell-specific via surface modification with various targeting agents on the other hand made these carriers an attractive option in the field of therapeutics [5].

In the past 15 years, some major breakthroughs in liposome technology have fueled the rapid development of new pharmaceutical liposomal applications. In order to optimize the delivery of factors for maximum efficacy, novel methods have been proposed to increase the permeation rate of drugs temporarily and deliver the desired target compound in a time-regulated and locally restricted manner to the target site.

Lipid-based nanoparticles (LNPs) hold great promise as delivery vectors in the treatment of cancer, inflammation, and infections and are already used in clinical practice. Numerous strategies based on LNPs are being developed to carry drugs into specific target sites. The common denominator for all of these LNP-based platforms is to improve the payloads' pharmacokinetics, biodistribution, stability, and therapeutic benefit and to reduce adverse effects to a minimum. In addition, the delivery system must be biocompatible and nontoxic and avoid undesirable interactions with the immune system [2]. In addition, theranostic nanoparticles hold the potential to revolutionize future disease management. Since the last decade, there has been a growing interest in the engineering of various kinds of theranostic nanoparticles for simultaneous cancer imaging and therapy. Efficient targeting of theranostic nanoparticles to the tumor site is important for both diagnostic and therapeutic purposes.

2 Altered Pharmacokinetics Modify the Pharmacodynamic Efficacy and Toxicity of NPs

Nanoparticles as a drug delivery system possess numerous advantages over conventional therapies such as:

- Easy to alter the size and surface charge of nanoparticles, hence could be used for both passive and active drug targeting after parenteral administration.

- Altering the property of the matrix offers the chance of controlled release of medicaments.
- Nanocarriers are generally made of biodegradable substances, therefore do not remain in the body.
- Greater drug encapsulation can be obtained into the carriers without any chemical interaction; therefore, drug activity is fully retained compared to chemically modified conjugates.
- Biodistribution of therapeutics could be changed as per outer surface characteristics of the nanoparticles by late clearance of the drug in order to get the highest therapeutic potency with diminished undesired effects.
- Targeting moieties can be anchored to particle surface or guidance through magnetic-based targeting.
- Nanocarriers are designed for oral, nasal, parenteral, and ocular delivery.
- Due to their smaller size, they can penetrate through smaller capillaries, hence allowing optimal dug deposition at the target site [4].

Due to an exponential increase in surface area at nanometer levels, nanocarriers could have the capability to alter physiological interactions from the molecular level to the systemic level, creating the in vivo delivery of nanomaterial a fascinating research topic. The scope of nanomedicine has gone wider and wider in the last two decades. Nanocarriers are now made up of different types depends on the type of matrix used such as organic versus inorganic with an extraordinary control over the particle diameter, morphology, surface characteristics, drug encapsulation, and its release. However, their clinical transformation is comparatively slow and only a few commercial products such as liposomes or micelles. Regulatory guidelines for robust techniques of nanocarrier characterization are essential for assuring safety of nanomaterials. Novel nanocarriers are usually evaluated in terms of surface charge and ligand density, later on which decide their interactions with the cell surface. Conversely, in blood or other biological fluids, nanocarriers are easily covered with protein aura, which eventually dictates in vivo fates and therapeutic response [3].

3 Factors that Influence the Pharmacokinetics, Pharmacodynamics, and Toxicology of Theranostic NPs

Nanoparticles (NPs) are considered a promising tool in both diagnosis and therapeutics. Theranostic NPs possess the combined properties of targeted imaging and drug delivery within a single entity. While the categorization of theranostic NPs is based on their structure and composition, the pharmacokinetics of NPs are significantly influenced by the physicochemical properties of theranostic NPs as well as the routes of administration. Consequently, altered pharmacokinetics modify the pharmacodynamic efficacy and toxicity of NPs. Although theranostic NPs hold great promise in nanomedicine and biomedical applications, a lack of understanding persists on the mechanisms of the biodistribution and adverse effects of NPs.

Nanoparticles (NPs) possess a relatively small size in the nanorange (1–1000 nm) but have a significant advantage over atoms and molecules owing to a larger surface area per unit volume. NPs also have a greater formulating flexibility for various sizes and shapes with different chemical surface traits. Due to their versatile nature, they have been successfully used as both diagnostic and therapeutic tools. “Theranostics” refers to the development of compounds, which exhibit the characteristics of diagnostics and therapeutics in a single entity. The rapid advancement in nanotechnology has allowed the emergence of theranostic NPs, which have shown advantages of diagnosis and drug delivery as well as targeting the biomarkers of the disease at the molecular level. For the clinical use, however, the size of a NP has to be limited up to 220 nm because a standard 0.22 μm (220 nm) filter is used routinely in the clinic before injecting theranostic agents into the body. The National Nanotechnology Initiative (NNI) also defines “nanomaterials” as (1) research and technology development at the atomic, molecular, or macromolecular levels, in the length scale of approximately 1–100 nm range; (2) creating and using structures, devices,

and systems that have novel properties and functions because of their small and/or intermediate size; and (3) ability to control or manipulate at the atomic scale.

Although theranostic NPs hold great promise in nanomedicine and biomedical applications, a lack of understanding persists on the mechanisms of the biodistribution and adverse effects of NPs. An ideal theranostic NP model should possess several important properties. For delivery, NPs should act on the target tissues and demonstrate appropriate release kinetics of the drug in optimum concentrations at the site of action, illustrating their efficient therapeutic potency. Since it also possesses diagnostic abilities, it should help determine the precise location and characteristics of the disease. Along with these properties, it is very important that the NP should be nontoxic and easily excretable or eliminated from the body. There have been several reviews providing an in-depth outlook on the potential of NPs and their application in several aspects, such as their usage as theranostic agents in drug delivery and the application of theranostic NPs in cancer therapy, which is one of the most rapidly developing therapies involving nanosystems. Recognizing that the in vivo availability and efficacy of NPs are mainly determined by their pharmacokinetics (PK) and potential toxicity, we provide a brief review of these facets of theranostic NPs [1].

Regardless of their compositions, all theranostic NPs must be designed to have a reasonable half-life in blood, selective targetability, and effective elimination from the body after comprehensive delivery to the target site. To acquire these desired pharmacokinetic behaviors of NPs for clinical use, it is necessary to modulate the hydrodynamic diameter (HD), shape, composition, and surface characteristics of NPs. For instance, the overall HD of theranostic NPs is required to be <5.5 nm for renal clearance after complete targeting in order to achieve high signal-to-background ratio. In the following section, we discuss more details about the physicochemical properties of theranostic NPs in terms of size, shape, surface, composition, and route of administration.

The physicochemical properties of theranostic NPs are of significant importance in modulating PK because they determine the immediate pharmacological response in the body when the NPs are administered. Drugs with low bioavailability can have better drug dissolution rates by the technique of “nanosizing” a drug formulation, which would promote increased absorption of the drug. Also, NPs can prolong the half-life of drugs in blood circulation, which would otherwise be rapidly cleared or degraded. Since the PK plays a major role in determining the therapeutic efficacy and toxicity of the administered NPs, several key factors influencing the PK of NPs are discussed. In this section, we avoid reticuloendothelial system-mediated NP clearance and focus on smaller NPs and their theranostic aspects because larger NPs have slim chances of clinical translation. As previously reported, renal excretion is a preferred and desirable pathway for theranostic NPs compared with hepatic clearance because the NPs can be rapidly eliminated from the body while little cellular internalization/metabolism is involved, thus effectively minimizing body exposure to the NPs. Theranostic nanoparticles have the potential to transform cancer treatment by delivering high-quality images to the tumor. Their ability to precisely target the tumor site has been the subject of intense research.

Although theranostic nanoparticles can target tumors, their engineering still has challenges in terms of their in vivo capabilities. Theranostic nanoparticles are designed to be versatile and adaptable to various disease management applications. Their combined therapeutic and diagnostic capabilities can be utilized to identify and treat various diseases.

Active targeting of tumors has been shown to be very effective in the treatment of various types of cancer. Currently, theranostic nanoparticles are mainly used for target selection. However, their ability to effectively target tumors is still a major challenge. There are many ways to engineer ranostic nanoparticles. They can be used for drug delivery, photo bioimaging, and medical imaging. A similar method involves attaching contrast agents to nanoparticles. This method works by combining the therapeutic properties of

these agents with the imaging properties of the nanoparticles. Nanoshells, cages, and Cu-CuS are commonly used for achieving intrinsic and therapeutic properties. For achieving this, various surface modifications are performed. Although theranostic nanoparticles are in the early stages of their development, there are numerous efforts being made to improve their efficiency. Currently, they are being studied using various imaging and therapeutic nanoplatforms. An optimized targeting strategy for theranostic nanoparticles can prevent or minimize their accumulation in the tumor. This strategy involves the use of active molecules that can affect the vascular and lymphatic drainage of the tumor. Due to the wide variety of tumors and the unpredictable nature of their extravasation, the passive targeting strategy can be limited to its limitations in certain fast-growing tumors [7].

Theranostic nanoparticles are designed to actively target tumors. They are developed by conjugating various targeting ligands to recognize and target certain receptors that are overexpressed in tumor cells. Depending on the properties of a particular theranostic nanoparticle, its targeting ligands may be small molecules, antibodies, or protein fragments. Currently, only a few examples of these have been reported. Inspired by this, several works are being carried out to create targeted nano-beacons that can inhibit or activate the photodynamic activity of folate-controlled porphysomes after their internalization into the tumor.

Nanoparticles (NPs) are viewed as a promising tool in therapeutics. Theranostic NPs have the consolidated properties of designated imaging and medication delivery inside a solitary substance.

While the classification of theranostic NPs depends on their construction and creation, the pharmacokinetics of NPs are altogether impacted by the physicochemical properties of theranostic NPs. Thus, changed pharmacokinetics change the pharmacodynamic adequacy of NPs. In spite of the fact that theranostic NPs hold incredible guarantee in nanomedicine and biomedical applications, lesser understanding endures on the undesirable impacts of NPs.

Nanoparticles (NPs) have a moderately little size in the nanorange (1–1000 nm), NPs likewise have a more prominent defining adaptability for different sizes and shapes with various compound surface characteristics.

Because of their flexible nature, they have been effectively utilized in current drug delivery strategies. “Theranostics” display the attributes of both diagnostics and therapeutics. The quick progression in nanotechnology has permitted the development of theranostic NPs, which have shown benefits of analysis and medication conveyance just as focusing on the biomarkers of the sickness at the atomic level.

For the clinical use, nonetheless, the size of a NP must be restricted up to 220 nm on the grounds that a standard 0.22 μm (220 nm) size is utilized regularly for administration.

The National Nanotechnology Institute (NNI) likewise characterizes “nanomaterials” as examination and innovation improvement at the nuclear, sub-atomic, or macromolecular levels, in the length size of around 1–100 nm range; making and utilizing constructions, gadgets, and frameworks that have novel properties and capacities due to their little as well as halfway size; and capacity to control at the nuclear scale. In spite of the fact that theranostic NPs hold extraordinary guarantee in nanomedicine, furthermore biomedical applications, an absence of understanding perseveres on the components of the biodistribution and unfriendly impacts of NPs.

An ideal theranostic NP model ought to have a few significant properties. For drug delivery, NPs should be focused on the targeted tissues and exhibit suitable delivery of the drug at the site of activity, showing their effective strength. Since it additionally has analytic capacities, it should help decide the exact area and qualities of the illness.

Alongside these properties, it is vital that the NP ought to be non-harmful furthermore, effectively excretable or wiped out from the body. There have been a few researches giving a top to bottom point of view toward the capability of NPs and their application and their utilization as theranostic moiety in drug delivery and the use of theranostic NPs in malignant growth treatment.

Perceiving that the in vivo accessibility and viability of NPs are basically controlled by their pharmacokinetics (PK), it is important to mention these features of theranostic NPs [8].

The basic composition and therapeutic modality along with some pros and cons are summarized in Table 8.1.

The physicochemical properties of theranostic NPs are of critical significance in determining PK on the grounds that they decide the prompt pharmacological reaction in the body when the NPs are directed. Medications with low bioavailability can have better medication disintegration rates by the method of "nanosizing" a medication definition, which would enhance retention of the drug [12]. Also, NPs can delay the half-life of medications in blood stream. Since the PK plays a significant role in deciding the effectiveness of the regulated NPs, a few key elements impacting the PK of NPs need to be studied.

3.1 Size and Shape

The capacity of the NPs to enter the cell is dictated by both physicochemical boundaries and natural obstructions. Due to the high surface region to volume proportion (little size), they can enter the boundaries by infiltration through the cell membrane and deliver the medication inside the cell. It has been observed that an overall size range of 10–12 nm is ideal and offers high penetration and insignificant deposition in tissues. Picking an appropriate size in planning a NP is important as it coordinates which discharge pathway the medication would follow. For model, particles with a more modest size of <5.5 nm follow the course of renal excretion, though bigger estimated NPs are metabolized through the liver.

Also, selecting an appropriate carrier system is of high importance. NP frameworks, like liposomes and nanospheres, have been utilized in exact focusing of different illnesses with intravenous delivery of theranostic small particles. The drug-loaded carriers can control the effectiveness of drug delivery and furthermore ensure the safety of drug from inactivation as well as degradation, which can decrease its side effects. The cellular take-up is likewise impacted by the state of the NPs; for instance, stretched NPs are better absorbed than circular ones [3, 4].

3.2 Surface Property

A modification in the surface of NPs has significant effect on the physical, chemical, and biological nature of the therapeutic molecules in biological systems.

NPs can impart positive or negative charges on the surface, where the interactions with cell membrane change in different ways, which affects their absorption and distribution properties. NPs with positively charged surface show higher cell uptake as compared to negatively charged NPs due to electrostatic interactions.

Alteration of the NP surface with a neutral non-ionic polymer induces stability to the NP by minimizing opsonization and increasing blood circulation time, as exemplified by NPs coated with polyethylene glycol (PEG) on their surface as reported in a study. Surface property also plays an important role when the NPs reach biological fluids (e.g., blood). The surface of NPs is coated with a layer of proteins when they come in contact with the biological fluid. This layer plays a major role in determining the attraction of the NP to the cell membrane. Different NPs form different protein layers, and, thus, every type of NPs has different affinity for a particular protein in a biological fluid, thereby affecting the physicochemical characteristics, which would subsequently affect the rate and extent of biodistribution [4, 5].

3.3 Administration Route

The PK of a drug from a NP depends upon the route by which the drug has been administered, which modifies pharmacological efficacy of the drug. For instance, when bovine insulin was given orally by means of a pH-responsive NP system of chitosan and poly(γ-glutamic acid) to rats, it showed a greater bioavailability compared with subcutaneously injected insulin in diabetic

Table 8.1 Nanoparticle composition and therapeutic modality [5]

Class	NP type	Composition	Therapeutic modality	Pros	Cons
Inorganic NPs	Magnetic NPs	Iron oxide	Chemotherapy; SiRNA; magnetic hyperthermia	Intrinsic MRI contrast; thermal therapeutic agent	Interference in imaging
	QDs	Semiconductor	Chemotherapy; SiRNA; photodynamic therapy	Broadband absorption; small size; tunable emission band	High potential toxicity
	Silica NPs	Mesoporous silica	Chemotherapy; SiRNA	Multi-functionality; facile synthesis; solubility	Stability; need contrast agents
	Carbon NPs	Graphene oxide	Photothermal therapy; photodynamic therapy; chemotherapy	Large surface area; thermal therapeutic agent	Size control; difficulty in purification
		Carbon nanotubes		Size tunability; mechanical strength	High aspect ratio; difficulty in purification; poor solubility
	Gold NPs	Gold nanoshell	Photothermal therapy; chemotherapy	Size tunability; intrinsic thermal therapeutic agent; tunable in NIR region	Potential toxicity
		Gold nanorod	Photothermal therapy		High aspect ratio; toxicity; difficulty in therapeutic payload
	Others	CuS NPs	Photothermal; chemotherapy	Thermal therapeutic agent; tunable in NIR region	Potential toxicity
		MoS2 nano sheet	Photothermal; chemotherapy; SiRNA	Large surface area; thermal therapeutic agent	Need contrast agents; difficulty in size control
Organic NPs	Biological NPs	Naturally polymers and lipoprotein	Chemotherapy; siRNA	Biocompatibility; biodegradability	Need contrast agents; difficulty in size and degradability control
	Polymer NPs	Linear and branched polymer	Photodynamic therapy; chemotherapy	Biodegradability; flexibility; size tunability	Need contrast agents
	Dendrimers	Tree-like macromolecules	Chemotherapy	Size tunability; solubility	Limited synthesis; need contrast agents
	Liposomes	Phospholipid bilayers	Chemotherapy; siRNA	Conventional drug delivery; large payload	Need contrast agents; poor stability

patients [4, 9]. These oral NPs infiltrate the mucous layer of the intestinal tract and gradually destabilize and disintegrate due to their pH sensitivity. The increased bioavailability may be attributed to the pH-sensitive insulin release from the NPs. The difference in biodistribution of insulin and prolonged reduction of glucose levels between subcutaneous insulin and oral NPs could be because insulin, via the oral route, mimics the physiological pathway of the endogenously secreted insulin, which reaches the liver and helps to control the glucose levels in the body. In contrast, the insulin given by the subcutaneous route fails to mimic this since it enters the periph-

eral circulation, which is not the normal route of insulin production and secretion.

There are several publications concerning the effect of injection routes on the biodistribution and elimination of NPs. Very recently, the biodistribution, clearance, and tumor uptake of renally clearable carbon dots with three different injection routes, including intravenous, intramuscular, and subcutaneous administrations, were reported.

The blood clearance and urinary accumulation rate of administered NPs followed the order of intravenous > intramuscular > subcutaneous injections.

In addition, tumor uptake of carbon dots by subcutaneous and intravenous injections was higher than that by intramuscular injection. Such examples are indicative of the route-dependent therapeutic potential and clinical benefits of NP-based theranostic systems. Absorption, biodistribution, elimination, and pharmacologic and toxic effects of NPs are observed following different routes of administration [6].

The pharmacokinetics and pharmacodynamics of theranostic nanoparticles have been illustrated in Fig. 8.1.

3.4 Imaging and Therapeutic Modalities

The determination of imaging methodology is another significant segment for theranostic NPs. The utilization of negligible or noninvasive imaging methodology is valuable to portray the PK especially biodistribution as restorative adequacy of theranostic NPs. Current clinically accessible imaging modalities incorporate atomic imaging (positron emanation tomography (PET) and single photon emanation registered tomography (SPECT)), attractive reverberation imaging (MRI), processed tomography (CT), ultrasound (US), optical imaging, and photoacoustic (PA) imaging. In any case, for effective atomic imaging, the surface or center of NPs ought to be changed with different radioisotopes, paramagnetic particle chelates, or fluorophores, with the exception of utilizing inborn different NPs like iron oxide NPs, QDs, and color doped silica NPs. In view of the inborn affectability and tissue infiltration capacity of imaging modalities, the theranostic NPs could be pictured through noninvasive (more wanted) or insignificantly intrusive (less wanted) way in demonstrative techniques. The upsides and downsides of each imaging methodology are summed up in this segment; we portray remedial modalities of NPs [10, 11].

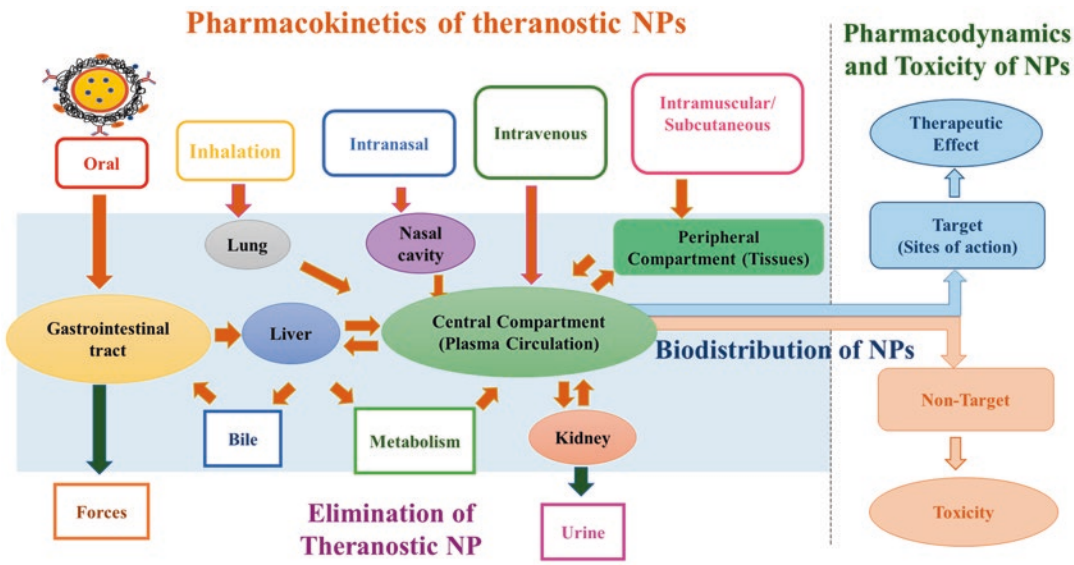

Fig. 8.1 Pharmacokinetics of theranostic NPs

3.5 Composition

Many therapeutic NPs are composed of several different elements with specific geometry/conformation such as core shell, core-satellite, linear, and hyper-branched structures. The little differences of the geometry or conformation can contribute to their in vivo performance such as absorption, biodistribution, elimination, as well as targeting ability [2]. In addition, the geometry/conformation changes of NPs and decomposition in in vivo environments can significantly affect toxicity.

The biodegradability of theranostic NPs relies on their chemical compositions. Polymeric NPs containing hydrolysable linkages, such as ester, ortho-ester, and anhydride, in their backbones are biodegradable in the body. The use of biodegradable polymers can significantly increase the elimination of NPs from the body and reduce the long-term toxicity. On the contrary, most inorganic NPs are not biodegradable. Such inorganic NPs remain for a relatively long period of time in the body due to their larger size and greater hydrophobicity compared with small molecules; therefore, concerns have been raised about the potential long-term toxicity of these NPs. Taken together, both physicochemical properties (i.e., surface charge, chemistry, and size of the NP) and exposure routes are critical factors that determine the PK of NPs, and these factors can be modified to control (enhance or decrease) the blood circulation and tissue permeation of the drug. On the other hand, poorly designed NPs can promote an enhanced delivery of the drug molecules to certain non-target tissues nonspecifically and cause undesirable side effects, which warrant the appropriate assessment of toxicity for the use of NPs [10].

3.6 Therapeutic Purpose

Chemotherapy

Since cancer is one of the leading causes of death worldwide, NP-based cancer therapy has great potential for overcoming biological barriers and selective targeting to desired sites.

Furthermore, NPs are relatively small and have greater affinity for the cell membrane, thus can easily enter the cancer cells after binding to the cell surface specifically through targeting ligands, which decreases nonspecific biodistribution and the toxicity in non-target organs. Polymeric NPs like liposomes and micelles have been used to solubilize hydrophobic drugs so that higher percentage of injected dose (%ID) can be achieved at the target site. Doxil, for example, is a PEGylated liposome coated on doxorubicin (DOX), where the PEG coating prevents the degradation of drugs by immune system and controls the release of drugs into the blood, resulting in a prolonged terminal half-life and higher drug efficacy. Another example is a QD-aptamer-DOX conjugate [QD-Apt(DOX)] for prostate cancer therapy. The QD-Apt(DOX) conjugate can perceive and render DOX at the target site by using the fluorescence resonance energy transfer (FRET) effect between DOX and QDs. The conjugate is composed of the following three parts: (1) therapeutic DOX, (2) targeted RNA aptamers, which are covalently attached onto the surface of QDs, and (3) diagnostic QDs for fluorescence imaging. This activatable system works by turning "on" the fluorescence by releasing DOX in the tumor cells, while the DOX-loaded QD-Apt is "off" in the normal cells [10].

Gene Therapy

Gene therapy implies the replacement of a faulty gene in the cell with a proficient gene or by overexpression or silencing of a gene by introducing a foreign DNA and modifying the cellular signaling. NPs have a capability to replace viral vectors as they are small in size and therefore can communicate with many biological moieties like cytokines and proteins. Although they possess some drawbacks, such as inefficient transfecting efficiency, these can be overcome by chemical modification of the functional groups. Magnetic NPs have been used in gene therapy by intercalation of the functional gene with the SPION and its effective transfection into the desired cell by high gradient magnets [13, 14].

4 Theranostic Applications and Pharmacodynamics of NPs

The application of theranostic NPs has been most successfully employed in cancer research. For theranostic and clinical applications, most NPs must have inert layer of surface coatings with polymeric or biological materials. In addition, selective targeting is also a desired property to overcome the limitations of conventional therapy and to minimize potential side effects.

There are two major strategies for efficient tumor targeting:

One is passive targeting, where, therapeutic NPs reach the tumor tissues through leaky endothelium surrounding tumor tissues through enhanced permeability and retention effect.

In contrast, active targeting is based on targeting ligands, such as antibody, aptamer, and peptide, on the NP surface which allow NPs to bind to the receptors overexpressed on cancer cells [15, 16]. In this section, several advanced examples of theranostic nanoplatforms have been discussed.

4.1 Synthetic Polymer NPs

Photosensitizer-conjugated amine functionalized polyacrylamide NPs prepared by oil-in-water microemulsion technique have been reported in some studies.

In some studies, for tumor-specific targeting, the surface of NPs was modified with cell-permeable peptide and biologically inert PEG. Once fluorophore-embedded NPs enter the tumor, the fluorescence dye lights up the tumor cells and the drug is photosensitized by irradiation, which specifically kills the cancer cells. In addition, Liu et al. reported polyelectrolyte-based polyprodrugs which possess imaging, chemotherapeutic, and photodynamic properties. The NPs were covalently conjugated to doxorubicin through a reactive oxygen species (ROS) cleavable linker. PEGylated polyelectrolytes efficiently produce ROS under light irradiation, which then not only kill the cancerous cells by photosensitization but also can release doxorubicin for chemotherapy. Light-triggered chemotherapy and photodynamic therapy have been combined to produce better results to cure cancers with synergistic advantages such as overcoming multiple drug resistance and improved therapeutic efficacy [13–15].

4.2 Biological NPs (Naturally Derived Polymers)

The self-assembled micellar nanocomplex (MNC) has been developed for delivery of protein drugs. Some research groups reported that simple sequential self-assembly of the epigallocatechin-3-O-gallate (EGCG) derivative, a major ingredient of green tea, with anticancer protein leads to the formation of stable micellar nanocomplex. The anticancer effect of Herceptin-loaded micellar nanocomplex (Herceptin–MNC) was investigated in vitro and in vivo and compared with those of bovine serum albumin (BSA)-MNC and free Herceptin. Herceptin-MNC exhibited a 2.3-fold greater accumulation in the tumor site, 29-fold longer blood half-life, and significantly higher anticancer effect in the tumor in comparison with free Herceptin [20–22].

4.3 Mesoporous Silica NPs

Mesoporous silica NPs have been used successfully in cancer therapy, mainly because of large surface area and pore volume and ease of surface modification. Recently, magnetic NPs or gold NPs were embedded into mesoporous silica NPs for thermally triggered drug release. An anticancer drug was loaded into porous cavities of mesoporous silica NPs, and porous structures were capped with thermally releasable molecule.

When external stimuli, such as magnetic field and NIR laser, are applied to these mesoporous silica nanoplatforms, drug release can be controlled precisely. This controlled release behavior is a very important feature in target specific therapy as it can overcome the side effects of conventional drug delivery system [21, 22].

4.4 Magnetic NPs

Another example of theranostic NPs in cancer is the use of magnetic NPs (MNPs). MNP-based theranostics can be divided into three ways in terms of therapeutic methods:

1. Hydrophobic drug or gene delivery
2. Thermal therapy in the magnetic field
3. Magnetic/mechanical controlling in cell signaling

Theranostic MNPs normally contain a superparamagnetic iron oxide core, which is used for MRI to detect the tumor, covered by a hydrophilic surface coat on the outside. They have been reported to be linked with an anticancer drug or siRNA to treat the tumor. As one of the important examples, Moore and coworkers have reported dextran-coated SPIONs for in vivo siRNA delivery. The amine-dextran-coated SPIONs were labeled with Cy5.5 dye for simultaneous optical imaging and covalently linked to thiolated siRNA duplex and myristoylated polyarginine peptides, which are membrane translocation modules, for intracellular delivery. This study showed advancement of siRNA delivery and silencing with imaging strategies. MNPs can be also developed by conjugating chemotherapeutic drugs on the surface of NPs to target and treat cancers [18]. Lee et al. have also developed a nanocarrier containing MNP conjugated to the anticancer drug gemcitabine [13]. These NPs deliver the drug by receptor-mediated endocytosis to its target, urokinase plasminogen activator receptor, and also allows in vivo MRI of the tumor [14].

Magnetic thermal therapy utilizes heat induced from MNPs in external high-frequency alternating magnetic field, which allowed us to control heat generation after specific targeting to tumor region of interest. Although external triggering is one of the advantages in magnetic field-induced thermal therapy, the efficacy is limited even with high concentration of therapeutic MNPs. Very recently, to control cell signaling, a magnetic switch method has been developed by using zinc-doped iron oxide MNPs. The thiolated MNPs were conjugated with antibody for targeting death receptor 4 (DR4) of DLD-1 colon cancer cells. When a magnetic field is applied to MNP bound DR4s on DLD-1 cells, clustering of DR4s was formed and apoptosis signaling pathways were induced [22].

5 Theranostic Nanoparticles Designed as Drug and Gene Delivery Vehicles

Cellular delivery involves the transport of various drugs and biomolecules. Drugs carried by nanoparticles can be protected from enzymatic degradation and lead to better absorption and distribution. Also, drug solubility and intestinal permeability often act as obstruction to the oral bioavailability of potential drugs. As a solution to this problem, hydrophobic drugs can be incorporated into nanoscale drug delivery vehicles and transported into cells. This ability allows us to re-examine promising drugs previously dropped from development due to poor solubility.

During the past decade, liposomes, micelles, and nanoemulsions have been developed as drug and gene delivery systems. Abraxane, a nano-sized albumin-bound paclitaxel emulsion, was approved by the US Food and Drug Administration for the treatment of metastatic breast cancer in 2005. Fewer allergic reactions were observed in patients using this nanoformulation compared to free paclitaxel. A nanoemulsion of docetaxel (ANX-514) showed bioequivalence and overall safety comparable to the Taxotere formulation of docetaxel. In addition, other drug and gene delivery systems based on polymers, dendrimers, as well as biomolecules are also at different stages of preclinical and clinical development. For example, compared with a standard paclitaxel formulation, ABI-007, a nanoparticle formulation of paclitaxel which is cremophor-free, can be more efficiently and safely administered at high doses with superior response. In clinical trials of this nanoparticle formulation, prolonged survival time with no severe hypersensitivity reactions was observed when treating metastatic breast cancer [14, 17].

Development of nanodrug and gene delivery systems requires an understanding of the absorp-

tion, distribution, metabolism, and excretion profiles of the nanomaterials.

This clinical profile is required not only to optimize the clinical effects of nanomaterials but also to provide guidance for their safe use.

5.1 Nanoparticles Constructed as Drug Carriers for Efficient Delivery

Nanosized carrier systems have the potential to prolong the half-life of the encapsulated drug in the body through enhanced permeation and retention (EPR) effects. A number of nanoparticle-mediated effects, such as improved chemical stability, controlled release from the nanoparticle, and protection of the drug from the immune system, may result in prolongation of a drug's half-life and increased therapeutic window.

Incorporation of drugs into nanodelivery vehicles has resulted in a new paradigm for lowering the adverse effects of chemotherapeutic drugs. Broad application of paclitaxel and doxorubicin is limited by their physiochemical properties that result in intolerable side effects. The replacement of paclitaxel's solubilizer, Cremophor, with amphiphilic cyclodextrin nanoparticles prevents paclitaxel from undesirable recrystallization in aqueous solutions and significantly reduces the drug's side effects such as hemolysis and cytotoxicity. When doxorubicin is loaded into biodegradable poly(D,L-lactide-co-glycolide) nanoparticles for oral chemotherapy, it exhibits not only reduced cardiotoxicity compared to free doxorubicin but also improved oral bioavailability [14, 15].

One of the major challenges in drug delivery is selectively targeting diseased tissues. The efficacy of cancer chemotherapy is greatly limited by the incidence of toxicity to healthy tissues, attributed to the lack of specificity exhibited by anticancer agents for cancerous cells. Recent research has led to development of nanocarrier systems for delivery of anticancer drugs with improved therapeutic efficacy and reduced side effects. A ferrocenyl diphenol tamoxifen derivative, incorporated into lipid nanocapsules, shows antiproliferative activity specific for malignant glioma cells, but it demonstrates low toxicity levels in normal brain cells. The biocompatible solid lipid nanoparticles has been developed for the specific delivery of docetaxel to hepatoma cells. Targeted delivery was achieved in this case by using a galactose moiety that recognized an asialoglycoprotein receptor upregulated on the hepatoma cells' surface. While increasing cellular uptake by hepatoma cells and drug accumulation in tumor, this targeted nanocarrier of docetaxel is well-tolerated in vivo, without impairing liver f unction, as observed histologically.

For anticancer drugs to be therapeutically effective, it is important to properly release the drug from the nanocarriers to deliver the drug into the malignant cells. Controlled release of drugs from nanoscale formulations has been observed in earlier studies. The encapsulation of temozolomide, which is a drug used to treat brain tumors, in solid lipid nanoparticles provided sustained-release of temozolomide, along with avoiding the adverse side effects such as cardiac and nephrotoxicity as usually caused by the conventional formulation.

In lung transplantation, liposomal delivery of lipophilic immunosuppressants such as tacrolimus has been observed to provide sustained release and less frequent administration of the drug, thus resulted in reduced dose-related toxicity. It has been demonstrated that an aerosolized nanoparticle formulation of the hydrophobic immunosuppressant, amorphous cyclosporine A, has an enhanced dissolution rate and, therefore, increased drug penetration and diffusion into lung tissue and the bloodstream. In addition, this nanoparticle formulation does not cause lung tissue irritation which is a frequent problem when using a solution-based pulmonary formulation [13–15].

In general, the two major challenges hampering ophthalmic drug delivery are the unique anatomical and physiochemical barriers of the eye and rapid precorneal drug loss. Liposomes and nanoparticles have been used to improve corneal penetration and achieve controlled delivery and sustained drug release. A biocompatible polymeric nanoparticle suspension loaded with sodium diclofenac has been developed. This sus-

pension does not irritate ocular tissues in vivo and has a favorable mean size for ophthalmic applications. Kao et al. successfully incorporated pilocarpine into chitosan/Carbopol nanoparticles for ocular applications.

These nanoparticles were observed to show little toxicity and a better prolonged release profile compared with pilocarpine in solution, gel, or liposomes. The easily modified characteristics of chitosan-based nanosystems render them suitable candidates for ophthalmic nanoformulations.

Nanoparticles can cross biological membranes in a non-destructive way without creating much toxicity. This property makes nanoparticles specially useful for improving drug bioavailability in the brain. Superoxide dismutase, a scavenger of reactive oxygen species, poorly penetrates the blood-brain barrier (BBB). When it is encapsulated in biodegradable poly(D,L-lactide-co-glycolide) nanoparticles, superoxide dismutase was demonstrated to cross the intact BBB and efficiently minimize the damage created by cerebral ischemia-reperfusion. In combination with focused ultrasound, which have the capability to locally and transiently disrupt the BBB, the magnetic nanoparticles loaded with chemotherapeutic agents can sufficiently penetrate the BBB and be deposited in the brain through both passive and active targeting, as monitored by MRI [15, 22].

5.2 Theranostic Nanoparticles for Future Customized Medication

Theranostic NPs can be employed for cancer chemotherapy, siRNA delivery, and photodynamic therapy. Small drug molecules have shortcomings including toxic side effects in normal tissues, inadequate specificity to tumor tissues, limited localization to tumor cells because of their hydrophobicity, and drug resistance. Theranostic NPs have the capabilities to overcome these problems in chemotherapy. Also, a theranostic NP delivery system can be useful for siRNA therapy. Theranostic NPs are efficient in enhancing the stability of siRNA in the blood stream after intravenous injection, thereby minimizing degradation by enzymes. Accepting the fact that naked siRNA can be eliminated from the blood within 5 min after administration through intravenous injection, prolonged circulation time of siRNA in NPs can be attributed to effective therapy. Also, it is observed in some studies that negatively charged siRNA cannot easily enter the cytosol of target cells, which can be solved by theranostic NPs for siRNA therapy. During photodynamic therapy, theranostic NP-based photodynamic therapy provides benefits such as reduced systemic toxicity and improved solubility in water as compared to conventional photodynamic therapy. The selective localization of photosensitizer molecules incorporated in NPs reach the target and can significantly lower the systemic toxicity related to classical photodynamic therapy. In addition, mostly photosensitizer molecules being used in photodynamic therapy can accumulate in biological media, leading to a change in their optical characteristics [6, 16].

5.3 Diagnostic Modalities in Theranostic Approaches

In theranostic strategies and applications, diagnostic imaging becomes necessary for establishing the presence and intensity of molecular targets for certain diseases. At present, several noninvasive imaging modalities are being utilized to detect molecular targets in vivo such as optical imaging, ultrasound (US) imaging, MR imaging, computed tomography (CT), and nuclear imaging which are single photon emission computed tomography (SPECT) and positron emission tomography (PET). These diagnostic modalities can be broadly classified into primary molecular imaging modalities and primary morphological/anatomical imaging modalities. The primary molecular imaging modalities are characterized by high sensitivity and involve optical imaging and PET/SPECT techniques, whereas primary morphological/anatomical imaging has features of high spatial resolution such as CT, US, and MRI. Particularly, optical imaging and PET/SPECT have capacity to detect molecular targets, which are important

in a disease process, thus making it more favorable for theranostic approaches. Recently, integrated molecular/anatomical systems (e.g., SPECT/CT) have been developed to aggregate the capabilities of individual imaging modalities.

- Diagnostic Capabilities

The diagnostic purpose of theranostic NPs is to detect the locations of disease, the disease status, and the response of disease to treatment. The increased binding at the site of interest is achieved by either passive or active targeting. The location and extent of NP signal after intravenous administration depends on cell surface receptors and measures the tumor's size and stage of tumor. NP signal process usually utilizes radionuclides or fluorophores. Also, the NPs have an intrinsic property for contrast, for example, iron oxide for MRI. NPs are often coated with ligands that target angiogenesis markers. For example, the RGD peptide binds to Rvβ3 integrin, and vascular epidermal growth factor (VEGF) binds to the VEGF receptor (VEGF-R) to identify angiogenic tumor.

Once bound, the NP can assist in monitoring resection or monitor response to therapy. Alternatively, passive targeting can be used for anatomic imaging rather than MI.

Diagnostic NPs involve superparamagnetic iron oxide (SPIO) and ultrasmall SPIO (USPIO) for MRI contrast and targeted SPIO NPs. That allows MI through MRI. Gold NPs are used for CT and radiograph contrast and MI through ligands. Silica nanoparticles have usefulness in MRI as gadolinium containers or to protect inner imaging cores. Optical diagnostic agents involve quantum dots (QDs), fluorophore-doped silica NPs, and fluorophore-doped polymeric NPs. Carbon nanotubes and gold nanorods can produce photoacoustic contrast. Surface-enhanced Raman scattering (SERS) NPs are utilized in multiplexed approaches. Some NPs are multimodal as they detect signal through more than one method such as fluorescence and MRI both [11, 14]. The diagnostic capabilities of nanoparticles are given in Table 8.2.

- Therapeutic Capabilities

The therapeutic capabilities of the NPs are diverse as it can assist in the drug delivery and drug release to the desired diseased areas. Conventionally, small molecule chemotherapeutics such as doxorubicin and paclitaxel were being delivered through NPs. Next-generation NP systems also can deliver siRNA for RNA interference with gene expression. It has been demonstrated that gold NPs not only assist cellular delivery of oligonucleotides but also stabilize them from nucleases. The release takes place due to the ablative effect of radionuclides loaded into NPs for degradation of the tumor cells, causing DNA damage and retarding cell growth. The release, which may also be in the form of heat or vibrational energy, can disrupt the structure of the cells and shrink the tumor size. Further, the therapeutic role also involves the surgery for tumor resection. NPs can contain an imaging agent, which can act as both diagnostic to determine tumor type, location, etc. and therapeutic that uses that image to guide tumor removal. Intraoperative imaging is visualization of diseased areas exposed during surgery and is especially useful, when the location of the tumor may change after presurgical imaging and during resection. Also, the therapeutic role can be disruption of a cellular or metabolic pathway. This approach utilizes a ligand to target the NP and disrupt cell regulation. An example of this is Herceptin-labeled NPs, which occupy the Her-2 cell surface receptors.

In drug delivery applications, the NP carrier stabilizes the payload, permitting a measured release of drug, reducing toxicity and side effects. Hydrophobic drugs are protected by the NP interior. Most therapeutic agents carrying NPs are in the form of liposomes or lipid-based complexes, as well as polymeric micelles or biodegradable polymer/drug composites. The therapeutic and diagnostic roles of nanoparticles are diverse as summarized in Table 8.3. The most common substrate is a blend of poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) (PLGA-PEG). Metallic NPs used in tandem with infrared heating are thermoablative NPs; nanoshells and

Table 8.2 Types of NPs. The diagnostic roles of nanoparticles [4]

Technique	Limitation	NP solution	NP type
CT	Sensitivity	Contrast	Gold, silver, iodine
Optical	Signal penetration	Intense signal Fingerprint spectra	Quantum dots Raman nanoparticle
MRI	Poor multiplexing	Contrast	Iron oxide/cd^{3+}
PET/SPET	Anatomic technique	Multimodal	Radiolabeled NP
Ultrasound	Spatial resolution	Contrast	Silica, nanobubble
Resection	Anatomic technique	Border delineation	MRI and/or fluorescent
Radiation therapy	Tumor location	Radio-NPs	Sir-spheres (microparticles)

Table 8.3 Types of NPs. The therapeutic and diagnostic roles of nanoparticles [4]

NP type	Description	Therapeutic role	Diagnostic role	Example
I	NP with endogenous contrast	Targeting ligand occupies cell pathway site	Imaging with site specificity phenotyping	Iron oxide NPs
II	NP caring imaging agent	Image-guided resection	Border delineation	Radiolabeled silica, florescent silica
III	NP caring therapeutic agent	Therapeutic release radioablation	Typing with site specificity	pH-responsive liposomes
IV	Labeled NP caring therapeutic agent	Therapeutic release	Imaging with site specificity	Fluorescent liposomes
V	NP responsive to external stimulus	Photothermal therapy, selective drug release	Thermal imaging, CT	Magnetic nanoparticles

nanorods are the most common examples. Sir-spheres are the trademarked name of yttrium-90-loaded nanoparticles used to treat liver cancers. These particles are injected into the hepatic artery and accumulate in the tumor where they ablate the tumor in vivo [19].

6 Challenges and Future Directions

Theranostic nanoparticles have the capabilities to bring revolution in the future disease management approaches. Since the last decade, there has been an emerging interest in the development of various kinds of theranostic nanoparticles for imaging and therapy. Efficient targeting of theranostic nanoparticles to the tumor site is important for both diagnostic and therapeutic purposes. However, challenges still exist in the development of biocompatible theranostic nanoparticles with high specificity for in vivo tumor targeting potential.

There are also several studies being carried out in developing activatable theranostic nanoparticles for even "smarter" cancer diagnostic imaging and chemotherapy. For example, an activatable theranostic prodrug was designed by conjugating SN-38 that is a topoisomerase inhibitor with piperazine-rhodol fluorophore using a self-immolative linker based on disulfide bonds. Such a product could assist real-time monitoring of the delivery and release of the SN-38 payload in the presence of intracellular thiols. With activatable theranostic nanoparticles, getting vital information related to the treatment response can also be possible, which can be very much useful during the decision-making process of doctors to alter treatment protocols at the right time.

Therefore, there is an inclination toward aggregating the diagnostic and therapeutic utilities of theranostic nanoparticles, resulting in more improved and customized disease management. For the purpose of clinical translation, many major challenges need to be crossed, such as the selection of the better nanoplatform, improvement in the ligand conjugation efficiency, and also in the development of an ideal synthetic technique with fewer steps, higher

reproducibility, and cost-effectiveness. Because of the high sensitivity and accurate quantification using diagnostic techniques such as positron emission tomography imaging, radiolabeling of FDA-approved therapeutic nanoparticles, such as Doxil (liposomal doxorubicin), could emerge as a highly effective strategy to enable the visualization and accurate determination of biodistribution, circulation half-life, and pharmacokinetics of theranostic nanoparticles, without compromising on drug loading capacity and safety profile. Conjugating targeting ligands to nanoparticles with intrinsic imaging and therapeutic characteristics, such as porphysomes and gold nanoshells, will be another useful way for developing future actively targeted theranostic nanoparticles for treatment of tumor.

The last decade has witnessed a wide expansion in development of several kinds of theranostic nanoparticles for cancer imaging and therapy. The studies on current status, challenges, and future prospects of actively targeted theranostic nanoparticles for cancer are the need of the hour. The development of theranostic nanoparticles which have properties of tumor specificity, safety, and simplicity will continue to be the research areas in the near future, promising a greater potential to be translated into the clinic practice.

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