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Nanotechnology-Based Targeted Drug Delivery in Cancer: Recent Advances, Challenges and Future Perspectives

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Abstract: Cancer is one of the major causes of morbidity and mortality worldwide. Conventional cancer treatments such as chemotherapy, radiotherapy and surgery are associated with several limitations, including poor drug specificity, systemic toxicity, inadequate drug concentration at the tumor site and development of drug resistance. Nanotechnology-based drug delivery systems have emerged as promising approaches for improving the therapeutic efficacy and safety of anticancer agents. Nanocarriers can improve drug solubility, stability, circulation time and bioavailability while facilitating targeted and controlled drug delivery. Various nanocarriers, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, polymeric micelles, dendrimers, nanoemulsions and inorganic nanoparticles, have been investigated for cancer treatment. Nanotechnology also enables active targeting through ligands such as antibodies, peptides and folic acid, as well as stimulus-responsive drug release in response to changes in pH, temperature, enzymes or redox conditions. Several nanomedicines have progressed from laboratory research to clinical applications. However, challenges related to toxicity, manufacturing, reproducibility, stability, tumor heterogeneity and regulatory approval remain. This review discusses the principles, types, mechanisms, applications, advantages, limitations and future perspectives of nanotechnology-based drug delivery systems for cancer therapy.

Keywords: Nanotechnology, cancer therapy, nanoparticles, targeted drug delivery, nanomedicine, liposomes, NLC, controlled release.

I. INTRODUCTION

Cancer remains one of the major global public health challenges, with a substantial burden of morbidity and mortality. The increasing incidence of cancer, together with population ageing and changes in lifestyle and environmental exposures, has created a growing need for effective and safer therapeutic strategies. Although significant advances have been made in cancer diagnosis and treatment, many patients continue to experience disease progression, recurrence, treatment-related toxicity, or resistance to therapy. (Bray et al., 2024; Shi et al., 2017).

Conventional chemotherapy remains an important component of cancer treatment and is frequently used either alone or in combination with surgery, radiotherapy, targeted therapy, or immunotherapy. Most conventional chemotherapeutic agents act by interfering with DNA synthesis, cell division, or other essential cellular processes. However, their lack of complete selectivity for malignant cells represents a major therapeutic limitation. Because many anticancer drugs also affect rapidly dividing healthy cells, treatment can result in adverse effects such as myelosuppression, gastrointestinal disturbances, mucositis, alopecia, and fatigue.

Another major limitation is the unfavorable pharmacokinetic profile of many conventional anticancer drugs. Poor aqueous solubility, rapid metabolism, inadequate tumor accumulation, and nonspecific distribution can reduce the concentration of the drug reaching the tumor while increasing exposure of healthy tissues. Consequently, achieving an effective concentration at the tumor site without producing unacceptable systemic toxicity can be difficult. (Shi et al., 2017; Bhatia et al., 2022).

Multidrug resistance is another important challenge in chemotherapy. Tumor cells may develop resistance through mechanisms such as increased drug efflux, alterations in drug targets, enhanced DNA repair, changes in apoptotic pathways, and modification of cellular drug metabolism. Tumor heterogeneity can further contribute to differences in treatment response among patients and within different regions of the same tumor (Holohan et al., 2013; Shi et al., 2017).

II. NEED FOR TARGETED DRUG DELIVERY IN CANCER

- 1) Selective drug delivery: Targeted drug delivery aims to deliver anticancer drugs preferentially to cancer cells or tumor tissues, potentially improving treatment selectivity (Peer et al., 2007).
- 2) Reduced systemic toxicity: Nanocarriers may reduce the exposure of healthy tissues to anticancer drugs, potentially minimizing damage to normal cells and organs (Shi et al., 2017).
- 3) Improved therapeutic efficacy: Targeted delivery systems can improve drug accumulation at the intended site and enhance therapeutic effectiveness when sufficient drug reaches the tumor (Mitchell et al., 2021).
- 4) Reduced side effects: By modifying drug distribution, nanocarriers may reduce certain treatment-related adverse effects, although the extent of toxicity reduction depends on the formulation and drug (Wicki et al., 2015).
- 5) Improved drug bioavailability: Nanocarriers can improve the apparent solubility, stability, and delivery of certain drugs, particularly poorly water-soluble anticancer agents (Mitchell et al., 2021).
- 6) Potential to address drug resistance: Some nanocarrier systems can improve intracellular drug delivery and may help address selected mechanisms of multidrug resistance (Peer et al., 2007; Shi et al., 2017).
- 7) Protection of the drug: Nanocarriers can protect encapsulated therapeutic agents from premature degradation and interactions with biological components (Blanco et al., 2015).
- 8) Controlled and sustained release: Nanocarriers can be designed to provide sustained drug release or respond to specific biological stimuli, helping regulate drug exposure over time (Mitchell et al., 2021).
- 9) Potential improvement in patient compliance: If a delivery system reduces adverse effects or dosing frequency, it may improve treatment acceptability. However, this benefit depends on the clinical performance of the formulation (Wicki et al., 2015).
- 10) Potential improvement in the therapeutic index: Targeted delivery may increase the difference between effective drug exposure at the tumor and toxic exposure to healthy tissues, potentially improving the therapeutic index (Shi et al., 2017).

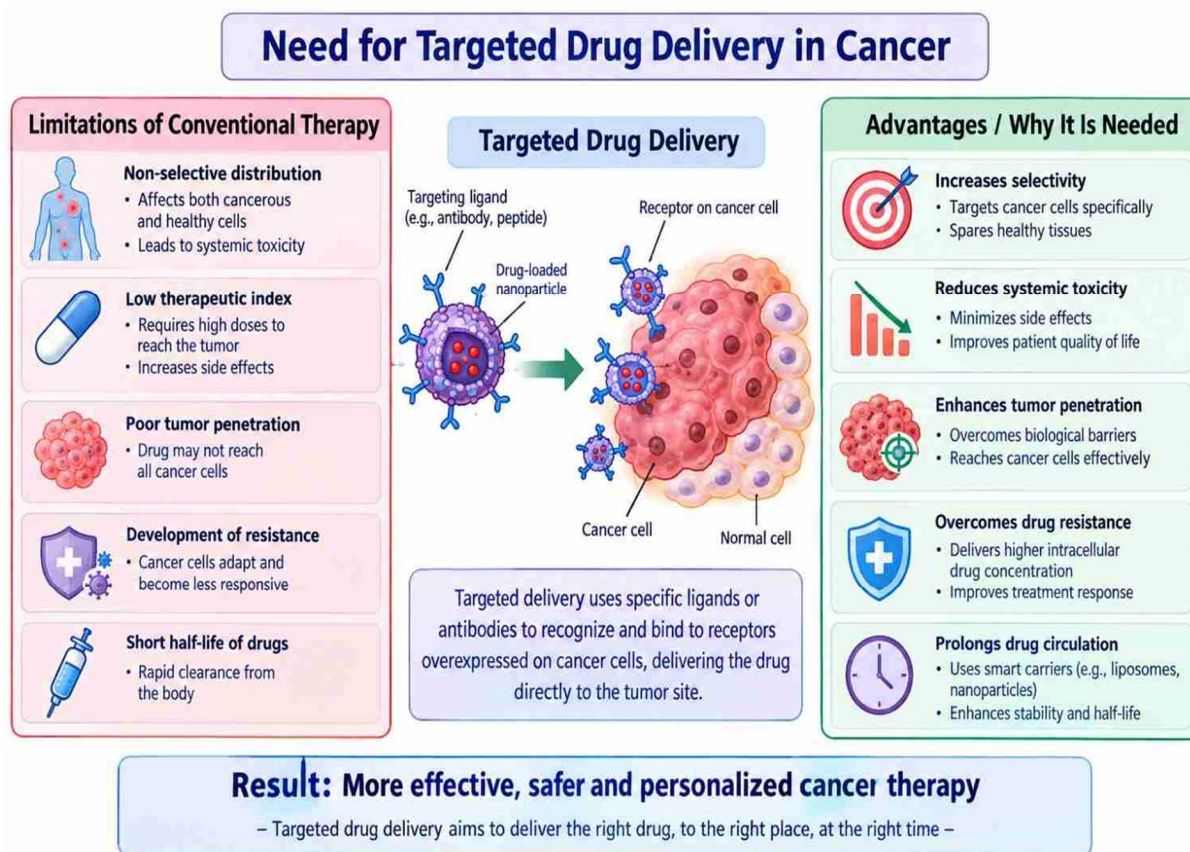


Figure 1. Need for Targeted Drug Delivery in Cancer: Limitations of Conventional Therapy, Mechanism of Targeted Delivery, and Its Potential Advantages

III. ROLE OF NANOTECHNOLOGY IN OVERCOMING THE LIMITATIONS OF CONVENTIONAL CANCER THERAPY

- 1) Targeted drug delivery: Nanoparticles can deliver anticancer drugs preferentially to tumor tissue through passive targeting, associated with the enhanced permeability and retention (EPR) effect, and active targeting, which uses ligands such as antibodies, peptides, or folic acid to recognize specific cellular targets (Peer et al., 2007; Mitchell et al., 2021).
- 2) Reduced toxicity: Nanocarriers may modify drug distribution and reduce exposure of healthy tissues to certain anticancer agents, potentially minimizing treatment-related toxicity (Shi et al., 2017; Wicki et al., 2015).
- 3) Improved solubility and bioavailability: Nanoparticles can improve the apparent solubility, stability, and delivery of poorly water-soluble anticancer drugs (Mitchell et al., 2021).
- 4) Controlled and sustained drug release: Nanocarriers can be engineered to release therapeutic agents gradually or in response to stimuli such as pH, temperature, and enzymes (Mi, 2020).
- 5) Overcoming multidrug resistance: Some nanoparticle systems may help address multidrug resistance by improving intracellular drug delivery and enabling the combined delivery of therapeutic agents (Peer et al., 2007; Shi et al., 2017).
- 6) Increased drug accumulation at the tumor site: Nanoparticle accumulation in tumors depends on factors such as vascular permeability, particle properties, tumor biology, and clearance mechanisms. Consequently, tumor delivery varies considerably between tumor types and patients (Wilhelm et al., 2016).
- 7) Combination therapy: Nanocarriers can be designed to deliver multiple therapeutic agents within a single formulation, providing opportunities for combination treatment (Peer et al., 2007).
- 8) Improved penetration into tumors: Nanoparticle size, surface characteristics, and interactions with biological barriers influence tumor penetration and cellular uptake (Blanco et al., 2015; Wilhelm et al., 2016).
- 9) Multifunctional therapy: Nanotechnology supports theranostic approaches that combine diagnostic imaging and therapeutic delivery, potentially enabling more informed treatment strategies (Mi, 2020).

IV. BASICS OF NANOTECHNOLOGY IN DRUG DELIVERY

Nanoparticles in Cancer Drug Delivery

Nanoparticles are colloidal drug-delivery systems generally ranging from approximately 1 to 1000 nm in size, although the term is commonly associated with nanoscale systems below 200 nm in many pharmaceutical applications. Their unique physicochemical properties, including high surface-area-to-volume ratio, tunable surface characteristics, and ability to encapsulate or associate with therapeutic agents, make them attractive carriers for cancer drug delivery. (Peer et al., 2007; Mitchell et al., 2021).

Nanoparticles can be designed to improve the pharmacokinetic and pharmacodynamic properties of anticancer drugs. They may enhance the solubility and stability of poorly water-soluble drugs, protect therapeutic molecules from premature degradation, and provide controlled or sustained drug release. By modifying particle size and surface characteristics, nanoparticle systems can also influence biodistribution and cellular uptake. (Blanco et al., 2015; Mitchell et al., 2021).

In cancer therapy, nanoparticles can facilitate passive targeting through preferential accumulation in tumors associated with abnormal tumor vasculature and impaired lymphatic drainage. This phenomenon is commonly referred to as the enhanced permeability and retention (EPR) effect. However, the extent of the EPR effect can vary considerably between tumor types and patients. Therefore, relying exclusively on passive targeting may not always provide sufficient tumor-specific delivery. (Wilhelm et al., 2016; Shi et al., 2017).

Active targeting can improve cellular specificity by functionalizing nanoparticle surfaces with molecules that recognize receptors or biomarkers expressed at higher levels on cancer cells or tumor-associated cells. Common targeting ligands include monoclonal antibodies, antibody fragments, peptides, aptamers, and small molecules such as folate. (5) After binding to the target, nanoparticles may undergo receptor-mediated cellular uptake, potentially increasing intracellular delivery of the therapeutic agent. (Peer et al., 2007; Mitchell et al., 2021).

V. PHYSICOCHEMICAL PROPERTIES OF NANOPARTICLES

The physicochemical properties of nanoparticles strongly influence their stability, drug-loading capacity, biodistribution, cellular uptake, targeting efficiency, and overall therapeutic performance. These characteristics are important when designing nanoparticle systems for effective and safe drug delivery (Blanco et al., 2015; Mitchell et al., 2021).

- 1) Particle size: Particle size affects biodistribution, cellular uptake, circulation time, and tumor accumulation. Smaller nanoparticles may show improved tissue penetration and cellular internalization, although their behavior depends on particle composition, surface characteristics, and the biological environment (Danaei et al., 2018; Blanco et al., 2015).
- 2) Particle size distribution (polydispersity): Polydispersity indicates the uniformity of particle size within a formulation. A narrow particle-size distribution generally indicates a more homogeneous nanoparticle preparation and can facilitate formulation characterization and reproducibility (Danaei et al., 2018).
- 3) Surface charge (zeta potential): Surface charge affects nanoparticle stability, interactions with biological membranes, protein adsorption, and cellular uptake. Highly charged particles may interact strongly with cell membranes but can also increase nonspecific interactions and toxicity (Nel et al., 2009; Mitchell et al., 2021).
- 4) Surface morphology and shape: Nanoparticle shape and surface morphology can influence cellular uptake, circulation, tissue penetration, and interactions with biological components. Different nanoparticle geometries may exhibit different biological behaviors (Blanco et al., 2015; Mitchell et al., 2021).
- 5) Surface area: Nanoparticles possess a high surface-area-to-volume ratio, which influences interactions with biological environments and provides opportunities for surface functionalization and drug association (Nel et al., 2009).
- 6) Drug-loading capacity and encapsulation efficiency: Drug-loading capacity represents the amount of drug associated with a given quantity of nanoparticles, whereas encapsulation efficiency represents the proportion of the initial drug successfully incorporated into the nanoparticle system. Both parameters are important during formulation development and optimization (Mitchell et al., 2021).
- 7) Surface hydrophobicity/hydrophilicity: Surface characteristics influence protein adsorption, interactions with cell membranes, colloidal stability, and biological distribution. Surface modification with hydrophilic polymers such as polyethylene glycol (PEG) can alter protein interactions and may prolong systemic circulation, depending on the formulation (Monopoli et al., 2012; Mitchell et al., 2021).
- 8) Stability: Physical and chemical stability are essential for maintaining particle size, drug content, surface properties, and therapeutic activity during storage and administration. Aggregation, drug leakage, oxidation, and degradation can compromise nanoparticle performance (Danaei et al., 2018; Mitchell et al., 2021).
- 9) Drug-release characteristics: The release profile determines how rapidly and for how long the drug is delivered. Nanoparticles can be designed for immediate, sustained, controlled, or stimuli-responsive drug release (Mitchell et al., 2021).
- 10) Biocompatibility and biodegradability: Nanoparticles intended for clinical use should have acceptable biocompatibility and, where appropriate, should degrade into products that can be safely metabolized or eliminated. These properties are important for minimizing toxicity and improving therapeutic safety (Nel et al., 2009; Anselmo & Mitragotri, 2019).

VI. TYPES OF NANOCARRIES USED IN CANCER THERAPY

A. Liposome

First discovered by Bangham et al., Liposomes are spherical vesicles composed primarily of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs. They are widely investigated as nanocarriers for cancer therapy because they can modify drug distribution and pharmacokinetics and, depending on their formulation, may reduce the toxicity of certain anticancer drugs (Allen & Cullis, 2013; Sercombe et al., 2015).

1) Structure of liposomes

A liposome consists mainly of:

Phospholipid bilayer – forms the outer membrane

Cholesterol – improves membrane stability

Aqueous core – can carry water-soluble drugs

Lipid phase – can incorporate lipophilic drugs

Surface modifiers such as PEG may be added to increase circulation time.

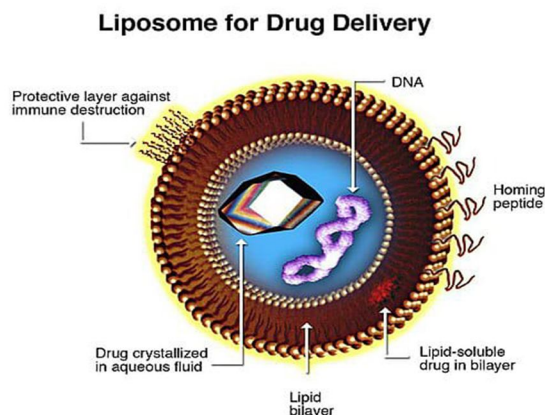


Figure 1. Structure of a Liposome for Drug Delivery Showing the Phospholipid Bilayer, Encapsulated Hydrophilic Drug, Lipid-Soluble Drug, Protective Surface Layer, and Targeting Peptides.

2) Types of liposomes

A. Conventional liposomes

Contain phospholipids and cholesterol and are relatively simple formulations.

B. PEGylated liposomes

PEG is incorporated on the surface to reduce rapid clearance by the reticuloendothelial system and prolong circulation.

C. Targeted liposomes

Their surfaces are modified with antibodies, peptides, folic acid, or other ligands to recognize specific targets.

D. Stimuli-responsive liposomes

Designed to release their drug in response to conditions such as pH, temperature, enzymes, or other stimuli. (Bulbake et al., 2017).

Methods of preparation

Common methods include:

- Thin-film hydration method
- Reverse-phase evaporation method
- Ethanol injection method
- Ether injection method
- Detergent removal method
- Freeze-thaw method

B. Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are colloidal drug-delivery systems composed of a solid lipid matrix stabilized by surfactants. They can incorporate therapeutic agents within the lipid matrix and are investigated for controlled drug release and improved drug delivery. Their physicochemical properties depend on lipid composition, surfactant concentration, particle size, and preparation method (Mehnert & Mäder, 2001; Müller et al., 2002).

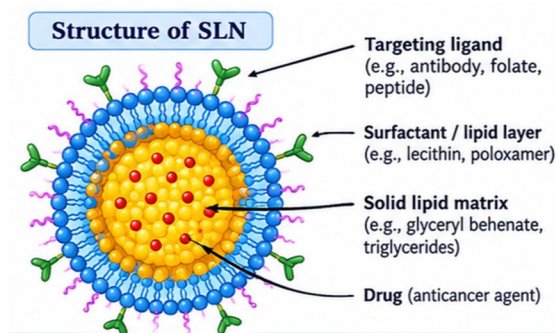


Figure 2. Structure of Solid Lipid Nanoparticles (SLNs) Showing the Solid Lipid Matrix, Surfactant Layer, Encapsulated Anticancer Drug, and Surface-Modified Targeting Ligands.

C. Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles are nanosized drug-delivery systems prepared using natural or synthetic polymers. They can encapsulate, adsorb, or chemically conjugate therapeutic agents and may provide controlled drug release. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) are widely investigated for drug-delivery applications, including cancer therapy.(Danhier et al., 2012; Kumari et al., 2010).

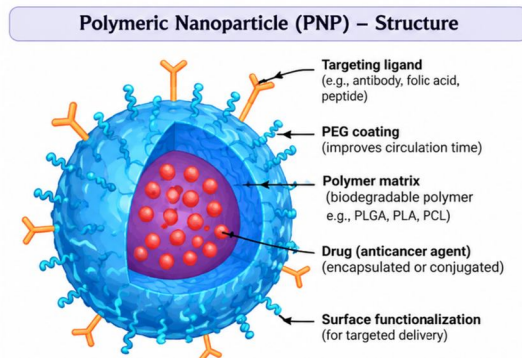


Figure 3. Structure of Polymeric Nanoparticles (PNPs) Showing the Polymer Matrix, Encapsulated Anticancer Drug, PEG Coating, Targeting Ligands, and Surface Functionalization for Targeted Drug Delivery in Cancer Therapy.

Common polymers used

Polymer	Major feature
PLGA	Biodegradable, widely used
PAL	Biocompatible and biodegradable
PCL	Slow drug release
Chitosan	Biocompatible and mucoadhesive
PEG	Improves circulation time
Poly(lactic-co-glycolic acid)	Controlled drug delivery

Table 1. Common Polymers Used in Polymeric Nanoparticles for Drug Delivery and Their Major Characteristics

D. Dendrimers

Dendrimers are highly branched, three-dimensional nanostructured polymers, typically ranging from 2–10 nm in size. They are characterized by a monodisperse molecular weight distribution and a well-defined, radially symmetric branching architecture. Their generation-dependent physicochemical properties can be precisely controlled through repetitive synthetic reactions, primarily using either the divergent method, in which synthesis proceeds from the central core toward the periphery, or the convergent method, in which dendritic branches are constructed from the periphery toward the core..(Mintzer & Grinstaff, 2011; Svenson & Tomalia, 2005).

Dendrimers possess several important advantages for drug delivery, including high drug-loading capacity, controlled and sustained drug release, improved solubility of poorly water-soluble drugs, enhanced bioavailability, biodegradability, and improved penetration across biological membranes. These properties arise mainly from their unique three-dimensional, highly branched architecture, which provides internal cavities and a large number of surface functional groups for drug encapsulation, conjugation, or surface modification(Esfand & Tomalia, 2001; Mignani et al., 2013).

Dendrimers are classified according to their generation number. The central core is designated as generation 0 (G0), while successive layers of branching are referred to as G1, G2, G3, and so forth. Increasing the generation generally results in an increase in molecular size, number of surface functional groups, and structural complexity.(Mintzer & Grinstaff, 2011; Svenson & Tomalia, 2005).

E. Nanostructured lipid carriers (NLCs)

Nanostructured lipid carriers (NLCs) are second-generation lipid-based nanocarriers composed of a mixture of solid lipids and liquid lipids (oils) stabilized by surfactants. They generally have a particle size in the nanometer range and are designed to improve the delivery of anticancer drugs.NLCs are investigated for their potential to improve the solubility, stability, and controlled delivery of therapeutic agent(Müller et al., 2002; Beloqui et al., 2016).

Anticancer drug	Potential benefit of NLC formulation
Paclitaxel Ho	Improved solubility and controlled delivery
Docetaxel	Enhanced cellular uptake and sustained release
Doxorubicin	Controlled delivery and potential reduction of systemic toxicity
Curcumin	Improved solubility, stability and bioavailability
Methotrexate	Improved delivery and sustained drug release
Tamoxifen	Enhanced delivery of poorly soluble drug
5-Fluorouracil	Controlled and potentially targeted delivery

Table 2. Anticancer Drugs Encapsulated in Nanostructured Lipid Carriers (NLCs) and Their Potential Benefits in Cancer Therapy

F. Nanoemulsions

Nanoemulsions are colloidal dispersions consisting of nanosized droplets of one liquid phase distributed in another immiscible liquid phase, usually stabilized by surfactants or emulsifiers. They may be formulated as oil-in-water or water-in-oil systems. Nanoemulsions are investigated for drug delivery because they can improve the solubilization and dispersion of poorly water-soluble compounds. Their performance depends on the formulation composition, droplet size, stability, and route of administration (Gupta et al., 2016; Solans et al., 2005).

G. Inorganic Nanoparticles

Inorganic nanoparticles, including gold nanoparticles, iron oxide nanoparticles, and mesoporous silica nanoparticles, have been investigated for applications in cancer diagnosis, imaging, and therapy. Gold nanoparticles have optical properties that can be exploited in diagnostic and photothermal applications, while iron oxide nanoparticles have magnetic properties useful for imaging and other biomedical applications. Mesoporous silica nanoparticles offer a porous structure that can accommodate therapeutic molecules. However, their clinical suitability depends on factors such as particle size, surface properties, biodistribution, biodegradation, and potential toxicity (Colombo et al., 2012; Dykman & Khlebtsov, 2012; Mamaeva et al., 2013).

VII. MECHANISMS OF TUMOR TARGETING

A. Passive Targeting

Passive targeting is based on differences between tumor and normal tissues. Tumors may exhibit abnormal vasculature and impaired lymphatic drainage, which can promote the accumulation of appropriately designed nanoparticles. This phenomenon is commonly associated with the enhanced permeability and retention (EPR) effect (Maeda et al., 2013).

However, the extent of EPR-mediated accumulation varies considerably between tumor types, individual patients, and tumor microenvironments. Therefore, passive targeting does not guarantee effective nanoparticle accumulation in every tumor (Wilhelm et al., 2016; Danhier, 2016).

B. Active Targeting.

Active targeting involves attaching specific ligands to the surface of nanoparticles. These ligands can recognize receptors or other molecular targets that are more abundant on certain cancer cells

Ligand–receptor interactions may promote nanoparticle binding and cellular internalization, potentially improving intracellular delivery of anticancer drugs. However, active targeting does not necessarily increase the total amount of nanoparticles reaching a tumor; its effectiveness depends on ligand selection, receptor expression, nanoparticle properties, and biological barriers (Blanco et al., 2015; Mitchell et al., 2021).

ExamplesAnother include:

- Antibodies
- Peptides
- Folic acid
- Aptamers
- Carbohydrates

Active targeting may increase cellular uptake and improve intracellular drug delivery.

C. Stimuli-Responsive Targeting

Stimuli-responsive nanoparticles are designed to release their drug payload in response to specific conditions.

Types include:

- pH-responsive Passivesystems
- Temperature-responsive systems
- Enzyme-responsive systems
- Redox-responsive systems
- Light-responsive systems
- Magnetic-responsive systems

Depending on their design, these approaches can help control drug release, improve spatial or temporal delivery, and support combined imaging and therapy. Their effectiveness depends on the stimulus, carrier composition, drug-release mechanism, and tumor environment(mi,2020).

VIII. APPLICATIONS IN DIFFERENT TYPES OF CANCER

A. Breast Cancer

Nanocarriers have been investigated for delivering chemotherapeutic agents, genes, and other therapeutic molecules in breast cancer. Liposomal formulations can alter drug distribution and pharmacokinetics, potentially improving the therapeutic index of selected anticancer agents. Their benefits depend on the formulation and clinical setting (Barenholz, 2012; Shi et al., 2017).

B. Lung Cancer

Nanoparticles are being investigated for systemic and pulmonary delivery of anticancer agents. Pulmonary formulations may enable local drug administration, while systemic nanocarriers may alter drug distribution. Their effectiveness depends on particle properties, administration route, tumor characteristics, and drug-release behavior (Paranjpe & Müller-Goymann, 2014; Wicki et al., 2015).

C. Brain Cancer

The blood–brain barrier (BBB) is a major obstacle to delivering many therapeutic agents to brain tumors. Nanocarriers are being investigated to improve drug transport across or around this barrier through approaches such as surface modification and receptor-mediated transport. However, delivery to brain tumors remains challenging, and successful transport depends on the carrier design and the characteristics of the tumor and BBB (Blanco et al., 2015; Saraiva et al., 2016).

D. Colon Cancer

Nanotechnology-based drug-delivery systems are being investigated for colorectal cancer to improve drug solubilization, control drug release, and potentially enhance delivery to tumor tissue. Oral and targeted delivery approaches may also help address barriers to drug absorption and distribution. Their effectiveness depends on the formulation, route of administration, and tumor biology (Pridgen et al., 2013; Shi et al., 2017).

E. Ovarian Cancer

Nanocarriers, including liposomal formulations, have been investigated for delivering anticancer agents in ovarian cancer. Encapsulation can modify drug distribution and pharmacokinetics and may reduce certain dose-limiting toxicities. However, reductions in toxicity and improvements in therapeutic outcomes depend on the specific formulation and should be supported by clinical or experimental evidence (Barenholz, 2012; Wicki et al., 2015).

IX. ADVANTAGES OF NANOTECHNOLOGY-BASED DRUG DELIVERY OVER CONVENTIONAL DRUG DELIVERY

Nanotechnology-based drug delivery systems offer several potential advantages over conventional drug-delivery approaches, particularly in cancer therapy. These advantages arise from the ability to engineer nanoparticles with controlled size, surface properties, drug-loading capacity, and release characteristics.

A. Improved drug targeting

Nanoparticles can facilitate preferential delivery of anticancer drugs to tumor tissues through passive targeting and can be further modified with specific ligands for active targeting. This may improve drug accumulation at the desired site.(Blanco et al., 2015; Mitchell et al., 2021).

B. Reduced systemic toxicity

By improving the distribution of drugs toward tumor tissues and reducing exposure of healthy tissues, targeted nanoparticle systems may decrease the systemic toxicity associated with conventional chemotherapy.(Wicki et al., 2015; Anselmo & Mitragotri, 2019).

C. Controlled and sustained drug release

Nanoparticles can be designed to release their therapeutic payload gradually, helping maintain drug concentrations over an extended period and potentially reducing the frequency of administration.(Kamaly et al., 2016).

D. Improved solubility and bioavailability:

Many anticancer drugs have poor aqueous solubility. Nanoparticle systems can improve the apparent solubility and dissolution behavior of such drugs and may enhance their bioavailability.(Peer et al., 2007; Mitchell et al., 2021).

E. Protection of therapeutic agents

Encapsulation can protect drugs and biological molecules from premature degradation, metabolism, or unfavorable interactions before reaching the intended site of action.(Peer et al., 2007; Blanco et al., 2015).

F. Improved pharmacokinetic properties

Nanoparticles can modify drug distribution, circulation time, metabolism, and elimination, potentially providing a more favorable pharmacokinetic profile than the free drug.(Anselmo & Mitragotri, 2019; Wicki et al., 2015).

G. Enhanced cellular uptake

Nanoparticles can facilitate cellular internalization through endocytosis and, when appropriately designed, can improve intracellular delivery of therapeutic agents.(Peer et al., 2007; Mitchell et al., 2021).

H. Ability to overcome biological barriers

Certain nanoparticle systems can be engineered to improve drug transport across biological barriers and enhance delivery to difficult-to-reach tissues. This is particularly relevant to tumors with complex microenvironments.(Blanco et al., 2015).

I. Co-delivery of multiple therapeutic

Nanoparticles can potentially carry two or more therapeutic agents within the same delivery system, allowing coordinated delivery of combination therapies.(Peer et al., 2007; Shi et al., 2017).

J. Versatile surface modification

The nanoparticle surface can be functionalized with antibodies, peptides, aptamers, polymers, or other molecules to modify biodistribution, improve targeting, or provide stimuli-responsive drug release.(Mitchell et al., 2021; Monopoli et al., 2012).

X. LIMITATIONS AND CHALLENGES

Despite considerable progress, several challenges remain.

Biological challenges

- heterogeneity
- Variable nanoparticles accumulation
- Protein corona formation
- Rapid clearance by mononuclear phagocyte system
- Limited penetration into solid tumor

Formulation challenges

- Aggregation
- Physical and chemical instability
- Drug leakage
- Scale-up difficulties
- Batch-to-batch variability.(Mitchell et al., 2021; Monopoli et al., 2012).

XI. TOXICITY AND SAFETY CONSIDERATIONS

- 1) Cytotoxicity: Nanoparticles may damage normal cells as well as cancer cells. Their interaction with cellular membranes and intracellular structures can cause cell injury, oxidative stress, and cell death.(Sharma et al., 2021)
- 2) Oxidative stress: Some nanoparticles can increase the formation of reactive oxygen species (ROS). Excessive ROS production may damage DNA, proteins, and lipids, resulting in cellular dysfunction(Nel et al., 2009; Sharma et al., 2021)
- 3) Immunotoxicity: Nanoparticles may activate immune cells, trigger inflammatory responses, or cause unwanted immune reactions. Some formulations may also activate the complement system, potentially leading to infusion-related reactions.(Nel et al., 2009)
- 4) Hepatotoxicity: The liver is an important site for nanoparticle uptake and clearance. Certain nanoparticles may accumulate in liver tissue and cause inflammation, oxidative stress, or liver-cell injury, depending on their composition and dose.(Sharma et al., 2021)
- 5) Nephrotoxicity: Nanoparticles or their degradation products may affect the kidneys. Renal toxicity depends on factors such as particle size, chemical composition, exposure level, and elimination pathway.(Sharma et al., 2021)
- 6) Hematological toxicity: Nanoparticles administered intravenously may interact with red blood cells, platelets, and plasma proteins. Possible effects include hemolysis, altered blood coagulation, platelet activation, and changes in blood-cell counts(Urbán et al., 2019).
- 7) Genotoxicity: Certain nanomaterials may cause DNA damage directly or indirectly through oxidative stress and inflammation. Genotoxicity testing helps assess the potential for mutations and other genetic abnormalities.(Nel et al., 2009)

XII. RECENT ADVANCES

Recent research has focused on multifunctional nanocarriers capable of combining several therapeutic functions in a single system. Important areas include:

- 1) Combination nanotherapy – simultaneous delivery of two or more drugs.
- 2) Nanocarrier-mediated gene delivery – delivery of siRNA, miRNA or other nucleic acids.
- 3) Immunotherapy delivery – nanocarriers for immune-modulating agents.
- 4) Stimuli-responsive nanoparticles – controlled drug release triggered by tumor-specific conditions.
- 5) Theranostic nanoparticles – integration of diagnosis/imaging and therapy.
- 6) Personalized nanomedicine – development of delivery systems based on individual tumor characteristics.

XIII. FUTURE PERSPECTIVES

The future of nanotechnology-based cancer therapy is expected to focus on improving targeting specificity, tumor penetration and safety.

Artificial intelligence and computational modeling may assist in optimizing nanoparticle formulations and predicting drug–nanocarrier interactions. Combination of nanotechnology with immunotherapy, gene therapy and personalized medicine may further improve treatment outcomes.

However, successful translation from laboratory research to clinical practice will require standardized manufacturing methods, robust characterization, reproducible performance and comprehensive safety evaluation.

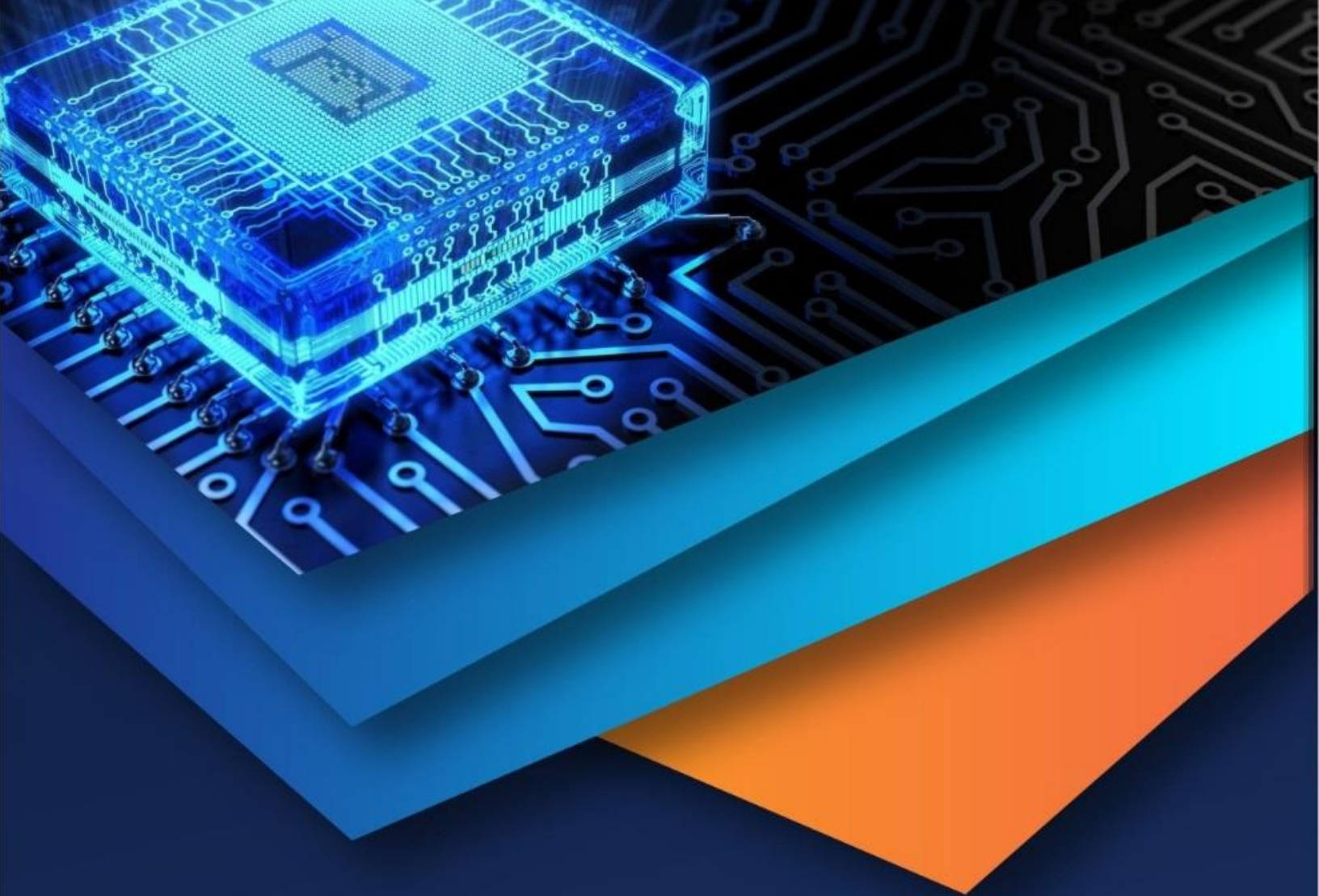
XIV. CONCLUSION

Nanotechnology-based drug delivery systems represent an important advancement in cancer therapy. Nanocarriers can improve the solubility, stability, pharmacokinetic properties, and controlled release of anticancer drugs while providing opportunities for targeted delivery (Mitchell et al., 2021; Wicki et al., 2015). Liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), micelles, dendrimers, nanoemulsions, and inorganic nanoparticles have demonstrated significant potential in preclinical and clinical research (Shi et al., 2017; Anselmo & Mitragotri, 2019). Nevertheless, biological variability, toxicity, manufacturing complexity, and regulatory challenges continue to limit their widespread application (Agrahari & Agrahari, 2018; Hua & de Matos, 2024). Continued research combining nanotechnology with targeted therapy, immunotherapy, gene therapy, and personalized medicine may contribute to safer and more effective cancer treatment (Shi et al., 2017; Wicki et al., 2015)..

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