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NANOCARRIER-BASED APPROACHES FOR ENHANCED ANTICANCER DRUG DELIVERY

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ABSTRACT

Over recent years, nanotechnology has emerged as a transformative approach for delivering therapeutic agents in cancer management. A persistent clinical obstacle in oncology is the tendency of tumor cells to develop multidrug resistance (MDR) against conventional chemotherapeutic agents. To address this issue, significant technological progress has been made in engineering delivery systems capable of transporting anticancer drugs to tumor sites with improved drug loading. A wide variety of nanotechnology-based drug delivery systems have been developed for tumor targeting and have yielded encouraging outcomes in cancer management. This review explores the significance of nanocarriers in treating various cancer types and examines their role in targeted drug delivery. Preparation techniques and recent progress in nanocarrier platforms—including polymeric nanoparticles, micelles, nanotubes, dendrimers, magnetic nanoparticles, solid lipid nanoparticles (SLNs), and quantum dots (QDs)—are also discussed, along with the associated challenges and limitations.

KEYWORDS: Nanomaterials, drug delivery, anticancer therapy, nanoparticles, preparation methods, clinical applications.

INTRODUCTION

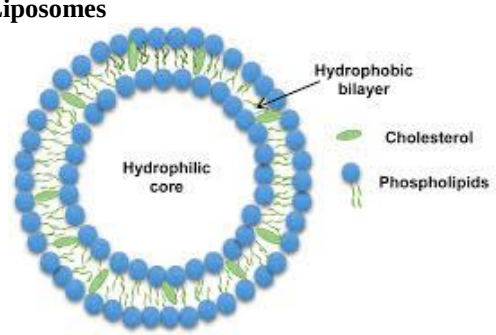
Cancer is the second leading cause of death worldwide**.** Although chemotherapy remains a cornerstone of cancer treatment, it non-selectively damages rapidly dividing healthy cells, resulting in severe adverse effects. An additional complication is MDR, through which cancer cells acquire the ability to resist multiple therapeutic agents simultaneously. To address these drawbacks, researchers have designed Smart Drug Delivery Systems (SDDSs) that utilize nanocarriers to transport drugs selectively to tumour sites, thereby improving treatment outcomes and minimizing collateral damage to healthy tissues. Despite notable advancements in cancer diagnosis and treatment modalities, conventional approaches—including surgery, radiation therapy, and chemotherapy—continue to demonstrate several shortcomings. These include non-targeted drug distribution, harmful side effects, reduced bioavailability, rapid drug elimination from the body, and the emergence of multidrug resistance, all of which compromise both drug efficacy and patient quality of life.

Nanocarriers

function across a broad size spectrum, typically up to 1,000 nm. Their development is primarily motivated by the need to enhance therapeutic efficiency while minimizing drug toxicity. Studies have demonstrated that nanocarrier-based drug delivery improves biodistribution profiles and administration routes with favorable safety characteristics. Drug delivery via nanocarriers can occur through passive or active mechanisms, enabling precise delivery to target sites with reduced dosing and greater therapeutic control. Nanocarrier systems effectively address critical shortcomings of existing drugs, such as non-specific biodistribution, rapid systemic clearance, unregulated drug release, and poor bioavailability. Nanocarriers investigated for oncological applications encompass liposomes, polymeric nanoparticles, dendrimers, micelles, solid lipid nanoparticles, nanogels,

carbon-based nanomaterials, and inorganic nanoparticles. These systems offer several advantages including enhanced drug solubility, extended blood circulation, improved tumor penetration, and reduced adverse effects. Contemporary nanocarrier platforms can further be engineered through surface modifications to incorporate targeting ligands and sti.

1. Liposomes



Liposomes are closed, spherical vesicles composed of phospholipid bilayers enclosing an aqueous interior. Their unique architecture enables encapsulation of hydrophilic drugs within the aqueous core and hydrophobic drugs within the lipid bilayer. Surface-engineered variants, such as PEGylated liposomes, exhibit extended systemic circulation and reduced immunogenicity. Smart liposomal formulations have been developed to release their drug payload specifically in the acidic tumor microenvironment.

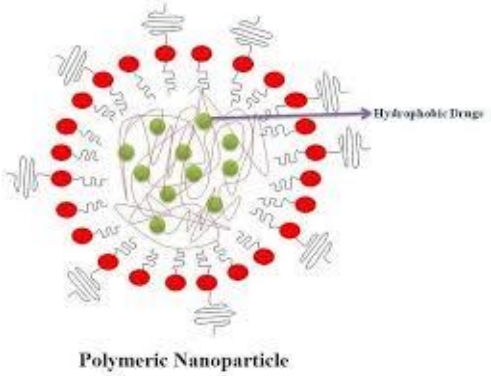
ADVANTAGES

- Excellent biocompatibility and non-toxicity
- Capable of co-encapsulating both hydrophilic and lipophilic drugs
- Improves drug solubility and pharmacokinetic parameters
- Provides protection from enzymatic degradation

DISADVANTAGES

- Relatively slow drug transport rates
- Limited physical stability

2. Polymeric Nanoparticles



Polymeric nanoparticles are constructed from biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) or polycaprolactone (PCL), enabling sustained and controlled drug release. Surface functionalization allows conjugation of targeting ligands and stimuli-responsive coatings, facilitating site-specific drug delivery. For instance, nanoparticles formulated with pH-labile polymers selectively release their drug cargo in the acidic tumor environment.

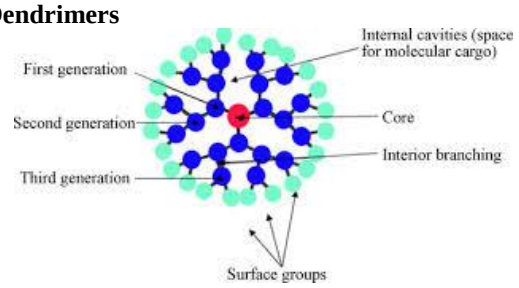
ADVANTAGES

- High biocompatibility
- Capable of solubilizing lipophilic drugs
- Surface groups amenable to conjugation with targeting moieties

DISADVANTAGES

- Limited drug loading capacity
- Primarily suited for lipophilic drug molecules.

3. Dendrimers



Dendrimers are highly branched, tree-like macromolecular structures that radiate from a central core. They are frequently synthesized using naturally derived or synthetic building blocks, including sugars, nucleotides, and amino acids. Their suitability for drug delivery arises from well-defined molecular weights, numerous branching points, spherical geometry, monodisperse character, and an average diameter in the range of 1.4–1.45 nm.

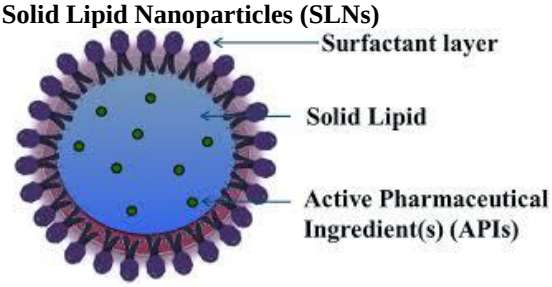
ADVANTAGES

- Water-soluble and biocompatible
- Favorable pharmacokinetic behavior
- Capable of encapsulating and delivering diverse bioactive compounds

DISADVANTAGES

- Suboptimal drug release kinetics
- Rapid systemic clearance
- Potential cytotoxicity at higher concentrations

4. Solid Lipid Nanoparticles (SLNs)



SLNs are colloidal carrier systems ranging from 50 to 1,000 nm, stabilized in physiological fluids. The drug is incorporated into a solid lipid matrix composed of fatty acids and glycerides. These systems have demonstrated considerable clinical utility. For example, chitosan-coated lipid nanoparticles loaded with curcumin (CUR), prepared via cold dilution, have shown efficacy in suppressing the proliferation of PANC-1 pancreatic cancer cells. Lipid nanocarriers co-loaded with paclitaxel (PTX) and 5-fluorouracil (5-FU), such as the Intelex system, have been employed in male patients with liver cancer, where the lipid matrix protects the drug from enzymatic degradation in plasma. Additionally, SLNs co-incorporating sorafenib (SOR) and superparamagnetic iron oxide nanoparticles have been explored for targeted therapy of HepG2 hepatocellular carcinoma cells.

ADVANTAGES

- Enhanced drug absorption
- Protection of encapsulated drugs from degradation
- Fabricated from generally recognized as safe (GRAS) materials
- Sustained drug release profiles
- Versatile for various administration routes

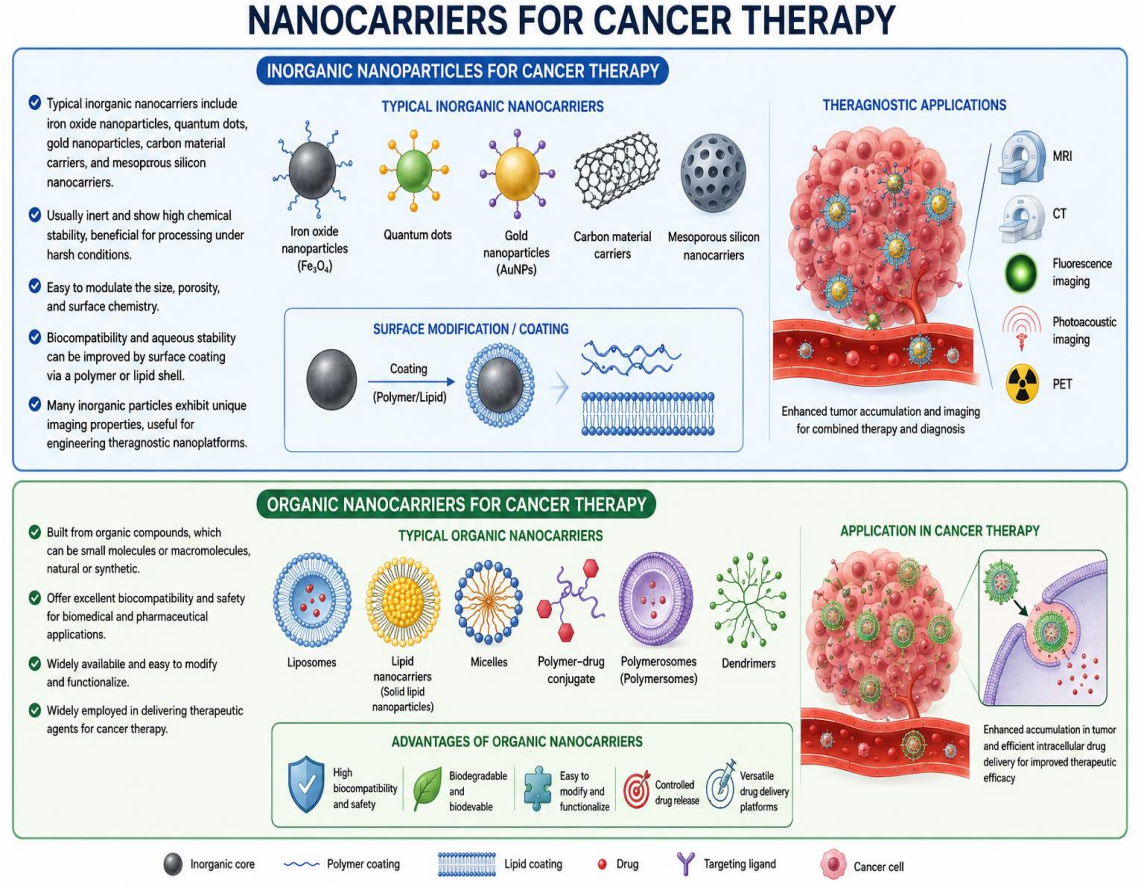
DISADVANTAGES

- Limited drug loading capacity
- Drug expulsion during storage (polymorphic transitions)
- Tendency for particle aggregation
- Surfactant-related complications
- Risk of burst release

Nanocarriers for Antitumor Drug Delivery

Benefits of Nanomedicines

Nanomedicines offer substantial advantages in drug delivery across multiple dimensions. Nanoparticle platforms can improve the solubility of poorly water-soluble drugs without requiring organic solvents—exemplified by albumin-bound paclitaxel (nab-PTX). Nano-encapsulation further addresses drug instability issues. Nanocarriers enable manipulation of pharmacokinetic parameters and biodistribution profiles. A particularly impactful application is cancer therapy, where nanotechnology facilitates passive tumor targeting, enhances drug internalization through surface functionalization and active targeting strategies, and supports controlled release via multiple engineered mechanisms.



Inorganic Nanoparticles for Cancer Therapy

Based on the nature of their excipients, nanocarriers are broadly categorized as inorganic or organic. Inorganic nanocarriers include iron oxide nanoparticles, quantum dots, gold nanoparticles, carbon-based nanomaterials, and mesoporous silica nanoparticles. These materials generally exhibit chemical inertness and stability, enabling them to withstand extreme processing conditions. Their size, porosity, and surface chemistry are readily tunable. Biocompatibility and aqueous

stability can be achieved through surface coating with polymeric or liposomal layers. Importantly, inorganic nanoparticles possess intrinsic imaging capabilities, making them attractive for theranostic platform development.

Organic Nanocarriers for Cancer Therapy

Organic nanocarriers are derived from organic compounds and may consist of small molecules or macromolecules depending on their molecular weight and origin. The organic composition of these carriers confers superior biocompatibility and safety, which is particularly desirable for biomedical and pharmaceutical applications. Furthermore, organic materials are naturally abundant and highly amenable to structural modification. Commonly used organic nanocarriers in anticancer drug delivery include liposomes, lipid nanocarriers, polymeric micelles, polymer–drug conjugates, polymersomes, and dendrimers.

Methods of Preparation of Nanocarriers

1. Emulsification–Solvent Evaporation

Principle

The polymer and drug are co-dissolved in a volatile organic solvent, and the resulting mixture is emulsified in an aqueous surfactant solution. Removal of the organic solvent through evaporation produces drug-loaded nanoparticles.

ADVANTAGES

- Straightforward and widely adopted
- suitable for hydrophobic drug encapsulation
- high encapsulation efficiency.

LIMITATIONS

- Potential for residual organic solvent
- unsuitable for thermolabile drugs.

2. Nanoprecipitation (Solvent Displacement)

Principle

The polymer and drug are dissolved in a water-miscible organic solvent and introduced dropwise into an aqueous phase under continuous agitation. Rapid diffusion of the organic solvent drives spontaneous nanoparticle formation.

ADVANTAGES

- Simple
- reproducible and low energy
- generates uniform nanoparticle populations.

LIMITATIONS

- Best suited for hydrophobic drug molecules.

3. Ionic Gelation

Principle

Oppositely charged polymers—such as chitosan and sodium tripolyphosphate—interact electrostatically to form nanoparticles without the use of organic solvents.

ADVANTAGES

- Mild preparation conditions
- compatible with proteins and nucleic acids
- biocompatible.

APPLICATIONS

- Gene delivery
- protein delivery and anticancer drug delivery.

4. High-Pressure Homogenization

Principle

A drug–lipid mixture is passed through a narrow orifice under high pressure, producing nanosized particles through shear and cavitation forces.

ADVANTAGES

- Scalable process
- solvent-free
- particularly suitable for SLN fabrication.

5. Thin-Film Hydration (Liposome Preparation)

Principle

Lipids dissolved in an organic solvent are dried under reduced pressure to form a thin lipid film, which is subsequently hydrated with an aqueous buffer to generate liposomes.

ADVANTAGES

- Widely established method
- accommodates both hydrophilic and lipophilic drugs
- high drug-loading capacity.

6. Microemulsion Method

Principle

Nanoparticles are generated from a thermodynamically stable microemulsion system composed of oil, water, surfactant, and co-surfactant.

ADVANTAGES

- Narrow particle size distribution
- high physical stability.

7. Supercritical Fluid Technology

Principle

Supercritical carbon dioxide ($scCO_2$) serves as a solvent or anti-solvent to produce nanoparticles with precisely controlled dimensions.

ADVANTAGES

- Environmentally sustainable
- minimal solvent residue
- compatible with temperature-sensitive drugs.

8. Spray Drying

Principle

A drug-containing solution or suspension is atomized into a heated airstream, producing dried nanoparticles or microparticles.

ADVANTAGES

- Rapid
- easily scalable
- yields dry powder formulations suitable for inhalation or oral delivery.

9. Self-Assembly

Principle

Amphiphilic molecules spontaneously organize into ordered nanostructures such as micelles or vesicles upon dispersion in aqueous media, driven by hydrophobic and hydrophilic interactions.

APPLICATIONS

- Polymeric micelles
- liposomal vesicles
- drug-loaded nanocarrier systems.

Recent Advances in Nanocarrier-Based Cancer Therapy

1. Stimuli-Responsive Nanocarriers

- Smart nanocarriers designed to release drugs in response to endogenous or exogenous stimuli include pH-responsive
- thermo-responsive
- redox-responsive
- enzyme-triggered
- light-activated
- magnetically responsive
- ultrasound-responsive systems.

2. Targeted Nanocarriers

- Delivery strategies employ both passive targeting via the Enhanced Permeability and Retention (EPR) effect and active targeting using surface-conjugated ligands
- monoclonal antibodies
- Peptides or aptamers

3. Biomimetic Nanocarriers

- Biologically inspired platforms include cell membrane-coated nanoparticles
- exosome-derived delivery vehicles
- virus-mimicking nanostructures.

4. Multifunctional Nanocarriers (Theranostics

- Integrated systems combining diagnostic imaging with therapy include image-guided treatment
- photothermal therapy (PTT)
- photodynamic therapy (PDT).

5. Nucleic Acid Delivery

- Nanocarriers have been adapted for delivery of siRNA, mRNA, CRISPR/Cas9 components
- DNA constructs for gene-based cancer therapy.

6. Combination Therapy

- Multi-agent strategies include co-delivery of two or more chemotherapeutic drugs
- combined drug–gene delivery
- chemo-immunotherapy
- chemo-photothermal combinations.

7. Artificial Intelligence in Nanocarrier Design

- Computational approaches including machine learning algorithms and predictive modelling are increasingly applied to nanoparticle optimization and formulation development.

8. Personalized Nanomedicine

- Emerging paradigms include patient-tailored drug delivery systems
- precision oncology approaches
- biomarker-guided selection of nanocarrier platforms.

9. Clinical Translation

- FDA-approved nanomedicines and ongoing clinical trials continue to advance the field
- though commercialization barriers remain a significant challenge.

Targeted Drug Delivery Strategies

1. Ligand-Mediated Targeting

In ligand-based targeting, specific recognition molecules are conjugated to the nanoparticle surface to facilitate binding to receptors overexpressed on tumour cells.

Common ligands used

- Folic acid
- Transferrin
- Hyaluronic acid
- RGD peptides
- Aptamers

ADVANTAGES

- High cancer cell specificity
- reduced systemic toxicity
- enhanced cellular internalization;improved therapeutic outcomes.

2. Antibody-Mediated Targeting

Monoclonal antibodies are attached to nanocarrier surfaces to recognize and bind tumor-specific antigens, triggering receptor-mediated internalization of the drug-loaded carrier.

Common tumor targets

- HER2 (breast cancer)
- EGFR (lung and colorectal cancers)
- CD20 (lymphoma)

ADVANTAGES

- Exceptionally high target specificity
- improved treatment efficacy
- minimized off-target toxicity.

3. Receptor-Targeted Nanocarriers

Tumor cells frequently overexpress surface receptors compared to normal cells. Nanocarriers can be functionalized to selectively bind these receptors and exploit receptor-mediated endocytosis for intracellular drug delivery.

Target receptor examples

- Folate receptor
- Transferrin receptor
- Epidermal Growth Factor Receptor (EGFR)
- Integrin receptors
- CD44 receptor

Benefits

- Greater drug accumulation at the tumor site
- improved intracellular drug internalization
- potential for dose reduction.

4. Tumor Microenvironment-Responsive Systems

The tumor microenvironment (TME) differs from normal tissue in terms of pH, enzymatic activity, redox state, oxygen levels, and oxidative stress. Stimuli-responsive nanocarriers exploit these differences to trigger site-specific drug release.

System types

- pH-sensitive systems: Release drugs in the acidic TME (pH ~6.5–6.8)
- Enzyme-sensitive systems: Activated by matrix metalloproteinases (MMPs) abundant in tumor stroma
- Redox-sensitive systems: Triggered by elevated intracellular glutathione (GSH) in cancer cells
- Hypoxia-sensitive systems: Designed to release drugs in oxygen-deficient tumor regions
- ROS-sensitive systems: Activated by elevated reactive oxygen species in tumor cells

ADVANTAGES

- Spatially controlled drug release
- reduced premature leakage
- improved therapeutic index
- lower systemic toxicity.

Clinical Applications and Approved Nanomedicines

While the majority of nanocarrier systems remain at the experimental stage, several nanomedicine products have received regulatory approval and demonstrated clinical superiority over conventional chemotherapy.

1. Liposomal Doxorubicin (Doxil®/Caelyx®)

Doxorubicin encapsulated within PEGylated liposomes exploits the EPR effect to preferentially accumulate in tumor tissue while limiting systemic exposure. The liposomal formulation also protects the drug from premature degradation.

Approved indications

- Breast cancer
- ovarian cancer
- multiple myeloma
- AIDS-related Kaposi's sarcoma.

ADVANTAGES

- Reduced cardiotoxicity compared to free doxorubicin
- extended blood circulation
- preferential tumor accumulation
- lower systemic adverse effects.

2. Albumin-Bound Paclitaxel (Abraxane®)

Paclitaxel is conjugated to albumin nanoparticles, eliminating the requirement for toxic solvent vehicles used in conventional paclitaxel formulations. Albumin further facilitates active transport into tumor tissue via gp60-mediated transcytosis and SPARC binding.

Approved indications

- Metastatic breast cancer
- non-small cell lung cancer (NSCLC)
- pancreatic adenocarcinoma.

ADVANTAGES

- Improved drug solubility and bioavailability
- elevated intratumoral drug concentrations
- reduced incidence of hypersensitivity reactions
- improved patient tolerability.

Challenges and Limitations of Nanocarriers for Anticancer Drug Delivery

Despite substantial progress, nanocarrier-based drug delivery systems face a range of scientific, technical, and regulatory hurdles that continue to restrict their broad clinical adoption.

1. Toxicity and Biocompatibility

Although nanocarriers are generally engineered to be biocompatible, certain nanomaterials may elicit adverse biological responses.

KEY CHALLENGES

- Cytotoxicity from metallic nanoparticles
- induction of oxidative stress and inflammatory responses
- immune activation or hypersensitivity
- prolonged accumulation in the liver and spleen.

Proposed solutions

- Selection of biodegradable and biocompatible materials
- PEGylation and other surface modification strategies
- rigorous preclinical toxicological assessment.

2. Stability Concerns
Nanocarriers may undergo physical or chemical degradation during storage or upon systemic administration.

KEY CHALLENGES
- Particle aggregation
- drug degradation
- alterations in particle size and zeta potential
- shortened shelf life.

Proposed solutions
- Formulation optimization
- use of stabilizing agents and cryoprotectants
- development of appropriate storage protocols.

3. Premature Drug Leakage
Unintended drug release from nanocarriers before reaching the tumor reduces therapeutic efficacy and increases off-target effects.

KEY CHALLENGES
- Loss of encapsulated drug during storage
- uncontrolled drug release in the systemic circulation
- reduced drug concentration at the target site.

Proposed solutions
- Improvement of encapsulation efficiency
- development of stimuli-responsive carriers
- optimization of nanocarrier composition.

4. Manufacturing and Scale-Up:
Many nanocarrier formulations that perform well under laboratory conditions are difficult to manufacture at an industrial scale with consistent quality.

KEY CHALLENGES
- Inter-batch variability
- complex production workflows
- difficulty in maintaining uniform particle size
- elevated manufacturing costs.

Proposed solutions
- Standardized manufacturing protocols
- process automation
- implementation of Quality by Design (QbD) principles.

5. Regulatory Considerations
The regulatory pathway for nanomedicines is inherently more complex than for conventional drug formulations.

KEY CHALLENGES
- Absence of standardized characterization and evaluation methods
- limited long-term safety data
- stringent quality control requirements
- regulatory inconsistencies across jurisdictions.

Proposed solutions
- Development of harmonized international regulatory frameworks
- improved physicochemical characterization methods
- comprehensive long-term clinical safety studies.

6. Cost-Effectiveness
The development and commercial production of nanocarrier-based therapeutics is substantially more expensive than conventional pharmaceutical formulations.

KEY CHALLENGES
- High R&D expenditure
- costly raw materials
- need for specialized manufacturing infrastructure
- financial burden on patients.

Proposed solutions
- Enhanced manufacturing efficiency
- production scale-up to reduce per-unit costs
- development of cost-effective nanocarrier materials.

RESULTS
The experimental and preclinical findings reviewed herein highlight the significant therapeutic potential of specific nanocarrier formulations:

Chitosan-Coated Lipid Nanoparticles: CUR-loaded formulations effectively suppressed the proliferation of PANC-1 pancreatic cancer cells.

Intelex Lipid Nanocarriers: PTX- and 5-FU-loaded systems protected the drugs from enzymatic degradation, enabling effective plasma accumulation and clinical benefit in male patients with liver cancer.

Solid Lipid Nanoparticles: SOR- and superparamagnetic iron oxide nanoparticle-coloaded SLNs demonstrated successful dual-targeted treatment in HepG2 hepatocellular carcinoma cells.

CONCLUSION
Intelligent nanocarrier platforms have demonstrated considerable promise in transforming cancer therapy through their capacity to deliver therapeutic agents in a targeted, controlled, and efficient manner. These advanced delivery systems enhance treatment specificity while substantially reducing the adverse effects associated with conventional chemotherapy. Multiple nanocarrier types—including liposomal carriers, polymeric nanoparticles, and gold-based platforms—have demonstrated efficacy in both experimental and clinical settings. Tumor-targeting strategies exploiting the EPR effect and receptor-mediated mechanisms have proven particularly effective. The emergence of stimuli-responsive and theranostic platforms offers further opportunities for individualized cancer treatment. Nevertheless, significant challenges persist. Barriers to large-scale manufacturing, high production costs, and

complex regulatory requirements continue to impede broader clinical translation. Safety concerns, including potential nanoparticle cytotoxicity and immunogenic interactions, must also be resolved before these systems can achieve widespread clinical adoption. The integration of artificial intelligence and machine learning in nanocarrier design holds significant promise for further optimizing therapeutic performance and accelerating the development of next-generation oncological nanomedicines. In summary, smart nanocarrier systems represent a highly promising frontier in the development of novel, effective approaches to cancer treatment.

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