REVIEW PAPER

Nanocarriers in Oncology Drug Delivery: From Current Strategies to Future Perspectives

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ABSTRACT
The constraints of conventional chemotherapy have been overcomed by nanotechnology, greatly advancing cancer treatment. Nanoformulations reduce systemic toxicity while improving drug stability, solubility, biodistribution and tumor accumulation. By selectively delivering therapeutic medications to tumors through active targeting ligands, increased permeability and retention (EPR) effect, nanoparticles increase the effectiveness of treatment. For a variety of nanoformulations, such as lipid-based carriers and gene-delivery platforms, this review describes design concepts, manufacturing methods as well as functionalization strategies. It also assesses critical characterisation parameters and assessment models. Clinically approved nanomedicines, continuing clinical trials and issues including tumor heterogeneity with expensive production are also covered. Promising ideas like AI-driven optimization and tailored nanomedicine could progress the science and demonstrate the revolutionary potential of cancer treatments based on nanoformulations in contemporary oncology.

Keywords: Nanomedicine, cancer therapy, nanoparticles, targeted delivery, polymeric nanoparticles, clinical translation.
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INTRODUCTION

Cancer continues to be one of the world's leading causes of illness and mortality, posing a significant public health concern in both industrialized as well as developing countries. The treatment of cancer is still hampered by a number of issues, including nonspecific drug distribution, systemic toxicity, multi-drug resistance, poor solubility of chemotherapeutic agents, rapid elimination, and insufficient drug accumulation at the tumor site, despite significant advances in molecular diagnostics, targeted therapies and immunological approaches[1]. Nevertheless being clinically proven, conventional chemotherapy regimens frequently have a limited therapeutic index, which can result in serious dose-related side effects and decreased patient compliance. These difficulties have sparked a great deal of research interest in drug delivery methods based on nanotechnology, known as nanoformulations, as a revolutionary platform for cancer treatments[2] .

Improved drug encapsulation, enhanced permeability and retention (EPR) effect-mediated tumor targeting, controlled and sustained release, protection of labile therapeutic molecules, and the possibility of site-specific delivery through active targeting ligands are all made possible by the special physicochemical and biological benefits of nanotechnology[3].

Numerous nanoformulations, such as liposomes, polymeric nanoparticles, dendrimers, micelles, solid lipid nanoparticles (SLNs), gold nanoparticles, carbon nanotubes, nanoemulsions, quantum dots, exosomes, and stimuli-responsive nanosystems, have been created and thoroughly investigated for cancer therapy. Each of these nanocarriers has an unique benefits, including improved solubility for hydrophobic anticancer medications, biocompatibility, stealth qualities through PEGylation, co-delivery of several therapeutic agents, and possible integration with diagnostic elements, which could lead to the developing field of theranostics. Precision oncology has been transformed by the ability to integrate imaging capabilities with targeted drug release, which enables therapy administration and treatment response monitoring[4].

In addition to increasing the effectiveness of drug delivery, the development of nanoformulations has made it easier to repurpose and reformulate already available

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chemotherapeutic drugs like paclitaxel, doxorubicin, cisplatin, docetaxel and curcumin. For example, albumin-bound paclitaxel and liposomal doxorubicin are the examples of ground

breaking discoveries that were effectively implemented in clinical settings, exhibiting decreased cardiotoxicity and enhanced therapeutic results[5].

IMPORTANT PLATFORMS FOR NANOFORMULATION

Lipid-based systems

In the therapy of cancer, lipid-based nanocarriers such as liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid–polymer hybrid nanoparticles are essential. They make it possible to encapsulate both hydrophilic and hydrophobic medications, improving their solubility and lowering their toxicity. While SLNs and NLCs provide improved stability and controlled release for lipophilic anticancer medicines, hybrid nanoparticles enhance circulation and drug retention[6].

Nanoparticles Made of Polymer

In addition to synthetic polymers like PLGA, PLA, and PEG-PLA for controlled degradation and release, polymeric nanocarriers use natural materials like chitosan, alginate and gelatin for mucoadhesive conveyance. Through micelles composed of amphiphilic block copolymers, they improve the stability and solubility of weakly water-soluble anticancer medications. Nucleic acid transport and cancer vaccines are two examples of applications; however, complex manufacturing, possible burst release, and repeatability-impairing polymer quality variability are disadvantages[7].

Dendrimers

Dendrimers are homogenous, highly branching macromolecules that are useful for drug loading and cancer treatments because of their carefully regulated structure, which enables accurate drug conjugation and targeting. However, the requirement for significant surface changes to guarantee stability and safety, the high manufacturing costs, and the possible cytotoxicity of some cationic forms limit their clinical application[8].

Inorganic Nanoparticles

Gold nanoparticles, iron oxide nanoparticles, and mesoporous silica nanoparticles are inorganic nanocarriers with unique physical features that can be used to cure cancer. While gold nanoparticles are used for photothermal therapy and tailored treatments, iron oxide nanoparticles serve as MRI contrast agents and enable magnetic hyperthermia. The high pore volumes of mesoporous silica nanoparticles improved the medication loading and release[9].

Protein-based and Biomimetic Carriers

Natural carrier proteins, such albumin nanoparticles (like Abraxane®), improve hydrophobic chemotherapeutics' solubility and tumor accumulation. Because of their inherent biological similarity, biomimetic nanoparticles covered with membranes from cancer cells, red blood cells, or platelets enhance immune evasion, circulation, and tumor targeting. Despite their superior biocompatibility and decreased immunogenicity, these carriers present a number of difficulties, such as difficult membrane separation, batch variability, and industrial scaling constraints[10].

TARGETING MECHANISMS AND FUNCTIONALIZATION

The ability of nanocarriers to deliver medications to tumors selectively is improved by targeting mechanisms and functionalization.

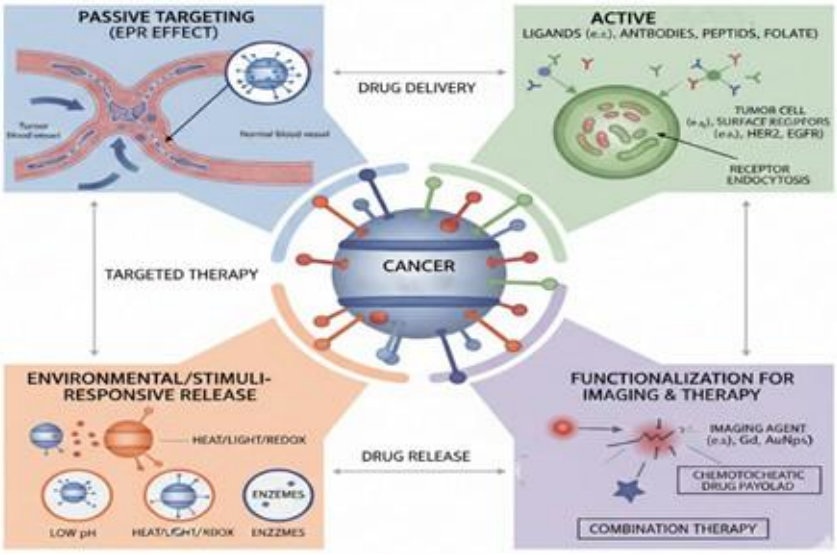

Fig. 1: Targeting mechanisms and functionalization

Passive targeting (EPR)

The enhanced permeability and retention (EPR) effect allows nanoparticles to be passively targeted in tumors by leveraging aberrant vasculature and inadequate lymphatic drainage. Compared to free drugs, nanocarriers with a size range of 20 to 200 nm can penetrate tumor tissue more successfully, increasing therapeutic concentrations and lowering systemic exposure. However, because to things like dense stroma, restricted blood flow, or hypoxia, EPR efficiency varies greatly between people and tumor types. EPR efficacy is also impacted by patient-specific circumstances like inflammation and vascular normalization[11].

Active targeting

Active targeting improves selectivity in cancer treatment by coating nanoparticles with ligands that bind to overexpressed receptors on cancer cells or tumor vasculature. Even in malignancies with weak increased permeability and retention (EPR) effects, ligands such folic acid, aptamers, RGD peptides, and antibody fragments boost intracellular drug delivery and targeting by facilitating receptor-mediated endocytosis[12].

Stimuli-responsive systems

Drugs are released in tumor settings via stimuli-responsive nanotechnology carriers via certain processes. Drugs are eliminated in acidic environments by pH-responsive mechanisms[13]. While enzyme-responsive nanoparticles activate with tumor-secreted enzymes, redox-responsive carriers break down at high glutathione levels. In addition to improving tumor selectivity, intracellular transport, and reducing the premature release of sensitive chemicals, externally triggered devices react to a variety of stimuli enabling precise control[14].

Multifunctional nanocarriers

Targeting ligands, therapeutic medications, and imaging moieties are all combined in multifunctional nanocarriers to build integrated theragnostic platforms. While targeting components like antibodies improve tumor selectivity, imaging components like fluorophores and MRI contrast agents allow real-time tracking of biodistribution and therapy response[15].

FORMULATION METHODS FOR NANOCARRIERS USED IN CANCER

Top-Down Approach

Top-down methods create nanoparticles by employing mechanical, thermal, or shear-based forces to break bulk materials like lipids, polymers. Common procedures include ball milling or wet media milling, which utilize grinding beads to shatter particles, and high-pressure homogenization, which uses cavitation and high pressure to decrease particle size[16]. These methods are frequently employed to increase the solubility of medications that are poorly soluble in water, making them appropriate for the commercial synthesis of nanocrystals. In general, top-down procedures are repeatable, scalable, and compatible with current

pharmaceutical machinery. They do, however, need a lot of energy, which might produce heat and jeopardize the stability of medications which are sensitive to heat. Additionally, they provide little control over the production of consistently shaped or very tiny (<50 nm) nanoparticles, and contamination from milling medium may be an issue. A summary of different top- down methods was given in (Table 1) [17-22].

Table I: Major Nanoformulations Methods Used in Cancer Nanomedicine

Method	Category	Common Nanocarriers	Suitable Drugs	Key Benefit	Limitations	Applications in Cancer Therapy
Emulsification–Evaporation	Bottom-up / Hybrid	PLGA NPs, PLA NPs, polymeric micelles	Mainly hydrophobic drugs (Paclitaxel, Docetaxel)	High encapsulation of hydrophobic drugs; controlled release	Requires organic solvents; batch-to-batch variation	Widely used for chemotherapeutics and combination therapy
Nanoprecipitation (Solvent Displacement)	Bottom-up	Polymeric NPs, hybrid nanoparticles	Hydrophobic and some amphiphilic drugs	Simple, mild, reproducible	Low loading for hydrophilic drugs; fast mixing affects size	Used for encapsulating small-molecule chemotherapeutics and siRNA–polymer hybrids
Microfluidics	Bottom-up	Lipid nanoparticles (LNPs), polymeric	All classes: hydrophobic, hydrophilic, nucleic acids	Precise particle size control; scalable; continuous production	Requires specialized devices; cost higher than	Used for mRNA cancer vaccines, RNAi delivery,

		NPs, liposomes			classical methods	targeted liposomes
Solvent Diffusion (Solvent Displacement–Diffusion)	Bottom-up	Polymeric nanoparticles, nanospheres	Mainly hydrophobic drugs	Better control of particle size vs classical emulsions	Limited for hydrophilic drugs; requires miscible solvents	Used for polymeric NP delivery of anticancer agents and imaging probes
High-Pressure Homogenization	Top-down	SLNs, NLCs, lipid dispersions	Hydrophobic drugs, lipophilic compounds	Industry-scale, reproducible, solvent-free	Heat generation may degrade thermosensitive drugs	Used for SLN/NLC-based delivery of paclitaxel, curcumin, doxorubicin

Bottom-Up Approach

Bottom-up approaches create nanoparticles via molecular self-assembly or controlled precipitation, rather than breaking down bulk material. To produce particles with specific size and shape, processes including nanoprecipitation, solvent displacement, emulsification–evaporation, and microfluidic-assisted mixing depend on regulated supersaturation, diffusion, and nucleation. By varying solvent ratios, mixing speed, polymer concentration, or microfluidic flow parameters, these techniques provide exceptional tunability. They work well for encasing delicate medications, proteins, or nucleic acids and use a lot less energy than top-down techniques[23].

CHARACTERIZATION TECHNIQUES

Characterizing cancer nanocarriers is crucial for evaluating their physicochemical properties, stability, drug-loading efficiency, and interaction with biological systems as mentioned in (Figure 2). These parameters determine how effectively nanocarriers circulate, target tumors, and release therapeutic agents, ensuring their safety and performance in cancer treatment.

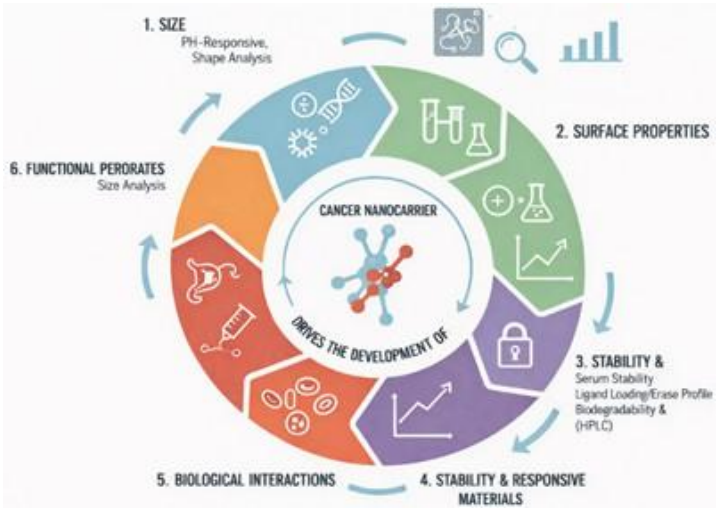

Fig. 2: Schematic diagram for the characterization of cancer nanocarriers

Physicochemical Characterization

Particle Size & Polydispersity Index (DLS, NTA)

Dynamic light scattering (DLS) is a fast method for determining the size distribution in colloidal systems because it determines the hydrodynamic diameter and polydispersity index (PDI) of nanoparticles based on variations in scattered light as particles undergo Brownian motion[24]. By monitoring the motion of individual particles under a laser beam, nanoparticle tracking analysis (NTA) enhances DLS by giving number-based assessments of particle size and concentration[25].

Shape and Morphology (TEM, SEM)

Transmission electron microscopy (TEM) offers high-resolution imaging that shows the size, shape, and internal structure of nanoparticles, enabling accurate assessment of crystalline characteristics and core–shell topologies. Particle roughness, porosity, and aggregation may be seen with the use of scanning electron microscopy (SEM), which provides comprehensive surface morphology and topography information[26].

Surface Charge (Zeta Potential)

Zeta potential study indicates surface charge and colloidal stability in suspension by measuring the electrostatic

potential at the sliding plane of the nanoparticle. Because of electrostatic repulsion, very positive or negative zeta potential values are typically associated with good stability, but near-neutral charges may need steric stabilization (such as PEGylation). Predicting biological interactions, aggregation behaviour, and the possibility of nonspecific protein adsorption in blood all depend on this characteristic[27].

Surface Chemistry (FTIR, XPS)

Drug–excipient interactions, polymer changes, and surface coatings may all be detected using Fourier-transform infrared spectroscopy (FTIR), which detects functional groups and chemical bonds on the surface of nanoparticles[28]. X-ray photoelectron spectroscopy (XPS) verifies effective ligand attachment, coating effectiveness, and chemical purity by quantifying the elemental composition and oxidation states of surface atoms[29].

Crystallinity and Thermal Behavior (XRD, DSC)

X-ray diffraction (XRD) reveals drug encapsulation stages, polymorphism, and structural transitions in polymer or lipid matrices by differentiating between crystalline and amorphous phases[30]. By measuring thermal processes including melting, glass transition, and breakdown, differential scanning calorimetry (DSC) enables evaluation of drug-carrier interactions and formulation stability[31].

Drug Loading & Release Characterization

Quantifying the amount of drug effectively integrated into the nanocarrier is the main goal of drug loading characterization. UV-Visible spectroscopy, HPLC, or LC-MS are used to assess drug loading capacity (drug mass relative to total nanoparticle mass) and encapsulation efficiency (% of drug entrapped compared to the starting quantity)[32]. In vitro release studies, which frequently use dialysis or sample-and-separate techniques, evaluate how medications are released over time under physiological or tumor-mimicking settings. Diffusion, degradation, or stimulus-responsive processes can be better understood by using release kinetics models (zero-order, first-order, Higuchi, Korsmeyer–Peppas). These evaluations help the improvement of carrier composition and production process and provide regulated, predictable medication delivery[33].

Biological Assays

Biological tests assess the cellular and molecular interactions of nanoparticles with biological systems. Serum proteins that adsorb onto nanoparticle surfaces and impact biodistribution, immunological recognition while the cellular absorption is identified by protein corona profiling. Complement activation tests measure immune pathway activation to evaluate inflammatory potential[34]. The compatibility of nanoparticles with red blood cells is determined via haemolysis experiments. MTT and LDH assays are examples of cytotoxicity tests that measures the membrane damage and cell viability following exposure to it. Confocal microscopy is used to see intracellular localization on the other hand flow cytometry is used to quantitatively quantify cellular uptake. When combined, these tests offer vital insights on immunological interactions, biocompatibility, and treatment efficacy[35].

***In Vivo* Biodistribution Analysis**

The distribution, accumulation, and clearance of nanoparticles in animal models are determined via *in vivo* biodistribution approaches[36]. Non-invasive, real-time tracking of tagged nanoparticles in tissues is made possible by imaging-based techniques including MRI, PET, CT, and fluorescence imaging. These techniques help evaluate targeting efficiency, circulation half-life, and tumor accumulation. Inductively coupled plasma mass spectrometry (ICP-MS) offers very sensitive elemental analysis of organs and blood following animal sacrifice, providing accurate quantitative biodistribution profiles for inorganic nanoparticles (such as gold, iron oxide, and silica)[37].

Preclinical Evaluation

***In Vitro* Evaluation**

The effectiveness, toxicity, and biological interactions of nanoparticles are initially evaluated in vitro. Using tests like MTT, LDH, or flow cytometry, conventional 2D cell culture models which include both tumor and normal cell lines allow for quick screening of cytotoxicity, cellular uptake, and proliferation effects[38]. These techniques are especially useful for assessing drug release kinetics, nanoparticle penetration, and distribution within solid tumors. Before turning to animal research, combining 2D and 3D models provides a more thorough knowledge of therapeutic potential and safety[39].

***In Vivo* Evaluation**

In vivo studies evaluate the biodistribution, tumor targeting, and therapeutic effectiveness of nanoparticles in a whole-organism setting. Although they lack organ-specific microenvironments, murine xenograft models in which human tumor cells are subcutaneously implanted offer quick assessment of anticancer efficacy[40]. Tumor vasculature, invasion, and metastasis are more accurately replicated in orthotopic models, which implant tumors in their original tissue. Tumorigenic genes are expressed endogenously in genetically modified mice (GEMMs), simulating human tumor growth and the immunological responses. Patient-derived xenografts (PDX) enable customized treatment research by preserving the histology and heterogeneity of the donor tumor[41].

Pharmacokinetics and Toxicity

The absorption, distribution, metabolism, and excretion (ADME) of nanoparticles are described by pharmacokinetic and toxicology studies, which also provide acceptable dosage guidelines. ADME investigations use imaging or quantitative elemental analysis to monitor the circulation, accumulation, metabolization, and clearance of nanoparticles in organs. In animal models, the maximum tolerated dose (MTD) is the largest dose that does not result in intolerable toxicity. In order to assist regulatory filings and guide the design of clinical trials, these studies together establish safe dosage schedules, forecast human pharmacokinetics and detect any off-target effects[42].

CHALLENGES AND CURRENT LIMITATIONS

Tumor Heterogeneity and Microenvironment

Effective nanoparticle administration is severely hampered by tumor heterogeneity and the intricate tumor microenvironment. Drug accessibility varies both spatially and temporally due to variations in vascularization, oxygenation, and extracellular matrix composition. Hypoxic areas can change medication metabolism and decrease the penetration of nanoparticles, which limits the effectiveness of treatment. High interstitial fluid pressure further hinders extravasation from blood vessels into the tumor interstitium. Furthermore, there is heterogeneity both within the same tumor (intra-tumoral) and across tumors in different patients (inter-tumoral), which results in inconsistent medication distribution and varied uptake. Multifunctional nanocarriers with improved penetration, sensitive drug release, and integration with treatments that alter the milieu, such vascular normalizers or stromal-depleting agents are necessary to overcome these obstacles[43].

Variability of the EPR Effect

Passive nanoparticle accumulation in tumors is caused by the increased permeability and retention (EPR) effect, however its validity in humans varies greatly. Human tumors show considerable variation in vascular permeability, artery density, and lymphatic outflow, despite the fact that preclinical models frequently show strong EPR-mediated absorption. Inconsistent therapy results might arise from factors that impact nanoparticle accumulation, including tumor type, size, stage, and previous treatment. EPR can also be used with stimulus-responsive carriers or active targeting ligands to improve delivery specificity and make up for low EPR in tumours with limited vascularization[44].

Immunological Interactions

Complex interactions between nanoparticles and the immune system may restrict their effectiveness and safety. When nanoparticle surfaces cause complement activation, it might result in complement activation-related pseudoallergy (CARPA), which is characterized by brief hypersensitivity events such as dyspnea, dermatitis or hypotension. Opsonization, or the adsorption of plasma proteins onto the surfaces of nanoparticles, reduces the circulation time and tumor growth by marking particles for macrophage identification and reticuloendothelial system (RES) clearance. The degree of immunological recognition is influenced by surface chemical, size, and shape. Treatment plans may be limited by the exacerbation of immunogenic reactions caused by repeated dosage. To guarantee safe translation into human medicine, thorough preclinical immunotoxicity testing is necessary. This includes complement activation, cytokine release and hemocompatibility studies[45].

Scale-Up and Cost

The development of nanomedicine confronts major obstacles in terms of cost-effectiveness and large-scale production. It is challenging to reliably replicate several laboratory-scale optimized nanoparticle production methods in large quantities, such as solvent evaporation, high-pressure homogenization, and microfluidics. It is theoretically challenging to maintain exact control over particle size, polydispersity, surface chemistry, and drug loading throughout scale-up, and variations can have an impact on safety and efficacy[46]. Production costs are further raised by intricate sanitation, purification and the quality control processes. These elements limit access to therapy and economic feasibility by raising overall production costs. To address repeatability and cost concerns, scalable bottom-up techniques, continuous production technologies, and standardization under Good production Practices (GMP) are being developed[47].

Complex Characterization Requirements

The nanoscale size, large surface area, and intricate physicochemical characteristics of nanomedicines make them particularly difficult to characterize. In contrast to traditional small molecules, the size distribution, shape, surface chemistry, surface charge, and aggregation state of nanoparticles can have a substantial impact on immunological interactions, cellular uptake and biodistribution. Because little variations in synthesis or formulation might result in significant changes in pharmacokinetics or toxicity, batch-to-batch variability is a serious problem. Thus, thorough physicochemical characterization, including particle size analysis (DLS, NTA), morphology (TEM, SEM), surface functionalization (XPS, FTIR), crystallinity (XRD, DSC), and stability investigations under physiologically relevant circumstances, is required for regulatory consideration[48].

Nano-Specific Regulatory Considerations

In addition to requiring that nanomedicines adhere to traditional pharmacology and toxicological criteria (ADME, MTD, cytotoxicity), regulatory bodies like the FDA (U.S.) and EMA (Europe) additionally assess endpoints unique to nanoparticles[49]. These include the persistence of inorganic or non-biodegradable residues in organs, as well as the effects of the protein corona on biodistribution and cellular absorption. Unexpected interactions between nanoparticles and biological systems may result in long-term accumulation, inflammation, or complement activation. Additional testing, such as thorough immunotoxicity tests, genotoxicity, hemocompatibility, and nanoparticle clearance kinetics, is frequently included in regulatory review[50,51]. In order to guarantee both efficacy and safety, the regulatory framework integrates conventional toxicology with nanospecific behavior, emphasizing a risk-based approach. (Table 2)[52-64] summarises all regulatory Considerations for Cancer Nanocarriers.

Table II: Regulatory Considerations for Cancer Nanocarriers

Regulatory Aspect	Key Requirements (Summary)	Regulatory Agency Focus (FDA/EMA/ ICH)	Data Needed from Researchers	Challenges for Nanoformulations	Expected Outcome
1. Nanomaterial Characterization	Nanocarrier size, PDI, charge, morphology, crystallinity must be fully defined.	FDA Nanotechnology Guidance, EMA Reflection Paper on Nanomedicines	DLS, TEM/SEM, zeta potential, XRD, FTIR data	Batch variability, lack of standardized methods	Establish material identity and ensure reproducibility
2. Critical Quality Attributes (CQAs)	Identify properties affecting safety and efficacy (size, release rate, surface chemistry)	ICH Q8–Q10, FDA QbD guidelines	Full list of CQAs with acceptance criteria	Mapping nanoparticle behavior to CQAs is complex	Predictable performance and stability
3. Manufacturing & Process Control (GMP)	Scalable, controlled, and validated process using Quality-by-Design	FDA cGMP (21 CFR 210/211), EMA GMP Directive	Process flows, DoE optimization, CPP–CQA mapping	Microfluidics or emulsification scale-up challenges	GMP-compliant process suitable for clinical supply
4. Stability & Shelf-Life	Physical and chemical stability under multiple conditions	ICH Q1A–Q1E	Stability studies: size, aggregation, leakage, potency	Nanocarrier aggregation and drug leakage	Defined product shelf-life and storage conditions
5. Sterility & Endotoxin Requirements	Mandatory for injectable nanocarriers	USP <71> <85>	Sterility testing, endotoxin LAL assay	Sterilization may alter particle properties	Safe for parenteral use
6. In vitro Biological Evaluation	Cytotoxicity, hemocompatibility, immune response screening	ISO 10993	MTT, hemolysis, complement activation tests	Correlation to in vivo outcomes is limited	Early safety confirmation
7. In vivo Toxicology (Preclinical Safety)	PK, biodistribution, acute/chronic toxicity	FDA GLP, ICH M3(R2), EMA preclinical guidelines	Rodent + non-rodent studies	Nanoparticle accumulation in RES organs	Safety margin established for clinical trials
8. Immunotoxicity Assessment	Evaluate complement activation, cytokine storm risk	FDA Immunotoxicity Guidance	Cytokine panels, complement activation assays	Nanoparticles may cause unexpected immune activation	Immunological safety profile established
9. Biodistribution & Clearance	Must demonstrate predictable distribution and elimination	FDA/EMA imaging & bioanalysis requirements	IVIS, PET/MRI, ICP-MS, LC-MS data	Long-term retention of nanoparticles in organs	Understanding of exposure + clearance pathways

10. Drug Release Kinetics	Controlled and reproducible release is required	ICH Q6A	In vitro release profile and IVIVC attempts	Achieving physiologically relevant release models	Consistent therapeutic exposure
11. Product–Device Combination Issues	Applicability when nanocarrier is delivered via a device (injector, pump)	FDA Combination Product Guidelines	Human factor studies, device compatibility	Device interactions may alter formulation	Categorization and regulatory clarity
12. Clinical Trial Requirements	PK/PD profile, dose escalation, safety, tumor delivery	FDA IND, EMA IMPD	Phase I–III clinical trial protocols	Variability in tumor EPR effect among patients	Clinical translation and market approval
13. Post-Market Surveillance	Monitor long-term toxicity and immunogenicity	FDA/EMA Pharmacovigilance Guidelines	PSUR, safety updates, real-world data	Long-term nanoparticle fate is uncertain	Continuous risk–benefit assessment

Harmonized Guidelines and Long-Term Safety Monitoring

Global standards for the characterisation, production, and long-term safety of nanomedicines are still lacking. Strict adherence to Good Manufacturing Practices (GMP) with strong quality control for medication loading, surface chemistry, particle size, and batch repeatability is advised by agencies. Preclinical safety examination, including repeated dosage and long-term toxicity studies, is emphasized in regulatory advice, particularly for non-biodegradable or long-circulating nanoparticles[65]. Long-term safety monitoring and post-marketing pharmacovigilance are essential for identifying uncommon side events or toxicity linked to accumulation. In order to promote innovation in nanotherapeutics, maintain patient safety, and enable consistent regulatory review, standardized protocols for nanomedicine testing, reporting and clinical monitoring are being created globally[66].

EMERGING TRENDS AND FUTURE DIRECTIONS

Emerging cancer nanocarrier trends include the development of smarter, more precise systems that respond to tumor-specific stimuli, combine diagnostic and therapeutic functions, and improve immune regulation. Highly focused and flexible cancer therapies are being made possible by developments like gene-editing nanoplatforms, biomimetic nanoparticles, and customized nanomedicine. To fully achieve the potential of nanocarriers in precision oncology, future initiatives will focus on enhancing clinical translation through scalable production, improved safety profiling, and patient-specific design

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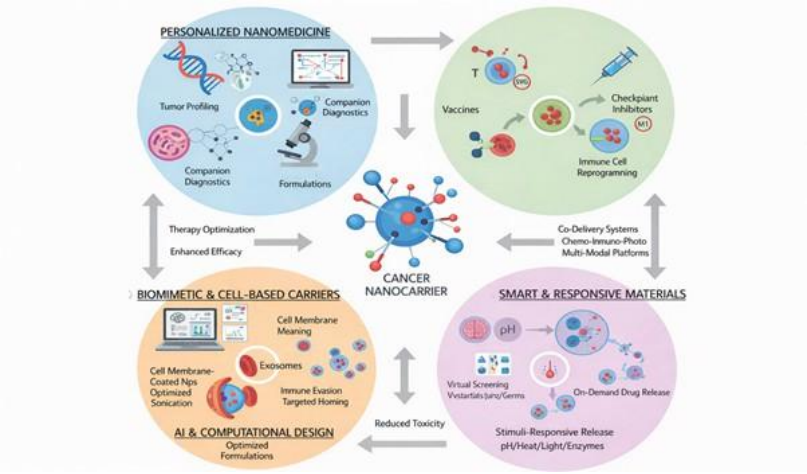

Fig. 3: Emerging Trends and Future Directions of cancer nanocarriers

Personalized Nanomedicine

Personalized nanomedicine tailors drug delivery systems to specific patient profiles by analyzing tumor molecular signatures, genetic alterations and biomarkers to guide therapy. Patients who are most likely to benefit from certain nanoparticle-based therapies can be identified

using companion diagnostics, such as imaging modalities and genetic analysis. Through this method, medication kind, dose, and carrier design may be optimized for improved effectiveness and less off-target toxicity[67,68]. To improve accumulation and therapeutic response, nanocarriers can be designed to target certain receptors or microenvironmental characteristics specific to a patient's tumor. Patient-specific ligands, pH-responsive release mechanisms, or flexible dosage regimens are examples of personalized formulations. This approach links traditional oncology with precision medicine by combining nanotechnology and precision diagnostics, potentially reducing inter-patient variability and optimizing therapy results while reducing systemic toxicity[69].

Immuno-Nanotherapeutics

Nanoparticles are used in immuno-nanotherapeutics to improve or modify the immune systems ability to fight cancer. By delivering checkpoint inhibitors, cytokines, or adjuvants to tumours, nanoparticles can enhance cytotoxicity and immune recognition[70]. To elicit strong antigen-specific T-cell responses, vaccine formulations incorporate tumor-associated antigens within nanoparticles. Moreover, nanoparticles can improve anti-tumor immunity by reprogramming tumor-associated macrophages from immunosuppressive M2 phenotypes to pro-inflammatory M1 states[71]. Combinatorial approaches combine immune modulators with radiation or chemotherapy to increase treatment efficacy in a synergistic way. Targeting ligands or biomimetic coatings enhance accumulation in tumor locations or lymphoid organs. Additionally, immuno-nanotherapeutics reduce systemic immune-related adverse effects by enabling spatiotemporal regulation of immune activation. This approach, which combines immunotherapy with nanomedicine, aims to increase clinical response rates in patients with diverse or resistant malignancies by overcoming immune evasion mechanisms[72].

Combination therapies

Co-delivery systems combine many treatment modalities into a single nanoplatform, including gene therapy, immunomodulators, chemotherapy and phototherapies. By concurrently focusing on complimentary pathways, this strategy improves synergistic effects and combats drug resistance. By safeguarding delicate biomolecules and guaranteeing coordinated action, multifunctional nanoparticles enable spatiotemporal control of drug release. For instance, photothermal agents in conjunction with gene therapy sensitize tumors to treatment, whereas chemo-immunotherapy nanocarriers can induce death while stimulating immunological responses. These platforms enhance patient outcomes, optimize dosage and lessen systemic toxicity[73-75].

Smart and responsive materials

In reaction to internal triggers (pH, enzymes, redox conditions) or external stimuli (light, heat, ultrasound), stimuli-responsive nanoparticles selectively release their payload[76]. In order to increase local concentration in tumors while protecting healthy tissues, polymers and hybrid materials can be designed for precise, on-demand drug release. These devices have the ability to give feedback-controlled administration which react to the heterogeneity of the tumor microenvironment and thus, dynamically modifying to release kinetics. By using biodegradable and biocompatible ingredients, long-term buildup is reduced and safe removal is guaranteed[77].

AI and computational design

Artificial intelligence and machine learning speed up nanomedicine development by predicting optimum formulations, drug loading, release kinetics, and biodistribution. Virtual screening for safety and effectiveness of polymer architectures, nanoparticle morphologies, and surface chemistries is made possible by computational modeling[78]. Preclinical testing time is shortened using AI algorithms that evaluate pharmacokinetics, toxicology, and immunogenicity profiles. At the end, data-driven techniques streamline regulatory procedures and improve the repeatability of nanotherapeutic research by enabling individualized dosage, anticipating off-target effects and optimizing combination tactics[79].

Biomimetic and cell-based carriers

Cell membrane-coated or exosome-derived nanoparticles take advantage of biocompatibility, immunological evasion and inherent homing capabilities. These biomimetic carriers decrease clearance by the mononuclear phagocyte system, increase circulation time and promote the targeted tumor accumulation. Specificity can be further enhanced by functionalization with ligands or surface proteins. These systems can imitate endogenous signalling and deliver chemotherapeutics, siRNA, or immunomodulators, which reduces systemic toxicity and is particularly successful for malignancies that are difficult to treat[80,81].

CONCLUSION

Numerous drawbacks of traditional cancer treatment, such as low drug solubility, systemic toxicity and multidrug resistance which may be addressed by nanotechnology-based drug delivery systems. Nanoformulations greatly increase therapeutic effectiveness and safety by facilitating targeted delivery, controlled release and enhanced drug accumulation at tumor locations. Combination therapy and integration with imaging for theranostic applications have also been made possible by developments in liposomes, polymeric nanoparticles, metallic systems and stimuli-responsive platforms. Nanomedicine continues to evolve as a formidable tool in contemporary oncology, with a tremendous promise to enhance patient outcomes and enable the creation of more precise and effective cancer therapies, despite obstacles such as large-scale manufacture and regulatory approval.

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