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Advances in Designing Nanoparticles for Site-Specific Chemotherapy with Reduced Side Effects

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Abstract
Conventional chemotherapy is hindered by poor tumor specificity, systemic toxicity, and limited therapeutic efficacy, often leading to severe side effects and treatment resistance. These challenges have driven the development of nanoparticle-based drug delivery systems that offer targeted, site-specific chemotherapy with improved safety profiles. This review provides a comprehensive examination of the various types of nanoparticles utilized in cancer drug delivery, including inorganic, organic, and hybrid systems, alongside key design strategies like targeting mechanisms, physicochemical optimization, surface functionalization, and controlled drug release. Case studies and preclinical applications in drug delivery and radiation sensitization are presented. A comparison with conventional chemotherapy highlights the enhanced safety profiles of nanotherapeutics. Finally, we discuss challenges and future directions, highlighting the potential of nanoparticles to revolutionize cancer treatment by improving efficacy and minimizing toxicity.

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1. Introduction

Cancer remains a leading cause of mortality worldwide, necessitating continuous advancements in treatment strategies. Chemotherapy, a cornerstone of cancer therapy, often involves systemic drug administration to control or eradicate cancerous cells (Chidambaram, Manavalan and Kathiresan, 2011; Fymat, 2017; Saini, 2022). However, conventional chemotherapeutic approaches are frequently limited by their non-selective nature, resulting in significant damage to healthy, rapidly proliferating cells and subsequent adverse effects (Edis *et al.*, 2021). These limitations underscore the critical need for innovative strategies that can enhance drug efficacy while minimizing systemic toxicity.

Nanotechnology has emerged as a transformative field in therapeutic delivery, holding immense potential to revolutionize cancer treatment (Iturrioz-Rodríguez, Correa-Duarte and Fanarraga, 2019). By engineering materials at the nanoscale, researchers can design nanoparticles with tailored properties that overcome the limitations of traditional chemotherapeutics (Blanco, Shen and Ferrari, 2015). Nanoparticles can be designed to selectively target cancer cells, improve drug pharmacokinetics, and enable controlled drug release at the tumor site, ensuring a higher concentration of therapeutic agents at the targeted site (Y.-R. Zhang *et al.*, 2019). This targeted approach maximizes drug efficacy and significantly reduces the systemic toxicity commonly associated with conventional chemotherapy (Nikolova, Kumar and Chavali, 2022). One of the key advantages of nanoparticles in cancer therapy is their ability to exploit the enhanced permeability and retention effect (Harish *et al.*, 2022). Tumor blood vessels exhibit unique characteristics, including larger pore sizes and impaired lymphatic drainage, which allow nanoparticles to preferentially accumulate within the tumor microenvironment (Yan *et al.*, 2020).

Furthermore, surface modification of nanoparticles enables targeted delivery by conjugating them with specific ligands that bind to receptors overexpressed on cancer cells (Yanes and Tamanoi, 2012). This active targeting strategy further enhances the selectivity of drug delivery, minimizing off-target effects and improving therapeutic outcomes (Mahdavi Firouzabadi *et al.*, 2022).

This review provides an overview of recent advances in the design of nanoparticles for site-specific chemotherapy, focusing on reducing side effects and improving patient outcomes. We explore various types of nanoparticles, key design strategies, preclinical and clinical applications, and future directions in this rapidly evolving field. By highlighting the potential of nanotechnology to overcome the limitations of conventional chemotherapy, this review aims to provide insights into the development of more effective and less toxic cancer treatments.

2.0 Types of Nanoparticles for Cancer Drug Delivery

Nanoparticles (NPs) have revolutionized cancer drug delivery by enabling targeted, efficient, and less toxic therapeutic options. They are broadly categorized into organic, inorganic, and hybrid nanoparticles, each with distinct properties and applications. Below is a detailed overview of these types:

2.1 Organic Nanoparticles

Organic nanoparticles are composed of carbon-based materials and are known for their biocompatibility and versatility.

Liposomes**:** Liposomes are spherical vesicles with one or more phospholipid bilayers, capable of encapsulating both hydrophilic and hydrophobic drugs (Figure 1). They enhance drug solubility, stability, and bioavailability. Notably, liposomal formulations like Doxil (liposomal doxorubicin) have been approved for clinical use, demonstrating reduced cardiotoxicity compared to conventional doxorubicin (Lee, 2019).

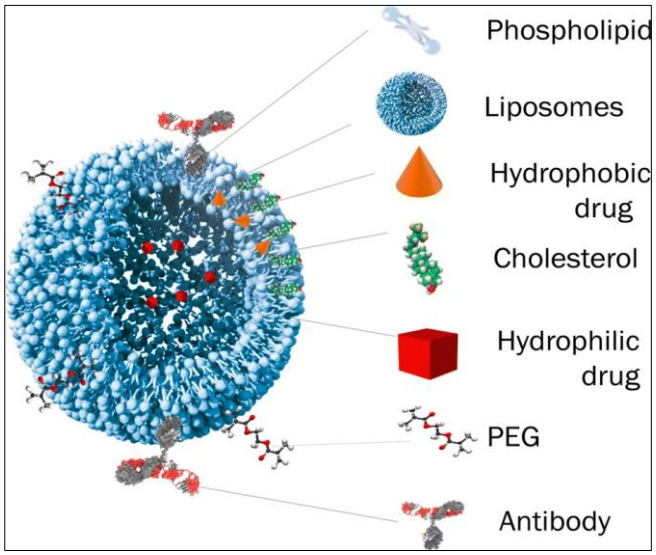

Fig 1: Schematic structure of a stable antibody–liposome encapsulating hydrophobic and hydrophilic drugs.

Hydrophilic drugs like doxorubicin can be encapsulated in the aqueous compartment. Hydrophobic drugs like amphotericin B, paclitaxel, and docetaxel, can be encapsulated in the non-polar compartment (Beltrán-Gracia *et al.*, 2019).

Polymeric Nanoparticles: These nanoparticles are formed from biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers (PLGA) (Calzoni *et al.*, 2019). They allow controlled and sustained drug release, improving therapeutic efficacy. For instance, Onivyde® (liposomal irinotecan) utilizes such technology for enhanced delivery in pancreatic cancer treatment (Frampton, 2020).

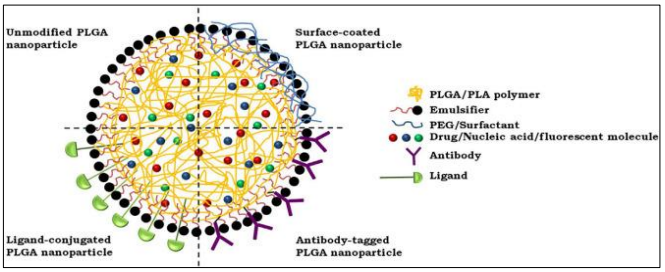

Fig 2: PLGA/PLA polymeric nanoparticle for encapsulation and transport of phytochemicals (Sajid *et al.*, 2019).

Dendrimers: Dendrimers are highly branched, tree-like macromolecules with a central core, interior branches, and terminal functional groups (Figure 3). Their structure allows precise control over size and surface functionality, enabling high drug-loading capacity and targeted delivery. Studies have shown that dendrimers can effectively deliver anticancer drugs while minimizing systemic toxicity (Luong *et al.*, 2016; Chis *et al.*, 2020).

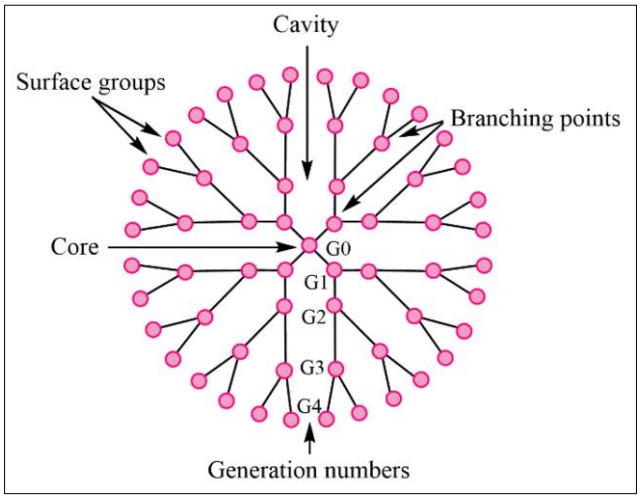

Fig 3: Dendrimer basic structure. Generation number is indicated as G0, G1, G2, G3 and G4 (Chis *et al.*, 2020).

Polymeric Micelles: Formed by the self-assembly of amphiphilic block copolymers, polymeric micelles have a hydrophobic core and hydrophilic shell (Figure 4). Polymeric micelles are particularly useful for delivering poorly water-soluble drugs (Xu, Ling and Zhang, 2013). Their small size and stability in aqueous environments make them suitable for intravenous administration.

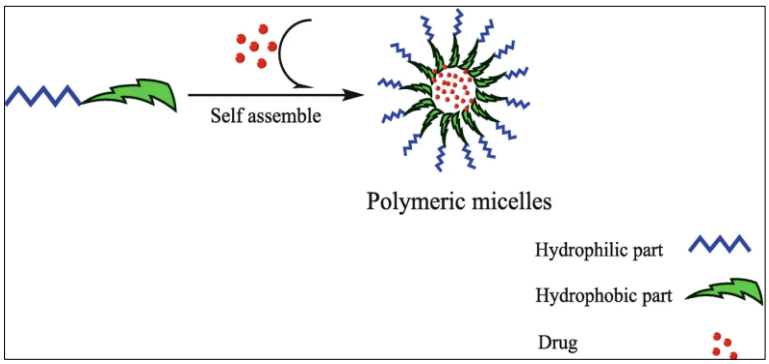

Fig 4: Association of polymeric micelles by self-assembling process (Khan *et al.*, 2018).

Nanogels: Nanogels are hydrophilic, three-dimensional polymer networks capable of swelling in water and responding to environmental stimuli (Figure 5). They can encapsulate a variety of therapeutic agents and release them in a controlled manner. For example, chitosan-based nanogels have been developed for targeted delivery of doxorubicin to colorectal cancer cells, showing enhanced efficacy and reduced side effects (Tian, Liu and Liu, 2021).

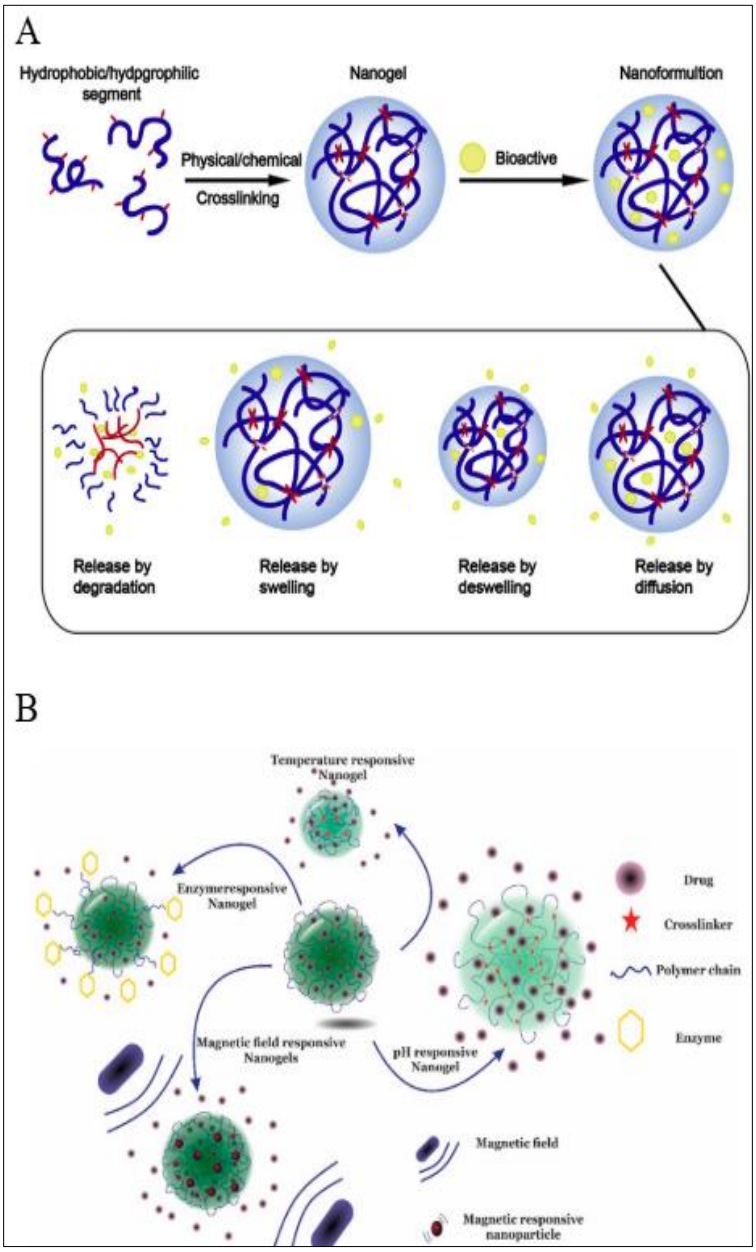

Fig 5: Schematic representation of (A) synthesis and the release behavior of nanogels (Yunhan Zhang *et al.*, 2022) and (B) different stimuli-responsive nanogels in response to temperature, enzyme, the magnetic field, and pH in drug delivery applications (Ghaeini-Hesaroeiye *et al.*, 2020).

2.2. Inorganic Nanoparticles

Inorganic nanoparticles are composed of metals or metal oxides and offer unique optical, magnetic, and electronic properties beneficial for cancer therapy. Inorganic nanoparticles (INPs) represent a promising innovation in cancer therapy due to their unique physicochemical properties that enable enhanced targeting, reduced systemic toxicity, and improved drug delivery precision (Bayda *et al.*, 2018). Engineered with biomimetic coatings such as cell membranes, INPs can better evade the immune system and selectively accumulate at tumor sites, increasing therapeutic efficacy (Yuanyuan Zhang *et al.*, 2022). These nanoparticles also support multifunctional roles, including theranostic applications that combine treatment with real-time disease monitoring. Various forms of INPs such as silica, gold, and magnetic nanoparticles serve as versatile carriers for chemotherapeutic drugs, making them powerful tools in the evolving landscape of targeted cancer treatments (F. Wang *et al.*, 2016).

Gold Nanoparticles (AuNPs): AuNPs are renowned for their biocompatibility and ease of functionalization (Verma, Lal and Van Noorden, 2015). They can convert absorbed light into heat, making them suitable for photothermal therapy (Figure 6). Additionally, AuNPs can be conjugated with targeting ligands for selective drug delivery (Wang *et al.*, 2020).

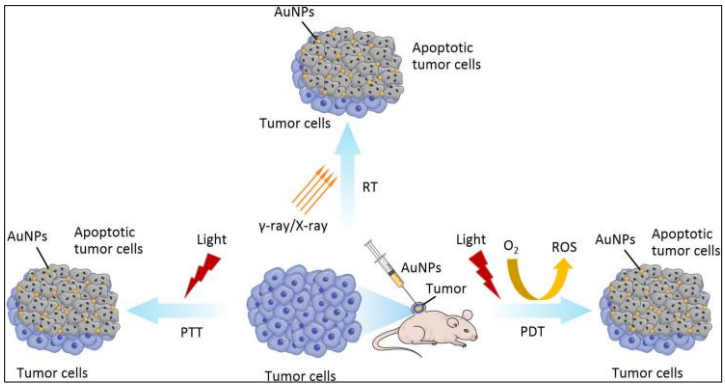

Fig 6: Photothermal therapy (PTT), photodynamic therapy (PDT), and radiation therapy (RT) applications of AuNPs (Hu *et al.*, 2020).

Magnetic Nanoparticles: Typically composed of iron oxide, these nanoparticles can be guided to tumor sites using external magnetic fields. They also serve as contrast agents in magnetic resonance imaging (MRI), aiding in diagnosis and monitoring (Bhattacharyya *et al.*, 2011).

Silica Nanoparticles: Mesoporous silica nanoparticles possess a high surface area and tunable pore sizes, allowing for high drug loading and controlled release. Their surface can be modified with various functional groups for targeted delivery (Ojea-Jimenez *et al.*, 2013).

Quantum Dots: Quantum dots are semiconductor nanoparticles that exhibit unique optical properties, such as size-tunable fluorescence. They are primarily used for imaging applications but have potential in theranostics when combined with therapeutic agents (Nasirzadeh, Nazarian and Hayat, 2016).

2.3. Hybrid Nanoparticles

Hybrid nanoparticles combine organic and inorganic components to leverage the advantages of both (Yadav and Otari, 2019). For instance, a hybrid nanoparticle may consist of a polymeric shell encapsulating a magnetic core, enabling both targeted drug delivery and imaging capabilities. The following section delves into the types, applications, advantages, and challenges associated with hybrid nanoparticles in cancer drug delivery.

Lipid-Polymer Hybrid Nanoparticles (LPHNPs): LPHNPs integrate a polymeric core with a lipid shell, merging the structural integrity and controlled release features of polymers with the biocompatibility and drug-loading efficiency of lipids (D'Souza and Shegokar, 2016). This configuration facilitates the encapsulation of both hydrophilic and hydrophobic drugs, offering improved stability and targeted delivery. For instance, Genexol-PM, a paclitaxel-loaded LPHNP, has demonstrated enhanced therapeutic outcomes in breast cancer treatment (Persano, Gigli and Leporatti, 2021).

Metal-Organic Hybrid Nanoparticles: These nanoparticles combine metallic components, such as gold or iron oxide, with organic molecules, enabling multifunctionality (W. Wang *et al.*, 2016). Gold-based hybrids can be utilized for photothermal therapy, where they convert light into heat to ablate tumor cells, while iron oxide hybrids serve as contrast agents in magnetic resonance imaging (MRI) and facilitate magnetic targeting (Tarkistani, Komalla and Kayser, 2021).

Polymer-Protein Hybrid Nanoparticles: By conjugating polymers with proteins, these hybrids leverage the biological functionality of proteins and the tunable properties of polymers (Kiran *et al.*, 2021). Such systems can self-assemble into micelles or nanoparticles, offering high drug-loading capacities and stimuli-responsive release profiles. For example, bovine serum albumin (BSA)-polymer hybrids have been developed for the delivery of chemotherapeutic agents like camptothecin (Khalili *et al.*, 2021).

Mesoporous Silica-Based Hybrid Nanoparticles: Mesoporous silica nanoparticles (MSNs) can be functionalized with various organic or inorganic materials to create hybrids with enhanced drug-loading capacities and controlled release mechanisms (Kundu *et al.*, 2020). These hybrids can be engineered to respond to specific stimuli, such as pH or redox conditions, ensuring targeted drug release within the tumor microenvironment.

3. Strategies for Nanoparticle Design in Cancer Therapy

Designing nanoparticles for cancer therapy involves four key strategies: targeting mechanisms, physicochemical optimization to control circulation and tumor penetration, surface functionalization, and drug release for precise release at the tumor site. Together, these design principles enhance treatment efficacy while minimizing off-target toxicity.

3.1 Targeting Mechanisms of Nanoparticles in Cancer Treatment

Targeting mechanisms of nanoparticles in cancer treatment are critical for achieving selective drug delivery, improving therapeutic efficacy, and minimizing damage to healthy tissues. With the development of nanotechnology, both passive and active targeting strategies have been extensively explored and optimized to overcome the biological barriers associated with conventional cancer therapies.

Passive targeting primarily relies on the physiological characteristics of tumors, particularly the Enhanced Permeability and Retention (EPR) effect (Figure 7). Tumor vasculature is typically irregular, dilated, and leaky due to rapid and aberrant angiogenesis, which permits nanoparticles especially those in the 10–200 nm size range to passively extravasate and accumulate in tumor tissues more than in normal tissues (He *et al.*, 2019). Additionally, poor lymphatic drainage in tumors leads to prolonged nanoparticle retention, further increasing drug concentration at the site. The physicochemical properties of nanoparticles such as particle size, shape, surface charge, and hydrophilicity can significantly influence this accumulation. For example, smaller nanoparticles may penetrate deeper into tumor interstitium, while surface modifications such as PEGylation can prolong circulation times and reduce clearance by the mononuclear phagocyte system (Yao *et al.*, 2020). Nanoparticles can also be engineered to respond to tumor microenvironmental cues like acidic pH, hypoxia, or redox gradients, thereby enhancing drug release specificity.

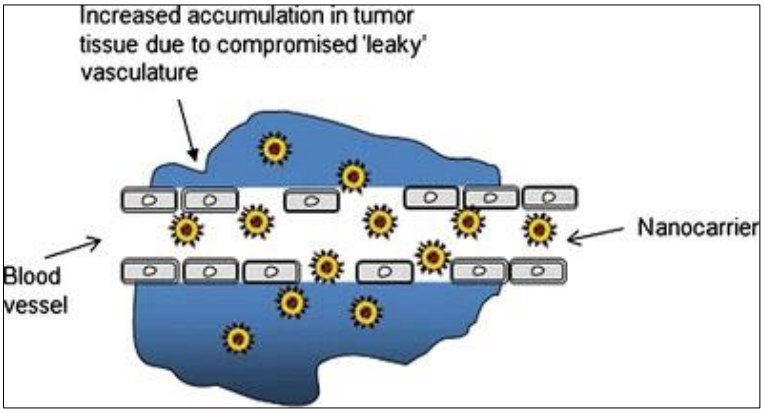

Fig 7: Schematic illustration of passive targeting via the EPR effect (Sawant and Torchilin, 2012).

Active targeting involves functionalizing the nanoparticle surface with biological ligands that can specifically bind to receptors overexpressed on cancer cells, thereby facilitating receptor-mediated endocytosis (Figure 8). Common ligands include monoclonal antibodies (e.g., trastuzumab targeting HER2), peptides (e.g., RGD peptides targeting integrins), aptamers, folic acid, and transferrin (Fatima *et al.*, 2021). These ligands enable precise interaction with cancer-specific biomarkers and promote internalization of the therapeutic payload, resulting in enhanced cytotoxicity at the target site with minimal impact on normal cells (Jaymes R. Beech, Soo J. Shin, Jeffrey A. Smith and Kimberly A. Kelly, 2013). A novel approach known as Cell Membrane Permeability Targeting (CMPT) has been developed to further improve delivery efficiency. CMPT focuses on increasing the permeability of cancer cell membranes to facilitate deeper penetration of nanoparticles, thus enhancing uptake in both primary tumors and metastatic sites (He *et al.*, 2019). This method may involve engineering the surface of nanoparticles with membrane-disrupting peptides or fusogenic lipids that transiently destabilize cancer cell membranes without harming normal cells.

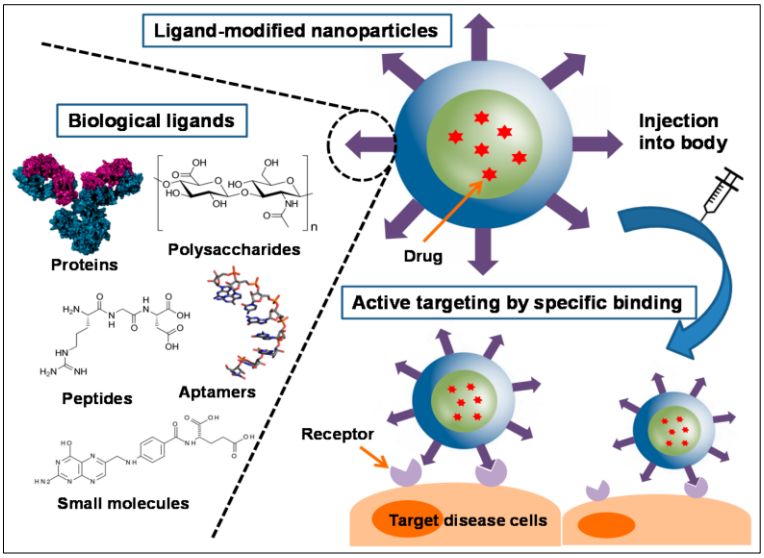

Fig 8: Illustration of biological ligands for active targeting of nanoparticle drug carriers (Yoo *et al.*, 2019).

To maximize therapeutic impact, hybrid nanoparticles that combine passive and active targeting strategies are increasingly being designed. These systems first exploit the EPR effect to reach the tumor site and then utilize ligand-receptor interactions to achieve cell-specific uptake. Such a dual-targeting approach improves the biodistribution, retention, and internalization of nanoparticles within tumors, leading to higher therapeutic payload delivery. Moreover, these platforms often incorporate stimuli-responsive elements that trigger drug release in response to specific tumor-associated signals, such as pH change, enzyme activity, or temperature variations (Yao *et al.*, 2020). By integrating multiple functional modules into a single nanocarrier, hybrid systems can also address challenges such as multidrug resistance, limited penetration into dense tumor matrices, and rapid systemic clearance. These next-generation nanocarriers represent a significant step toward personalized and precision cancer therapy.

3.2 Controlling Physicochemical Properties of Nanoparticles

Size: Nanoparticle size critically affects circulation time, tumor accumulation, and cellular uptake. For the Enhanced Permeability and Retention (EPR) effect to target tumors, nanoparticles with a diameter of 10–200 nm are ideal, allowing passive accumulation in tumor tissues due to leaky vasculature (Yetisgin *et al.*, 2020). Smaller nanoparticles (<10 nm) may be rapidly cleared by renal filtration, whereas larger ones (>200 nm) are more likely to be sequestered by the mononuclear phagocyte system or poor tissue penetration, reducing their therapeutic efficacy (Yetisgin *et al.*, 2020).

Shape: Shape: Nanoparticle shape influences cellular internalization and biodistribution, as non-spherical particles exhibit different hydrodynamic properties and cellular interactions compared to spherical ones (Zielińska *et al.*, 2021). Spherical nanoparticles are commonly used due to ease of synthesis and favorable biodistribution (Z. Zhang *et al.*, 2019). Elongated or rod-shaped nanoparticles may exhibit enhanced circulation times due to reduced uptake by phagocytic cells, while flattened or discoidal shapes can maximize surface area for drug loading and targeted delivery (Liang *et al.*, 2019). In other models, rod-shaped and disk-shaped nanoparticles have demonstrated enhanced tumor penetration and cellular uptake in certain models, attributed to their unique flow dynamics, surface interactions, deeper tumor penetration and superior margination (Jindal, 2017).

Surface Charge: Surface charge is also important because it governs interactions with blood components and cell membranes. Positively charged nanoparticles (NPs) demonstrate enhanced cellular uptake due to their electrostatic attraction to negatively charged cell membranes but are accompanied by increased toxicity and rapid clearance from circulation (Bhattacharjee *et al.*, 2013). The following sections elaborate on these dynamics. However, neutral or slightly negative NPs often have longer systemic circulation with reduced non-specific protein adsorption (Dadwal, Baldi and Kumar Narang, 2018; Tangthong *et al.*, 2021).

3.3 Surface Functionalization

Ligand Attachment: Cancer cells can undergo receptor-mediated endocytosis when the surfaces of nanoparticles are functionalized with ligands (such as transferrin or folic acid) or monoclonal antibodies which improves the specificity of medication distribution and internalization. For instance, it has been shown that folate-functionalized liposomes are more readily absorbed by cancer cells that express folate receptors (Angelopoulou *et al.*, 2019). Antibodies attached to nanoparticles can specifically recognize and bind to overexpressed tumor antigens, such as HER2 in breast cancer and EGFR in targeted treatment of colorectal and ovarian cancers (Petrilli *et al.*, 2021). These nanoparticles leverage the specificity of antibodies to deliver therapeutic agents directly to cancer cells, minimizing off-target effects and improving patient outcomes.

Stealth Coatings: The use of stealth coatings, particularly polyethylene glycol (PEG) and zwitterionic polymers enhances the circulation duration of nanoparticles by minimizing opsonization and subsequent detection by the reticuloendothelial system (RES) through creation of hydrophilic layer that reduces the binding of plasma proteins (Fam *et al.*, 2020). These coatings significantly increases the half-life of NPs in the bloodstream and shield NPs from immune recognition, allowing for prolonged systemic circulation, which is essential for targeted drug delivery (Fam *et al.*, 2020). However, repeated use of PEG can lead to the development of anti-PEG antibodies, which may compromise the effectiveness of PEGylated NPs (Hadjesfandiari and Parambath, 2018). Also, though PEGylation improves circulation, it can hinder drug release at target sites, necessitating alternative strategies for effective therapeutic outcomes (Amoozgar and Yeo, 2012). Due to thes shortcomings, recent studies suggest using natural materials, such as red blood cell membranes, as coatings to further reduce RES uptake and improve biocompatibility (Rao *et al.*, 2016).

3.4 Drug Loading and Release Mechanism

The method of drug loading and release in nanoparticle-based drug delivery systems for site-specific chemotherapy is crucial in establishing the therapy's effectiveness, safety, and accuracy. Therapeutic drugs can be directed to tumor tissues while lowering systemic toxicity by creating nanoparticles that can regulate the release of the medicine at certain times and locations.

Controlled Release Systems: Chemotherapeutic chemicals can be delivered consistently and predictably throughout time with controlled release devices, improving medication effectiveness and lowering dosage frequency. Typical tactics consist of drug release at a regulated pace by encapsulation in polymeric matrices like PLGA (poly(lactic-co-glycolic acid)), which break down gradually (Figure 9). These technologies improve medication bioavailability and minimise harm to healthy tissues by reducing drug leakage during circulation and delivering long-term release at the target location (Nikolova, Kumar and Chavali, 2022).

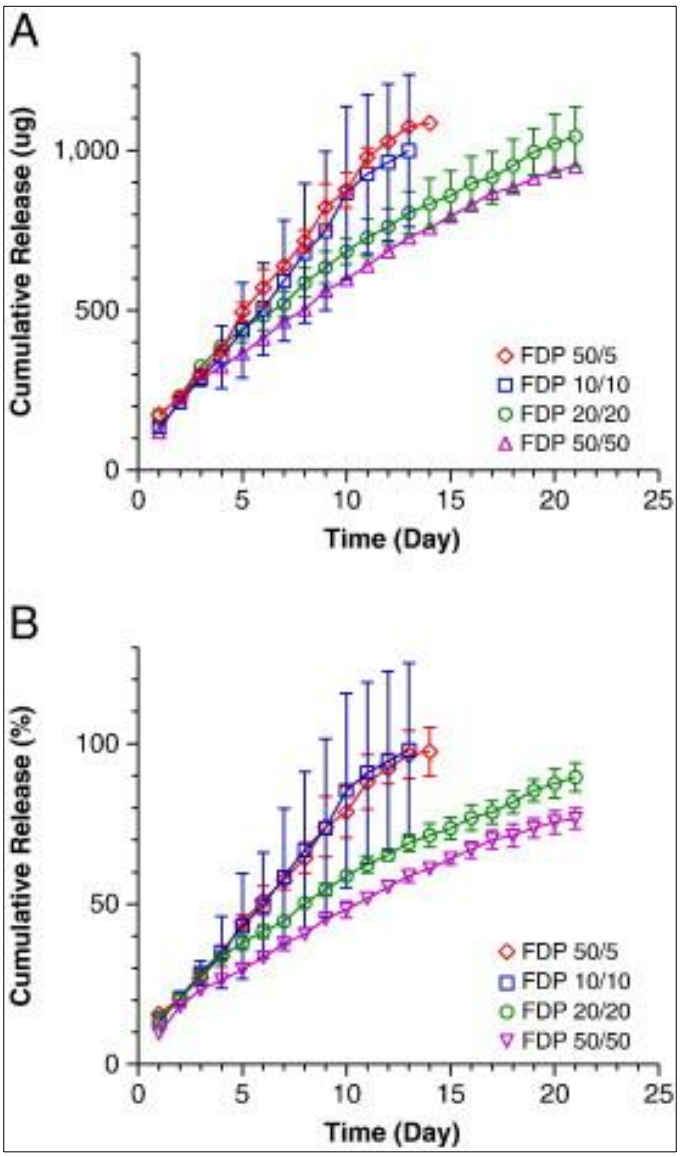

Fig 9: Release profiles in the cumulative amount (A) and in percent (B) of felodipine (FDP) from PLGA microparticles of four different dimensions (Acharya *et al*. 2010).

pH-Sensitive Release Mechanisms: The extracellular environment of tumor tissues is more acidic (pH ~6.5–6.8) than that of normal tissues (pH ~7.4), while the intracellular compartments, including lysosomes and endosomes, are much more acidic (pH ~5.0–5.5). They take advantage of this characteristic through: pH-sensitive linkers (such as Schiff base bonds or hydrazone) that degrade in acidic environments. pH-responsive substances that cause drug release by swelling or dissolving at lower pH levels, such as poly(β-amino esters). This improves treatment specificity and lowers systemic exposure by guaranteeing that the medication is delivered preferentially at the tumor site (Chu *et al.*, 2022).

Enzyme-Responsive Triggers: In cancer tissues and the tumor microenvironment, certain enzymes, such as cathepsins and matrix metalloproteinases (MMPs), are overexpressed. One way to engineer nanoparticles is with: When exposed to these enzymes, peptide sequences or enzyme-cleavable linkages that are stable in circulation break down. Liposomes or smart hydrogels that release the medication locally when they break down due to enzymatic activity. A further degree of specificity is offered by enzyme-triggered release mechanisms, which are especially advantageous for diverse tumor microenvironments (Fouladi, Steffen and Mallik, 2017).

4. Case Studies and Preclinical Applications of nanoparticles in cancer therapy

Nanoparticles (NPs) have revolutionized cancer therapy by enabling precise drug delivery, enhancing therapeutic efficacy, and minimizing systemic toxicity. Their unique physicochemical properties facilitate targeted treatment, real-time monitoring, and improved patient outcomes. This section delves into specific preclinical applications and case studies that underscore the transformative potential of NPs in oncology.

4.1 Drug Delivery Systems

Targeted Chemotherapy Delivery: NPs have been engineered to selectively transport chemotherapeutic agents to tumor cells, thereby reducing collateral damage to healthy tissues (Saha *et al.*, 2010). For instance, liposome-based and polymeric nanoparticles have demonstrated efficacy in enhancing drug solubility and stability, leading to improved therapeutic outcomes (Palazzolo *et al.*, 2018). These nanocarriers exploit the enhanced permeability and retention

(EPR) effect, allowing for preferential accumulation in tumor tissues.

Theranostic Applications: Theranostic nanoparticles integrate therapeutic and diagnostic functionalities, enabling simultaneous treatment and monitoring of cancer (Choi *et al.*, 2012). For example, certain nanoparticles have been designed to deliver chemotherapeutic drugs while also serving as contrast agents for imaging modalities like MRI or CT scans (Estelrich, Sánchez-Martín and Busquets, 2015). This dual capability facilitates real-time assessment of treatment efficacy and disease progression.

4.2 Radiation Sensitization

Enhancing Radiotherapy Efficacy: NPs have been employed as radiosensitizers to amplify the effects of radiation therapy. Gold nanoparticles (AuNPs), due to their high atomic number, enhance radiation dose deposition within tumors, leading to increased DNA damage in cancer cells (Wang *et al.*, 2020). Preclinical studies have shown that combining AuNPs with radiotherapy results in significant tumor regression compared to radiation alone (Spyratou *et al.*, 2017).

Overcoming Hypoxia-Induced Radioresistance: Tumor hypoxia is a known factor in radiotherapy resistance. NPs have been developed to address this challenge by delivering oxygen or oxygen-generating agents directly to hypoxic tumor regions. For instance, perfluorocarbon-based nanoparticles can transport and release oxygen within tumors, thereby enhancing the effectiveness of radiation treatment (Krafft, 2020).

4.3 Case Studies and Clinical Trials

A range of chemotherapeutic agents can be encapsulated and delivered directly to tumor tissues using nanoparticle platforms. One of the most researched formulations is liposomal doxorubicin (e.g., Doxil), which, when conjugated with monoclonal antibodies or folic acid, enhances active targeting to folate-receptor–expressing tumor cells, reducing systemic toxicity, especially cardiotoxicity, while improving drug accumulation at tumor sites (Sriraman *et al.*, 2016).

Polymeric nanoparticles, especially those made from PLGA and functionalized with RGD peptides, have been used for the targeted delivery of paclitaxel (Ghosh Dastidar, Ghosh and Chakrabarti, 2020). These systems selectively bind to αvβ3 integrins, which are overexpressed in tumor vasculature, improving site-specific accumulation and antitumor efficacy in metastatic breast cancer models (Ghosh Dastidar, Ghosh and Chakrabarti, 2020).

Furthermore, gold nanoparticles (AuNPs) surface-modified with hyaluronic acid and coupled with cisplatin have been used to target CD44 receptors, which are frequently overexpressed in a variety of malignancies (Lin *et al.*, 2021). This method greatly decreased nephrotoxicity, a serious adverse effect linked to the administration of free cisplatin, in addition to improving intracellular drug delivery (Bhise *et al.*, 2017; Lin *et al.*, 2021).

Ongoing clinical trials are exploring the potential of NPs in enhancing cancer treatment. For instance, studies are evaluating the use of iron oxide nanoparticles for targeted drug delivery and imaging in glioblastoma patients (Marekova *et al.*, 2020; Norouzi *et al.*, 2020). These investigations aim to validate the preclinical successes of NPs and establish their role in standard cancer care.

5.0 Comparison with Conventional Chemotherapy

Conventional chemotherapy's non-specific drug distribution causes dose-limiting toxicities cardiac, neurological, hematological, and gastrointestinal that compromise patient outcomes. In contrast, nanoparticle formulations use passive and active targeting along with controlled-release designs to concentrate therapeutics in tumors and spare healthy tissues (Table 1). The following sections examine how these strategies translate into reduced side effects and enhanced safety profiles (Section 5.1) and review preclinical toxicology data confirming biocompatibility and minimized off-target accumulation (Section 5.2).

5.1 Reduced Side Effects and Safety Profiles

Non-specific drug distribution throughout the body is often linked to conventional chemotherapy, which can lead to side effects such myelosuppression, gastrointestinal toxicity, cardiotoxicity, and neurotoxicity (Fu *et al.*, 2018). These adverse effects limit the dosage and frequency of administration in addition to lowering the quality of life for the patient.

In contrast, nanoparticle formulations enable targeted drug delivery, minimizing off-target exposure and improving patient tolerance. Infact, a fundamental advantage of nanoparticle-based drug delivery systems over conventional chemotherapy lies in their ability to reduce systemic toxicity and improve overall safety profiles (Table 1). By using both passive and active targeting techniques, nanoparticle-mediated chemotherapy overcomes these drawbacks and enables medications to preferentially accumulate in tumor tissues through ligand-receptor interactions and the increased permeability and retention (EPR) effect (Upponi and Torchilin, 2014). For example, it has been demonstrated that PEGylated liposomal doxorubicin formulations considerably reduce cardiotoxicity when compared to free doxorubicin without sacrificing therapeutic efficiency (Schmitt *et al.*, 2012). Comparably, paclitaxel-delivering polymeric nanoparticles have shown lower rates of peripheral neuropathy and hypersensitivity reactions than conventional solvent-based formulations (Lv *et al.*, 2014; Chou *et al.*, 2020). These enhancements are ascribed to the controlled release characteristics of nanoparticles, which aid in preserving therapeutic drug concentrations for prolonged periods of time while avoiding dangerous peak plasma levels.

5.2 Toxicological Assessments

Thorough toxicological analyses in preclinical models are necessary to evaluate the safety and biocompatibility of nanoparticle systems (Tirumala *et al.*, 2021). Evaluations of haematological parameters, liver and kidney function, major organ histopathology, and immunological responses are frequently included in studies. When compared to conventional chemotherapeutic treatments, targeted nanoparticles have continuously shown good safety profiles in murine models, with negligible changes in haematological indices, kidney function markers (BUN, creatinine), and liver enzymes (ALT, AST) (Huang *et al.*, 2021). For instance, gold nanoparticles coated with cisplatin decreased nephrotoxicity indicators while preserving their anticancer properties (Saifi *et al.*, 2019; Kadir *et al.*, 2020).

Moreover, decreased off-target accumulation, especially in the kidneys, spleen, and heart, has been demonstrated by pH-sensitive and enzyme-responsive nanoparticles, indicating improved biocompatibility and less systemic load (Setia *et*

al., 2022; W. Zhang *et al.*, 2022). According to these results, carefully designed nanoparticle systems greatly reduce the side effects that are often connected with chemotherapy while simultaneously enhancing therapeutic targeting.

Table 1: Comparison between Conventional and Site Specific Chemotherapy

Aspect	Conventional Chemotherapy	Site-Specific Chemotherapy (Nanoparticles)
Targeting Mechanism	Non-selective, affects both cancerous and healthy cells	Selective targeting using ligands for cancer cells (Chidambaram, Manavalan and Kathiresan, 2011; Saini, 2022)
Side Effects	High toxicity, damage to immune system and organs (Yan *et al.*, 2020)	Reduced side effects due to targeted delivery (Sutradhar and Amin, 2014)
Drug Localization	Poor localization, often leads to systemic exposure	Enhanced localization at tumor sites (Bashyal, 2018)
Drug Solubility	Limited solubility, often requires high doses (Chidambaram, Manavalan and Kathiresan, 2011)	Improved solubility and bioavailability(Chidambaram, Manavalan and Kathiresan, 2011)
Resistance to Treatment	Multidrug resistance is common (Chidambaram, Manavalan and Kathiresan, 2011)	Nanoparticles can overcome resistance mechanisms(Chidambaram, Manavalan and Kathiresan, 2011)
Fabrication Complexity	Standard preparation methods (Lally, Gettens and Sani, 2013)	Requires advanced engineering (Lally, Gettens and Sani, 2013)

6. Challenges and Future Directions

A number of significant obstacles prevent the broad clinical adoption of nanoparticle-based drug delivery for site-specific chemotherapy, despite the encouraging developments in this area. These include the challenges of clinical translation to large-scale manufacture, as well as the intricate regulatory constraints (Hua *et al.*, 2018). Resolving these problems is crucial to turning preclinical findings into a licensed, marketable medication.

Translating nanoparticle formulations from lab-scale research to industrial-scale production is still a significant impediment. The majority of preclinical research is carried out using manual, small-scale synthesis techniques that are difficult to adapt to Good Manufacturing Practice (GMP) guidelines (Operti *et al.*, 2021). Among the difficulties of scaling are; maintaining physicochemical uniformity across larger batches, ensuring encapsulation efficiency and stability during storage and transport and avoiding aggregation or degradation during formulation and delivery (Covarrubias *et al.*, 2022).

Furthermore, clinical translation necessitates economically feasible manufacturing procedures that are reliable and scalable. It took years of optimization for even clinically approved nanomedicines, such liposomal doxorubicin, to make it to market. Solutions for the creation of scalable and repeatable nanoparticles are provided by emerging technologies such as continuous manufacturing and microfluidic-assisted synthesis (Gdowski *et al.*, 2018). The paucity of clinical trial data for numerous nanoparticle formulations is another significant obstacle. Only a small number of candidates have progressed to human trials, despite the fact that several exhibit promise in animal models (Liu *et al.*, 2018). In addition to technology innovation, bridging this gap calls for cooperative frameworks between industrial players, regulatory bodies, and researchers.

The absence of standardized regulatory frameworks is one of the biggest challenges facing the development of treatments using nanoparticles (Ramos *et al.*, 2022). Complex, multipurpose systems that don't fit the conventional criteria of pharmaceuticals or biologics are frequently seen in nanomedicines (Paradise, 2019). Therefore, assessing these formulations in accordance with current rules presents difficulties for regulatory agencies such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) (Foulkes *et al.*, 2020). Key regulatory concerns include: characterization and repeatability of the size, shape, surface chemistry, and kinetics of drug release of nanoparticles. Long-term toxicity and biodistribution, particularly in tissues that are not the intended target. Batch-to-batch consistency, which is essential to guaranteeing both effectiveness and safety. Additionally, because nanoparticle-based medications are more complicated than standard pharmaceuticals, they frequently need more preclinical data, such as pharmacokinetics, immunogenicity, and thorough toxicological evaluations which result in longer development periods and greater expenses (Wang *et al.*, 2022).

7. Conclusion

By providing safer, more precise drug delivery options than conventional chemotherapeutics, nanoparticle-based chemotherapy has drastically changed the way cancer is treated. The intentional creation of nanoparticles to take advantage of both passive and active targeting processes is at the heart of these developments. The increased permeability and retention (EPR) effect, which occurs when nanoparticles build up in tumour tissues as a result of their leaky vasculature and inadequate lymphatic drainage, is used in passive targeting. As opposed to healthy tissues, this enables treatment medicines to concentrate more efficiently in the tumour microenvironment. By functionalizing nanoparticles with ligands such as antibodies, peptides, or small molecules that selectively bind to receptors that are overexpressed on cancer cells, active targeting expands on this basis. By minimizing the exposure of non-cancerous cells to cytotoxic chemicals and minimizing the negative side effects frequently linked to chemotherapy, this dual-targeting strategy greatly improves the accuracy of drug delivery. Controlled drug release, tumour penetration, and circulation time are further improved by optimising nanoparticle characteristics such as size, shape, and surface charge. Preclinical research has demonstrated enhanced effectiveness and decreased adverse effects in a number of cancer models, including ovarian and lung malignancies. Furthermore, biocompatible nanoparticles exhibit positive safety profiles that promote extended usage and an improved standard of living. Most importantly, these systems support personalised medicine by enabling the customisation of therapies according to tumour features and even including diagnostics for in-the-moment therapeutic monitoring.

8. References

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