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Research Article

# Preclinical And Translational Applications of Nanoparticulate Drug Delivery System in Hepatocellular Carcinoma

**Ashu Mittal[1], Raghav Dixit[2], Soma Das[3], Ramandeep Kaur[4], Kunal[5], Sanmati Kumar Jain[6], Tanya Gupta[7*]**

[1]Professor of Pharmaceutics, KIET School of pharmacy (KIET Group of institutions), Muradnagar, Delhi NCR 201206
[2]Assistant Professor, Himalayan School of Pharmaceutical Sciences, Swami Rama Himalayan University, Jolly Grant, Dehradun, 248016, India
[3]Associate Professor, Department of Pharmaceutical Technology, SOHMS Adamas University, Kolkata, West Bengal, India
[4]Assistant Professor, Department of Pharmacy, Pharmacy Academy, IFTM University, Moradabad, Uttar Pradesh, India
[5]R.P. Educational Trust Group of Institutions Bastara, Karnal
[6]Professor, Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Koni, Bilaspur, India
[7*]Apeejay Stya University, Palwal -Sohna road, Sohna, Gurugram, Haryana 122103

**Abstract**
Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality globally, with limited treatment options and poor prognosis for advanced stages. Nanoparticulate drug delivery systems (NDDS) have emerged as a promising therapeutic strategy, offering enhanced targeting, controlled release, and reduced off-target effects compared to traditional chemotherapeutic treatments. This review explores the preclinical and translational applications of NDDS in the treatment of HCC, focusing on the mechanisms by which nanoparticles improve drug delivery efficiency. Key nanoparticle types, including liposomes, polymeric nanoparticles, dendrimers, and metal nanoparticles, are discussed in terms of their formulation, advantages, and mechanisms of action such as the enhanced permeability and retention (EPR) effect, cellular uptake, and targeted release. Furthermore, the potential for combining NDDS with other therapeutic strategies, such as gene therapy, immunotherapy, and drug combinations, is examined to enhance treatment efficacy. Despite the promising results in preclinical models, significant challenges remain in the clinical translation of NDDS, including issues related to large-scale production, regulatory approval, biocompatibility, and long-term toxicity. Advances in nanoparticle engineering, including the development of multifunctional, biodegradable, and stimuli-responsive systems, are paving the way for overcoming these obstacles. This review highlights the current state of research and offers insights into the future prospects for the clinical application of NDDS in HCC treatment, emphasizing the importance of collaborative, multidisciplinary research to fully realize their potential in improving patient outcomes.

**Keywords** Hepatocellular carcinoma, NDDS, targeted drug delivery, nanomedicine

***Authors for correspondence:** Tanya Gupta **Email:.** tanya.gupta.tanisha413@gmail.com

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## 1.Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for approximately 75-85% of all liver cancer cases (Rochigneux *et al.,* 2020). It is a major global health concern, particularly prevalent in regions with high rates of hepatitis B and C infections, such as East Asia and Sub-Saharan Africa. According to global cancer statistics, HCC is among the leading causes of cancer-related deaths, contributing significantly to morbidity and mortality rates worldwide (Seong *et al.,* 2020). The development of HCC is often associated with underlying chronic liver diseases, such as cirrhosis, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD). The complex pathophysiology of HCC, marked by tumor heterogeneity and multiple genetic mutations, presents challenges for effective treatment (Latimer & Mott, 2015). Despite advances in medical science, the prognosis for HCC remains poor, especially in advanced stages where curative treatments like surgical resection or liver transplantation are often not viable. The five-year survival rate for patients diagnosed with HCC remains less than 20% in many cases, emphasizing the need for more effective therapeutic options (Socinski *et al.,* 2016). Current treatment strategies for HCC include surgical resection, liver transplantation, and loco-regional therapies such as transarterial chemoembolization (TACE) and radiofrequency ablation (Pai-Scherf *et al.,* 2017). Systemic therapies, including the use of targeted therapies like sorafenib and lenvatinib, have also shown efficacy in extending patient survival. However, these treatments often face limitations such as drug resistance, severe side effects, and non-specific targeting, which hinder their effectiveness and overall patient outcomes (Sun *et al.,* 2007).

### Role of Drug Delivery Systems in HCC Treatment

Traditional drug delivery approaches for HCC involve systemic administration, where therapeutic agents are dispersed throughout the body, potentially affecting both cancerous and healthy tissues (Georgoulias *et al.,* 2001). This non-specific distribution can lead to significant adverse effects, reduced drug concentration at the tumor site, and an overall decline in therapeutic efficacy. Additionally, the unique microenvironment of HCC, including factors such as hypoxia, elevated interstitial pressure, and dense extracellular matrices, poses significant barriers to drug penetration and absorption (Roca *et al.,* 2017). The limitations of conventional therapies underscore the need for innovative drug delivery systems that can enhance the specificity and efficiency of treatment. In this context, targeted drug delivery systems aim to localize and release the therapeutic agents directly at the tumor site, thereby improving drug concentration within the tumor while minimizing systemic exposure and associated side effects (Leudke *et al.,* 1990). These strategies hold potential to improve the therapeutic index of drugs and overcome the inherent challenges in treating HCC (Tomalia & Fréchet, 2002).

### Nanoparticulate Drug Delivery Systems (NDDS)

Nanoparticulate drug delivery systems (NDDS) represent a revolutionary approach in the field of oncology, offering solutions to many of the limitations of conventional treatment methods. NDDS are engineered materials typically in the range of 1 to 100 nanometers and include various structures such as liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles (Lynch *et al.,* 2004). These systems can be designed to encapsulate therapeutic agents, protecting them from degradation and facilitating targeted delivery to tumor sites (Jiang *et al.,* 2015). The advantages of NDDS over traditional drug delivery methods lie in their ability to improve the pharmacokinetics and bioavailability of drugs. By leveraging the enhanced permeability and retention (EPR) effect—a phenomenon where nanoparticles preferentially accumulate in tumor tissues due to their leaky vasculature—NDDS enable more efficient drug delivery to cancer cells while sparing healthy tissues. Additionally, NDDS can be functionalized with targeting ligands such as antibodies, peptides, or small molecules that bind specifically to cancer cell markers, enhancing the precision of drug delivery (Semete *et al.,* 2010). Moreover, nanoparticles can be engineered to respond to specific stimuli, such as pH changes, temperature, or enzymes present in the tumor microenvironment, allowing for controlled drug release (Chen *et al.,* 2018). This feature not only improves drug concentration at the target site but also reduces systemic toxicity. The versatility of NDDS also allows for the co-delivery of multiple therapeutic agents, opening up new possibilities for combination therapy to tackle drug resistance and improve treatment outcomes (Patra *et al.,* 2018). Overall, the application of NDDS in HCC holds significant promise, offering a platform for more effective and less toxic treatment options. However, while preclinical research has shown encouraging results, the path to clinical application involves addressing challenges related to large-scale manufacturing, biocompatibility, and regulatory approval. Understanding these aspects is essential for translating the potential of NDDS from the laboratory to clinical practice, where it could revolutionize the management of HCC (Senapati, Mahanta, Kumar, & Maiti, 2018).

## 2. Mechanisms of Nanoparticle-Based Drug Delivery

### Types of Nanoparticles Used

Nanoparticles have emerged as effective drug delivery systems due to their unique properties, such as small size, high surface area, and the ability to be modified for targeted delivery (Zhou & Zhou, 2015). Several types of nanoparticles are used in drug delivery systems, each with specific characteristics and benefits:

**1. Liposomes**: Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core. They can encapsulate both hydrophilic and hydrophobic drugs, making them versatile carriers. Liposomes are biocompatible and biodegradable, and their surface can be modified with

ligands for targeted delivery. Examples include Doxil (liposomal doxorubicin), which has been used in cancer treatment (Najlah *et al.,* 2017).

**2. Polymeric Nanoparticles**: These nanoparticles are made from biodegradable and biocompatible polymers such as polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and chitosan (Barnfield & Ellis, 2016). Polymeric nanoparticles can provide controlled and sustained drug release, enhancing therapeutic efficacy. Their structure allows for the encapsulation of drugs and surface modification with targeting molecules to enhance specificity (FDA, 2020).

**3. Dendrimers**: Dendrimers are highly branched, tree-like macromolecules with a central core and multiple functional groups on their surface. This unique architecture provides a high degree of surface functionality, enabling the attachment of drugs, imaging agents, and targeting ligands. The high drug-loading capacity and ability to precisely modify dendrimers make them promising candidates for drug delivery (Esim *et al.,* 2020).

**4. Metal Nanoparticles**: Metal nanoparticles, such as gold and silver nanoparticles, are used for both drug delivery and diagnostic purposes. Gold nanoparticles, in particular, are known for their easy surface functionalization and biocompatibility (Ramos-Esquivel *et al.,* 2017). They can be designed to deliver drugs and facilitate imaging, offering potential for theranostic applications.

**5. Other Types**: This includes lipid nanoparticles, solid lipid nanoparticles (SLNs), nanomicelles, and carbon-based nanoparticles like carbon nanotubes and graphene oxide. Each type offers unique properties suited for specific applications in drug delivery (Poonia, Kharb, Lather, & Pandita, 2016).

**Table 1: Different cytotoxicity assays for the evaluation of nanoparticles**

| Assays | Method of Detection | Description | Interaction with Nanoparticles | References |
|---|---|---|---|---|
| Tetrazolium based substrates: MTT, MTS, XTT, WST-1 assays | Colorimetric | NAD(P)H-dependent oxidoreductase or dehydrogenases in viable cells can reduce tetrazolium salt into purple-colored (MTT/MTS), orange-colored (XTT), or orange to purple (WST-1) formazan, which requires either solubilization/non-solubilization process prior to spectrophotometric analysis. | Carbon nanotubes (MTT) | (Ramos-Esquivel *et al.,* 2017) |
| | | | Carbon black (MTT) | (Esim *et al.*, 2020). |
| | | | Mn (WST-1) | (Najlah *et al.*, 2017). |
| | | | Mg (Tetrazolium salt) | (Barnfield & Ellis, 2016). |
| | | | Polyhedral oligomeric | (Chen *et al.*, 2018). |
| | | | Silsesquioxane (MTT) | (Patra *et al.*, 2018). |
| | | | Au (MTT) | (Lynch *et al.*, 2004). |
| | | | CdSe (MTS) | (Sun *et al.*, 2007). |
| | | | helical rosette nanotubes (RNT) (MTS) | (Seong *et al.*, 2020). |
| Sulforhodamine B (SRB) assay | Colorimetric | SRB binds stoichiometrically to proteins under mild acidic conditions and can be extracted using basic conditions; thus, the amount of bound dye can be used as a proxy for cell mass. | Au or other metals | (Pai-Scherf *et al.*, 2017). |
| | Fluorometric | | | |
| Alamar blue assay (resazurin) | Colorimetric | Metabolic activity of cells converts soluble resazurin dye into fluorescent resorufin with fluorescence emission. | CdSe | (Socinski *et al.*, 2016). |
| | Fluorometric | | $TiO_2$ | (Latimer & Mott, 2015). |
| Adenosine triphosphate (ATP) assay | Colorimetric | ATP present in viable cells will react with luciferin in the presence of luciferase, producing luminescence as the end product. | Au<br>Silica | (Mehnert & Mäder, 2001). |
| | Fluorometric | | | |
| | Luminometric | | | |
| Lactate dehydrogenase (LDH) leakage assay | Colorimetric | Monitoring the release of lactate dehydrogenase from compromised cells. | Au, Cu, Ag, $TiO_2$, ZnO | (Ganesan & Narayanasamy, 2017). |
| | Fluorometric | | Carbon nanotubes | (Scioli Montoto, Muraca, & Ruiz, 2020). |
| Trypan blue exclusion assay | Microscopy | Dye uptake in cells with compromised cell membrane. | | (Iqbal *et al.*, 2012). |
| Real time assay(Glo™ reagents) | Bioluminometric | Real time monitoring of viable cells based on luciferase–substrate reaction. | | (Chen *et al.*, 2017). |

**Mechanism of Action in Drug Delivery**

The efficacy of nanoparticle-based drug delivery hinges on their ability to deliver therapeutic agents directly to the tumor site, enhancing treatment efficacy while minimizing systemic toxicity (Goldberg, 2015). The primary mechanisms involved are:

**1. Enhanced Permeability and Retention (EPR) Effect**: Tumors often have a highly disorganized vasculature with large fenestrations, allowing nanoparticles to passively accumulate within the tumor tissue. This phenomenon, known as the EPR effect, enables nanoparticles to localize at tumor sites more effectively than traditional small-molecule drugs, which are more evenly distributed throughout the body (Chen *et al.,* 2017).

**2. Targeted Drug Release**: Nanoparticles can be engineered to release their payload in response to specific triggers within the tumor microenvironment, such as pH changes, enzymes, or temperature (Choi & Han, 2018). This ensures that the drug is released only at the target site, minimizing off-target effects and enhancing therapeutic outcomes.

**3. Cellular Uptake**: Once nanoparticles accumulate at the tumor site, their interaction with cancer cells can be mediated by endocytosis, where the nanoparticles are internalized by the cells and release their payload intracellularly (Quan *et al.,* 2015). This process allows for the effective delivery of drugs that act within the cell, such as chemotherapeutics or gene therapies (Ghasemiyeh & Mohammadi-Samani, 2018).

**Targeting Strategies**

Effective targeting of nanoparticles to tumor cells is crucial for maximizing their therapeutic potential. Targeting strategies can be broadly classified into passive and active targeting:

**1. Passive Targeting**: Passive targeting relies on the EPR effect for the accumulation of nanoparticles at the tumor site. Due to the leaky vasculature of tumors and reduced lymphatic drainage, nanoparticles of an appropriate size (typically 10–200 nm) can accumulate in the tumor tissue over time (Børresen *et al.,* 2020). While passive targeting is simple and effective, it lacks specificity to cancer cells alone and may result in drug delivery to non-cancerous tissues in some cases (Iqbal *et al.,* 2012).

**2. Active Targeting**: Active targeting is a sophisticated approach that enhances the specificity of nanoparticle-based drug delivery by functionalizing nanoparticles with specific ligands that bind to receptors overexpressed on the surface of cancer cells. This method significantly increases the precision of drug delivery and minimizes off-target effects. Among the commonly used ligands, monoclonal antibodies and their fragments are particularly effective as they can be attached to nanoparticles to specifically recognize and bind to antigens present on tumor cells (Garbuzenko *et al.,* 2019). Peptides, due to their small size and high binding affinity, also serve as valuable targeting agents for engaging cell surface receptors. Additionally, small molecules such as folic acid and aptamers have been employed to target receptors like the folate receptor, which is often overexpressed in certain types of cancer. The use of these ligands facilitates enhanced uptake of nanoparticles by cancer cells, thereby improving the efficacy of the delivered therapeutic agents (Khosa, Reddi, & Saha, 2018).

**3. Surface Modification**: The surface properties of nanoparticles can be modified to enhance circulation time, avoid rapid clearance by the mononuclear phagocyte system (MPS), and improve targeting. Polyethylene glycol (PEG) is a commonly used surface modifier that provides a "stealth" characteristic to nanoparticles, helping them evade the immune system and remain in circulation longer (Haider, Abdin, Kamal, & Orive, 2020).

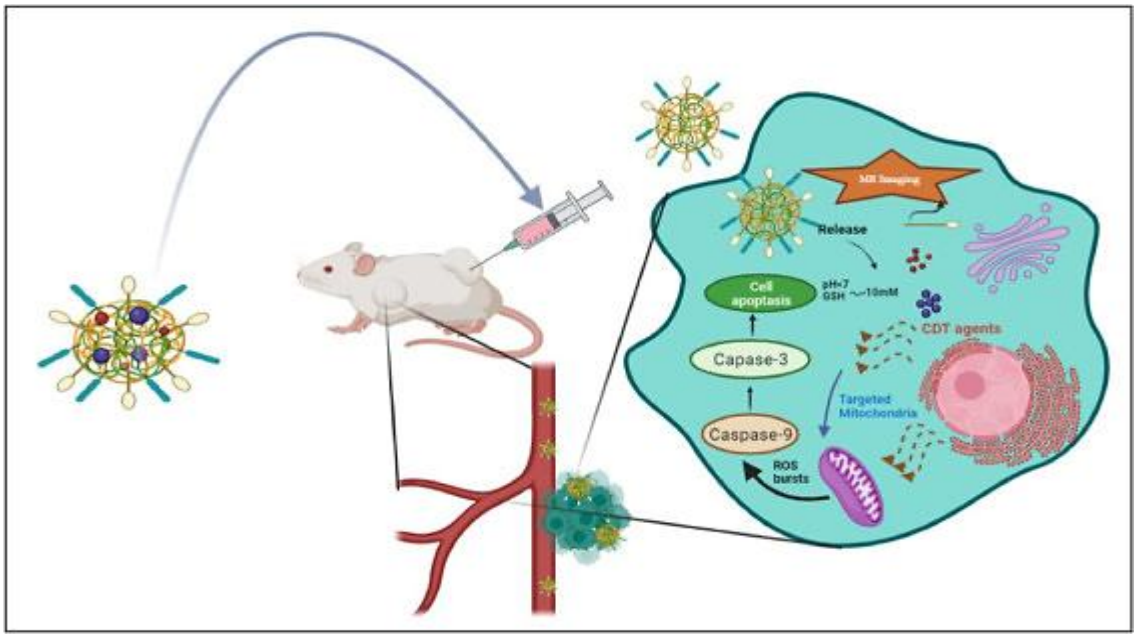


**Fig. 1. Schematic representation of Effect of chemodynamic therapeutic agents on the cell components (Deshpande *et al.*, 2017).**

## 3.Preclinical Studies of Nanoparticulate Drug Delivery in HCC

Preclinical research on nanoparticulate drug delivery systems for hepatocellular carcinoma (HCC) often begins with in vitro studies, which provide an initial evaluation of the efficacy and safety of these systems. In vitro experiments typically involve the use of cell culture models derived from human or animal HCC cell lines, such as HepG2, Huh7, and Hep3B. These models allow researchers to investigate the cellular interactions and therapeutic effects of nanoparticle formulations in a controlled environment (Scioli Montoto, Muraca, & Ruiz, 2020). Various assays are employed to assess the performance of nanoparticles in these studies. Cytotoxicity assays, such as MTT, WST-1, and CellTiter-Glo, measure the viability of cancer cells following exposure to nanoparticle-encapsulated drugs, indicating their anticancer potential. Drug uptake studies using fluorescence microscopy, flow cytometry, or confocal laser scanning microscopy help determine the internalization and distribution of nanoparticles within the cells. This provides insights into how effectively the nanoparticles penetrate cancer cells and release their payload. Additionally, apoptosis assays and cell cycle analysis are often conducted to evaluate the mechanisms through which the nanoparticles induce cancer cell death (Mehnert & Mäder, 2001).

### In Vivo Studies

After promising results are obtained from in vitro studies, in vivo studies are conducted to assess the therapeutic efficacy and safety of nanoparticulate drug delivery systems in a more complex biological setting(Bhatt *et al.,* 2022). These studies typically use animal models of HCC, such as xenograft models where human HCC cells are implanted into immunodeficient mice, or genetically engineered mouse models (GEMMs) that develop liver cancer spontaneously. These models closely mimic the tumor microenvironment and allow for the evaluation of nanoparticle behavior within the body (Ganesan & Narayanasamy, 2017).

In vivo studies focus on several important parameters:

- **Therapeutic Efficacy**: Tumor size reduction and survival rate are measured to assess the effectiveness of the treatment. Imaging techniques such as MRI, CT, or bioluminescence imaging may be used to monitor tumor progression over time(Dharmendra Bhati *et al.,* 2024).
- **Biodistribution Studies**: The distribution of nanoparticles throughout the body is tracked to determine the extent of their accumulation in the tumor versus non-target tissues. Techniques like fluorescent or radiolabeled nanoparticles are often employed for this purpose(Abhishek *et al.,* 2024).
- **Safety Profiles**: The toxicity of nanoparticle formulations is evaluated by monitoring animal weight, conducting blood tests, and examining histological samples of major organs to assess potential damage or inflammation. These safety studies are essential to ensure that the nanoparticles do not induce significant off-target effects or cause long-term harm (Mishra *et al.,* 2018;Makled, Nafee, & Boraie, 2017).

## 4.Translational Challenges in Nanoparticulate Drug Delivery

### Barriers to Clinical Translation

Despite the significant advancements demonstrated by nanoparticulate drug delivery systems in preclinical research, several barriers to clinical translation remain. One major challenge is scale-up and manufacturing. The production of nanoparticles at a laboratory scale is often highly controlled and tailored, but transitioning these processes to large-scale manufacturing can be complex. Ensuring consistency, quality, and reproducibility in large-scale production requires specialized equipment and rigorous process controls. Differences in manufacturing methods can result in variations in particle size, drug loading efficiency, and surface properties, all of which impact the safety and efficacy of the final product (Duan *et al.,* 2020;Mukherjee, Ray, & Thakur, 2009). Cost-effectiveness also poses a challenge. The development and production of nanoparticle-based therapies involve advanced technologies and high initial investments. The cost of scaling up production and navigating the regulatory landscape may be prohibitive for many pharmaceutical companies. Ensuring that these therapies remain economically viable while maintaining high safety and efficacy standards is essential for their eventual incorporation into standard treatment protocols(Rohit Kumar Trivedi *et al.,* 2024).

### Biocompatibility and Toxicity Issues

Biocompatibility and toxicity are significant concerns when translating nanoparticulate drug delivery systems to clinical use(Mangala *et al.,* 2024). While nanoparticles are designed to minimize toxicity and enhance targeted delivery, their long-term effects on the human body remain an area of active investigation. One of the main issues is understanding how nanoparticles interact with the immune system. Some nanoparticles may trigger an immune response, leading to rapid clearance from the bloodstream or potential adverse reactions. The immune response to nanoparticles can vary based on factors such as size, shape, surface charge, and the type of surface functionalization (Naseri, Valizadeh, & Zakeri-Milani, 2015). Long-term toxicity is another concern, as the persistence of certain nanoparticles in the body or their accumulation in vital organs could lead to unforeseen health issues. Metal nanoparticles, for instance, may pose risks if not properly metabolized and excreted, potentially causing oxidative stress or organ damage over time(Ghai *et al.,* 2022). Comprehensive toxicity studies that evaluate both short-term and chronic exposure to nanoparticles are therefore essential. Addressing these biocompatibility and toxicity issues requires careful design and surface engineering of nanoparticles to ensure they are both safe and effective. This includes using biocompatible materials, optimizing particle size to avoid rapid immune clearance, and incorporating stealth coatings such as polyethylene glycol (PEG) to prolong circulation time while reducing immunogenicity (Kedmi, Ben-Arie, & Peer, 2010).

## 5.Advances in Engineering and Functionalization of Nanoparticles

### Innovative Approaches for Enhanced Targeting

Recent advancements in nanoparticle engineering have led to the development of multifunctional nanoparticles designed to enhance targeting and therapeutic effectiveness in cancer treatment, including hepatocellular carcinoma (HCC). These multifunctional systems can perform several tasks simultaneously, such as targeted delivery, controlled release, and imaging. This integration enables theranostic applications—nanoparticles that combine therapy and diagnostics—allowing for real-time monitoring of drug delivery and tumor response, which can guide treatment adjustments (Maja, Željko, & Mateja, 2020). Stimuli-responsive nanoparticles represent another breakthrough in targeted therapy. These nanoparticles are designed to respond to specific stimuli present in the tumor microenvironment, such as pH changes, temperature shifts, enzymes, or redox potential. For example, pH-sensitive nanoparticles can release their drug payload when they encounter the acidic environment of a tumor, ensuring that the active agent is only released at the desired site. These advanced targeting strategies minimize damage to healthy tissue, enhance drug efficacy, and reduce side effects (Beltrán-Gracia *et al.,* 2019).

### New Materials and Techniques

The development of new materials and techniques has significantly expanded the scope of nanoparticle formulations. Hybrid nanoparticles combine multiple materials—such as polymers, metals, and lipids—to create carriers with enhanced properties, such as improved stability, drug loading, and controlled release capabilities. For example, lipid-polymer hybrid nanoparticles merge the biocompatibility of lipids with the structural integrity of polymers, resulting in a versatile delivery system suitable for various therapeutic agents (Lee *et al.,* 2017). Biodegradable carriers made from materials like polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and natural polymers such as chitosan and alginate have gained attention due to their safety profile and controlled degradation within the body. These biodegradable carriers are designed to release their payload gradually as they break down into non-toxic byproducts, reducing the risk of long-term accumulation and toxicity. Advanced fabrication techniques, such as microfluidics and self-assembly, have also revolutionized nanoparticle production. Microfluidics enables precise control over particle size and uniformity, resulting in more consistent formulations with predictable behavior in biological systems. Self-assembly techniques, where nanoparticles spontaneously organize based on specific interactions among their components, provide a scalable and efficient way to produce complex nanoparticle systems (Nomani & Govinda, 2016).

### Drug Combination Strategies

One of the significant benefits of nanoparticulate drug delivery systems is their ability to facilitate drug combination strategies, which can enhance the therapeutic outcome by addressing multiple pathways involved in tumor progression and resistance. Co-delivery systems can encapsulate multiple drugs within a single nanoparticle, ensuring synchronized delivery to the target site. For instance, nanoparticles that co-deliver chemotherapeutic agents with agents that inhibit specific resistance mechanisms can increase treatment efficacy and prevent tumor relapse. In addition to traditional drugs, nanoparticles can be engineered to deliver gene therapy agents such as small interfering RNA (siRNA), microRNA (miRNA), or DNA plasmids. This strategy can be used to modulate gene expression, silence oncogenes, or enhance the expression of tumor suppressor genes, providing a complementary approach to standard drug therapy (Immordino, Dosio, & Cattel, 2006). Combination with immunotherapy has also shown great promise. Nanoparticles can be used to deliver immune-modulating agents that stimulate the body's immune response against HCC. For instance, nanoparticles that release checkpoint inhibitors or cytokines directly at the tumor site can enhance the immune system's ability to recognize and attack cancer cells while reducing systemic side effects (Bozzuto & Molinari, 2015;Akbarzadeh *et al.,* 2013).

## Conclusion

The use of nanocarriers in the treatment of hepatocellular carcinoma (HCC) marks an exciting advancement in modern oncology, addressing many challenges associated with conventional therapies. Nanoparticulate drug delivery systems (NDDS) offer significant potential due to their enhanced ability to deliver drugs precisely to tumor cells, thereby improving therapeutic outcomes and minimizing damage to healthy tissues. These systems have been shown in preclinical studies to enhance drug targeting, control drug release, and reduce adverse side effects. Through engineering innovations such as active targeting with specific ligands, multifunctionality, and responsiveness to the tumor microenvironment, NDDS provide a more targeted and efficient approach to treating HCC. Despite these promising results, the clinical translation of NDDS still encounters considerable hurdles. Issues related to large-scale production, manufacturing consistency, and regulatory approval processes pose significant challenges. Additionally, ensuring the biocompatibility and safety of these systems, particularly their long-term effects, remains a critical area that requires more in-depth research. Understanding how nanoparticles interact with the immune system and whether they may trigger undesirable responses or accumulate in the body over time is essential to ensuring safe implementation. This path will pave the way for more effective, personalized, and safer therapeutic options, ultimately transforming patient care and improving outcomes for those affected by HCC.

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