Nanoparticle-Enhanced Drug Delivery Systems for Targeted Cancer Therapy

Muhit Rana [1*], Kashfia Haque[2], Dong-Jin Lim [3]

Abstract

Nanoparticle-enhanced drug delivery systems have emerged as a promising strategy to revolutionize cancer therapy by improving drug efficacy, minimizing side effects, and enabling targeted delivery. This review article provides a comprehensive overview of the current landscape of nanoparticle-based drug delivery systems for cancer therapy, focusing on recent advancements, challenges, and future perspectives. Subsequent sections cover the types of nanoparticles, their properties influencing drug delivery, principles of targeted drug delivery, advantages over conventional methods, and recent advances in nanoparticle-based drug delivery systems. Key topics addressed include the design and synthesis of nanoparticle formulations, targeting strategies in cancer therapy, in vitro and in vivo evaluation techniques, clinical translation of nanoparticle therapies, recent advancements such as smart nanoparticles and theranostic platforms, and future trends such as personalized medicine and immunotherapy. Overall, nanoparticle-based drug delivery systems offer a promising approach to overcome challenges associated with conventional cancer treatments, paving the way for personalized and targeted therapies that hold great promise in the fight against cancer.

Significance | Nanoparticle-based drug delivery enhances cancer treatment, minimizing side effects, improving efficacy, and enabling targeted therapy, revolutionizing cancer treatment.

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Introduction

Cancer remains one of the most significant global health challenges, posing a substantial burden on individuals, families, and healthcare systems worldwide (Parkin DM, et al., 2002). With its diverse forms and aggressive nature, cancer accounts for millions of deaths annually and continues to challenge medical science and innovation (Kamangar F, et al., 2006).

Conventional cancer therapies, such as chemotherapy, radiation therapy, and surgery, have been the cornerstone of cancer treatment for decades. While these approaches have shown efficacy in many cases, they often come with significant limitations and adverse effects (Debela DT et al, 2021). Chemotherapy, for instance, targets rapidly dividing cancer cells but can also harm healthy tissues, leading to debilitating side effects such as nausea, hair loss, and immunosuppression (Amjad MT et al, 2023). Moreover, conventional therapies may not effectively penetrate tumor tissues, leading to incomplete eradication of cancer cells and potential recurrence (Taberna M et al , 2020).

In light of these challenges, there has been a growing interest in developing more precise and effective treatment modalities. Targeted drug delivery systems have emerged as a promising strategy to enhance the efficacy and safety of cancer therapy. By precisely delivering therapeutic agents to tumor sites while sparing healthy tissues, targeted drug delivery systems aim to maximize therapeutic benefit while minimizing systemic toxicity (Tewabe A et al., 2021).

Nanoparticle-based drug delivery systems represent a cutting-

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edge approach in the field of targeted cancer therapy. Nanoparticles, with their unique size, surface properties, and drug-loading capabilities, offer several advantages over conventional drug delivery platforms. These nanoscale carriers can encapsulate or conjugate with therapeutic agents, protect them from degradation, and deliver them selectively to cancer cells through passive or active targeting mechanisms (Afzal O et al , 2022).

The integration of nanoparticles into drug delivery systems enables precise control over drug release kinetics, enhancing therapeutic efficacy and reducing off-target effects. Furthermore, nanoparticles can be engineered to respond to specific stimuli present in the tumor microenvironment, allowing for triggered drug release and site-specific action (Ngoepe M et al., 2013).

In this review article, we aim to provide a comprehensive overview of nanoparticle-enhanced drug delivery systems for targeted cancer therapy. We will discuss the principles underlying targeted drug delivery, the design and synthesis of nanoparticle-based carriers, targeting strategies, preclinical and clinical evaluation, recent advances, challenges, and future perspectives in the field. By exploring the multifaceted applications of nanoparticle-based drug delivery systems, we hope to contribute to the ongoing efforts to revolutionize cancer treatment and improve patient outcomes.

2. Nanoparticles in Drug Delivery: Types and Properties.

Nanoparticles, with their minute size and unique properties, are widely explored for drug delivery systems in cancer therapy (Table.1.). Among the various types of nanoparticles utilized in drug delivery, several prominent categories stand out:

2.1. Liposomes

Liposomes are one of the most extensively studied nanoparticle-based drug delivery systems. These spherical vesicles consist of lipid bilayers surrounding an aqueous core. Liposomes offer versatility in encapsulating both hydrophilic and hydrophobic drugs within their core or lipid bilayers, respectively. They provide controlled release kinetics, excellent biocompatibility, and the ability to protect encapsulated drugs from degradation (Figure 1).

The drug molecules are placed in the liposome's aqueous core, and the lipid bilayer shields them from the body's aqueous environment. Over time, the bilayer deteriorates, and the liposomes release their contents (Maleka P et al., 2018). Liposomes can carry both hydrophilic and hydrophobic molecules by dissolving hydrophobic chemicals into the membrane. The drug can be encapsulated within the inner aqueous space or embedded in the bilayer of liposomes by means of covalent, ionic, electrostatic, non-covalent, or steric interactions between drug molecules and lipids (Liu P et al., 2022).

To deliver the molecules to sites of action, the lipid bilayer can fuse with other bilayers such as the cell membrane (Figure1). For example, PEGylated liposomes gradually release their content into the extracellular fluid, which then enters cells either via diffusion or pinocytosis (Islam Shishir et al., 2019). Encapsulation of anti-cancer drugs within the liposomal system offers secure platforms for the targeted delivery of anti-cancer drugs for the treatment of cancer. This can help reduce the cytotoxic side effects of anti-cancer drugs on normal cells (Olusanya TOB et al., 2018).

2.2. Polymeric nanoparticles

Polymeric nanoparticles (PNPs) encompass a broad class of nanoparticles composed of synthetic or natural polymers. Materials such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), chitosan, and others are commonly used for their synthesis. Polymeric nanoparticles can be fabricated using various techniques, including nanoprecipitation, emulsion/solvent evaporation, and electrospraying. They offer tunable properties, sustained drug release, and the capacity to encapsulate both hydrophobic and hydrophilic drugs.

Polymeric nanoparticles (PNPs) are biocompatible, biodegradable, and have different chemical compositions, charges, and physical structures. They also have tunable drug release kinetics, which has made them commercially important. The two main types of PNPs are nanocapsules, which are a reservoir system, and nanospheres, which are a matrix system. PNPs can include polymeric micelles, liposomes, dendrimers, polymeric sponges, and colloidal carriers (Harish Bhardwa et al., 2023).

Solvent evaporation is the most common method used to prepare PNPs for drug delivery. Biocompatible and biodegradable polymers that do not cause an immunogenic response should be used at all times (Wei-Ren Ke et al., 2022).

Here are some examples of PNPs and their uses:

Chitosan

A biodegradable, biocompatible nanocarrier that has a positive surface charge and mucoadhesive feature, allowing it to connect to mucus membranes and release drugs in a sustained manner (Nikdouz A et al., 2022).

Lipid-polymer hybrid nanoparticles

A hybrid delivery system where the polymer nanoparticle core is surrounded by a liposomal layer (Priya Muralidharan et al., 2015).

Folic acid conjugated nanoparticles

A system with a mixed lipid monolayer shell and biodegradable polymer core that can deliver anticancer drugs with controlled, sustainable, and targeted delivery(Liu Y et al., 2010).

2.3. Metallic nanoparticles

Metallic nanoparticles, such as gold nanoparticles, silver nanoparticles, and iron oxide nanoparticles, possess unique physicochemical properties that make them attractive for drug delivery applications. These nanoparticles can be functionalized with targeting ligands and therapeutic agents for specific cancer targeting and imaging applications. Metallic nanoparticles offer excellent optical, magnetic, and catalytic properties, enabling multimodal imaging and synergistic therapeutic effects.

Metallic nanoparticles (MNPs) have unique properties that make them useful for drug delivery (Chandrakala, V. et al., 2022, Abdelkawi et al., 2023) . These properties include:

Large surface-area-to-volume ratio: This allows for surface modification.

Increased stability: This increases the half-life of the drug in circulation.

Enhanced biodistribution: This allows for efficient delivery to the desired target site.

Customizable surface chemistry: This allows for the design of nanoparticles that are specifically engineered to carry and deliver a particular drug.

Responsiveness to external stimuli: This can be used to control the drug release at the target site.

MNPs can be used in drug delivery systems for photodynamic therapy (PDT). PDT is a treatment that uses light, oxygen, and a light-absorbing photosensitizer (PS) to generate cytotoxic reactive oxygen species (ROS) (Chota et al., 2023). MNPs can also be used for targeted drug delivery of numerous diseases. After induction in the circulatory system, the drug-loaded MNPs can be controlled by an external magnetic field and guided to deliver the drug to specific points (Salma Mirza et al., 2020).

2.4. Dendrimers

Dendrimers are highly branched, tree-like macromolecules with well-defined structures and molecular weights (Figure 2.). These nanoparticles can encapsulate drugs within their interior void spaces and functionalize their surface with targeting ligands. Dendrimers exhibit high drug-loading capacities, precise control over size and structure, and potential for multifunctional drug delivery applications.

Dendrimers have unique properties that make them attractive for biological and drug-delivery applications (Basavaraj K. Nanjwade et al., 2009). These properties include:

Uniform size

High degree of branching

Water solubility

Multivalency

Well-defined molecular weight

Available internal cavities

Here are some types of dendrimers used for drug delivery:

1. PAMAM dendrimers

Poly(amidoamine) (PAMAM) dendrimers are a family of synthetic macromolecules with well-defined structures and compositions. They are three-dimensional molecules made of amide and amine subunits. These are the most common type of dendrimer and are suitable for many areas, including drug and gene delivery systems and regenerative medicine. They can be used as drug carriers in anti-cancer therapy. PAMAM dendrimers can carry the anticancer drug methotrexate and fluorescein for tracking (Bober Z et al., 2022).

2. Peptide dendrimers

Peptide dendrimers are branched macromolecules that contain peptide bonds. They are characterized by a central core, branching units, and surface functional groups. The size and complexity of peptide dendrimers are determined by the number of branching units and the size of the surface functional groups. Peptide dendrimers can be used for a variety of applications, including: Biomedical and biochemical uses, Immunogens, Inhibitors, and Mimetics. Dendrimers are biocompatible nanoparticle macromolecules that are used for their unique properties as carriers of other molecular structures. They can be used to improve the activity and efficiency of an active drug molecule and also to reduce its toxicity. Dendrimers have a spherical shape as opposed to linear polymers. Their unique properties make them prominent in tumor treatments. Dendrimers have biological properties such as polyvalency, self-assembling, electrostatic interactions, chemical stability, low cytotoxicity, and solubility. These varied characteristics make dendrimers a good choice in the medical field. These have been studied as useful drug delivery mechanisms. The drug can be attached through a covalent bond or through noncovalent encapsulation of the drug (Bethany M. Cooper et al., 2021).

3. DNA dendrimers

DNA dendrimers are nanocarriers that maintain the recognition functions of functional nucleic acids (FNAs). DNA nanomaterials have gained attention due to their programmability and multifunctionality. Dendrimers are polymeric macromolecules with a spherical shape. They have three main structural components (Hari Singh Nalwa. 2021):

A core unit that branches out

Building blocks with a branching point

Surface or terminal groups that form the chain ends

Entrapping drugs in dendrimers can improve solubility, stability, and dissolution. These properties can help to improve the drug's oral bioavailability. These can deliver drugs or functional nucleic acids into target cells in chemotherapy, immunotherapy, and gene therapy. They are also being applied in protein engineering for efficient directed evolution of proteins (Liu, L. et al., 2021).

2.5. Carbon-based nanoparticles

Carbon-based nanomaterials (CBNs) are a new class of materials that are used in various biomedical fields, including drug delivery. They are used in cancer therapy, gene delivery, and peptide delivery (Table 1). Carbon-based nanoparticles, including carbon nanotubes and graphene oxide, have garnered significant attention for drug delivery due to their unique physicochemical properties. These nanoparticles offer large surface areas, high drug-loading capacities, and the ability to penetrate cellular membranes for

intracellular drug delivery. Carbon-based nanoparticles can be functionalized with targeting moieties and imaging agents for theranostic applications (Sumer, B. D., & Gao, J. 2008).

CBNs are classified according to their shape and geometrical structure. The most common CBNs are carbon nanotubes, which are cylindrical in shape and can be categorized as single, double, or multi-walled. The properties of nanoparticles significantly influence their performance in drug delivery systems. Size dictates pharmacokinetics, cellular uptake, and biodistribution, with smaller nanoparticles (<100 nm) capable of exploiting the enhanced permeability and retention (EPR) effect for tumor accumulation. Shape plays a role in cellular internalization, with anisotropic nanoparticles potentially showing enhanced uptake due to their increased surface area.

Surface charge affects stability, protein adsorption, and cellular interactions, where positively charged nanoparticles may enhance cellular uptake through electrostatic interactions. Surface functionalization with targeting ligands enables specific recognition and binding to cancer cells or receptors, while stealth polymers like PEGylation improve circulation time and reduce immune recognition (Debnath, S. K., & Srivastava, R. 2021). CBNs can be functionalized with the help of single or multiple polymers by layering and thus help in targeting and biocompatibility (Ketan M. Ranch et al.2021).

3. Nanoparticle Properties Influencing Drug Delivery:

3. 1. Size of Nanoparticle: Nanoparticle size is a critical determinant of their behavior in drug delivery systems. Small nanoparticles, typically less than 100 nanometers, exhibit enhanced tumor accumulation via the enhanced permeability and retention (EPR) effect. This phenomenon allows nanoparticles to extravasate through leaky tumor vasculature and accumulate within the tumor microenvironment. Additionally, smaller nanoparticles demonstrate improved cellular uptake and penetration into tumor tissues, leading to enhanced therapeutic efficacy (Balogh, L. et al., 2007).

3. 2. Shape of Nanoparticles:

The shape of nanoparticles influences their interaction with biological systems and cellular uptake mechanisms. Anisotropic nanoparticles, such as rods, discs, and fibers, may exhibit enhanced cellular internalization compared to spherical nanoparticles due to their increased surface area and aspect ratio (Figure 3.). Additionally, nanoparticle shape can affect their circulation time, biodistribution, and tumor targeting ability, making it an essential parameter to consider in drug delivery system design (Truong, N. P. et al., 2014).

3. 3. Surface Charge:

Nanoparticle surface charge plays a crucial role in determining their stability, protein adsorption, and interactions with cell membranes. Positively charged nanoparticles may exhibit increased cellular uptake via electrostatic interactions with negatively charged cell membranes. Conversely, negatively charged nanoparticles may experience reduced cellular uptake but enhanced stability in biological fluids. The surface charge of nanoparticles can be modulated through surface functionalization to optimize their pharmacokinetics and targeting capabilities (Figure 3) (Bhattacharjee, S. 2016).

3.4. Surface Functionalization:

Surface functionalization enables the customization of nanoparticle properties to achieve specific drug delivery objectives. By attaching targeting ligands, such as antibodies, peptides, or aptamers, to the nanoparticle surface, selective binding to cancer cells or receptors overexpressed on their surface can be achieved. Moreover, surface functionalization with stealth polymers, such as polyethylene glycol (PEG), can improve nanoparticle circulation time by reducing opsonization and immune recognition. These modifications enhance the biocompatibility, targeting efficiency, and overall therapeutic performance of nanoparticle-based drug delivery systems (Navya, P. N. 2019).

3.5. Biocompatibility:

Biocompatibility is a critical consideration in nanoparticle-based drug delivery systems to ensure minimal adverse effects and immune responses upon administration. Biodegradable and biocompatible materials are preferred for nanoparticle synthesis to facilitate their clearance from the body and minimize long-term toxicity. Surface modification with biocompatible polymers or coatings can further enhance nanoparticle biocompatibility and reduce potential immunogenicity. By ensuring biocompatibility, nanoparticle-based drug delivery systems can achieve safe and effective therapeutic outcomes in cancer therapy (Nie, S. 2010).

4. Principles of Targeted Drug Delivery:

Targeted drug delivery represents a paradigm shift in drug delivery strategies, aiming to improve therapeutic outcomes while minimizing side effects by precisely delivering therapeutic agents to diseased tissues or cells. We will examine the concept of targeted drug delivery and explore the mechanisms by which nanoparticles are utilized for tumor targeting as follows.

4.1. Concept of Targeted Drug Delivery:

Targeted drug delivery involves the selective delivery of therapeutic agents to specific sites within the body, such as tumor tissues, while minimizing exposure to healthy tissues. This approach offers several advantages over conventional drug delivery methods, including increased drug efficacy, reduced systemic toxicity, and improved patient compliance. By targeting drugs directly to the site of action, targeted drug delivery can enhance therapeutic outcomes and minimize adverse effects (Devarajan, P. V., & Jain, S. 2015).

4.2. Mechanisms of tumor targeting using nanoparticles:

Nanoparticles offer versatile platforms for tumor targeting, employing various mechanisms to achieve selective accumulation within tumor tissues:

4.2.1. Passive targeting via enhanced permeability and retention (EPR) effect:

The EPR effect exploits the unique characteristics of tumor vasculature, which is often leaky and permeable compared to normal blood vessels. Nanoparticles can extravasate through these leaky blood vessels and accumulate within the tumor microenvironment due to their small size and prolonged circulation time (Figure 4.). The EPR effect is particularly advantageous for passive targeting of nanoparticles to solid tumors, where they can penetrate deep into the tumor tissue and release therapeutic agents locally (Torchilin, V. P. 2009).

4.2.2. Active targeting via ligand-receptor interactions:

Active targeting involves functionalizing nanoparticles with targeting ligands, such as antibodies, peptides, aptamers, or small molecules, that specifically bind to receptors overexpressed on the surface of cancer cells. By decorating nanoparticles with these targeting ligands, they can selectively recognize and bind to cancer cells, leading to enhanced cellular uptake and internalization of the nanoparticles (Figure 4 and 5.) . This targeted approach allows for precise delivery of therapeutic agents to cancer cells while sparing healthy tissues, thereby improving therapeutic efficacy and reducing off-target effects (Figure 4) (Torchilin, V. P. 2009).

4.2.3. Responsive targeting via stimuli-responsive nanoparticles:

Stimuli-responsive nanoparticles are designed to respond to specific cues present in the tumor microenvironment, such as pH, temperature, or enzymatic activity. Upon exposure to these stimuli, nanoparticles undergo changes in their physicochemical properties, such as size, shape, or surface charge, triggering drug release or cellular uptake. This responsive targeting strategy enables spatiotemporal control over drug delivery, enhancing therapeutic efficacy and minimizing systemic toxicity (Chen, W. et al., 2017).

5. Advantages of Nanoparticle-Enhanced Drug Delivery Systems:

Nanoparticle-enhanced drug delivery systems offer a myriad of advantages over conventional drug delivery methods, revolutionizing the landscape of cancer therapy. In this section, we delve into these advantages and explore how nanoparticle-based drug delivery systems surpass traditional approaches.

5.1. Comparison with conventional drug delivery methods:

Nanoparticle-enhanced drug delivery systems present a significant departure from conventional methods, which often rely on systemic administration of drugs leading to indiscriminate distribution throughout the body (Table. 2). Unlike conventional drug delivery, nanoparticles can be engineered to specifically target diseased tissues while minimizing exposure to healthy tissues, thereby enhancing therapeutic efficacy and reducing systemic toxicity as given in table 3 (Jong, D. S. 2008).

5.2. Enhanced therapeutic efficacy and reduced side effects:

One of the primary advantages of nanoparticle-based drug delivery systems is their ability to improve the therapeutic index of drugs by enhancing their accumulation at the target site. By precisely delivering therapeutic agents to the site of action, nanoparticles can achieve higher local drug concentrations, leading to improved treatment outcomes while minimizing systemic side effects. This targeted approach allows for the use of lower drug doses, reducing toxicity and improving patient tolerance to therapy. Nanoparticle-based drug delivery systems achieve enhanced therapeutic efficacy and reduced side effects in following ways (Xin, Y. et al., 2017):

5.2.1. Precise Targeting: Nanoparticles can be engineered to target specific cells, tissues, or organs within the body, thereby enhancing drug delivery to the site of action while minimizing exposure to healthy tissues. This targeted approach ensures that therapeutic agents reach their intended target in optimal concentrations, maximizing their therapeutic efficacy against cancer cells while sparing surrounding normal tissues.

5.2.2. Enhanced Drug Accumulation: Nanoparticles possess the ability to accumulate selectively within tumor tissues through passive and active targeting mechanisms. The enhanced permeability and retention (EPR) effect allows nanoparticles to extravasate through leaky tumor vasculature and accumulate within the tumor microenvironment, achieving higher local drug concentrations than conventional delivery methods. Additionally, active targeting strategies involving surface functionalization with targeting ligands further enhance nanoparticle accumulation within cancer cells, leading to improved treatment outcomes (Figure 5).

5.2.3. Controlled Drug Release: Nanoparticle-based drug delivery systems offer precise control over drug release kinetics, allowing for sustained and controlled release of therapeutic agents over extended periods. This controlled release profile ensures continuous exposure of cancer cells to therapeutic agents, optimizing their cytotoxic effects while minimizing fluctuations in drug concentration that can lead to systemic toxicity and drug resistance.

5.2.4. Reduced Systemic Toxicity: By delivering therapeutic agents directly to the site of action, nanoparticle-based drug delivery systems minimize systemic exposure of healthy tissues to cytotoxic drugs, thereby reducing the incidence and severity of systemic side effects. This targeted approach not only improves patient tolerance to therapy but also enables the use of higher drug doses at the tumor site, further enhancing therapeutic efficacy against cancer cells.

5.3. Improved pharmacokinetics and bioavailability of drugs:

Nanoparticles can overcome several limitations associated with conventional drug formulations, such as poor solubility, rapid clearance, and low bioavailability. By encapsulating drugs within nanoparticles, their stability can be enhanced, leading to prolonged circulation times and improved pharmacokinetics. Additionally, nanoparticles can protect drugs from enzymatic degradation and premature clearance, resulting in higher drug concentrations at the target site and improved therapeutic outcomes. Berry, C. C., & Curtis, A. (2003) have highlighted the concept of applications of nanoparticle based drug delivery as follows.,

5.3.1. Enhanced Drug Stability: Nanoparticles provide a protective environment for encapsulated drugs, shielding them from degradation by enzymes, pH variations, and other physiological factors. This enhanced stability prolongs the shelf life of drugs and prevents premature degradation during circulation, ensuring that therapeutic agents retain their potency until they reach the target site.

5.3.2. Prolonged Circulation Time: Nanoparticles can evade clearance by the reticuloendothelial system (RES) and prolong circulation times in the bloodstream. Surface modifications, such as PEGylation, create a stealth effect that reduces opsonization and recognition by phagocytic cells, thereby extending the circulation half-life of nanoparticles. Prolonged circulation times allow for sustained drug release and enhanced accumulation at the target site, improving therapeutic efficacy.

5.3.3. Improved Tissue Distribution: Nanoparticles can overcome physiological barriers and penetrate deep into tissues, including solid tumors, where conventional drugs may have limited access. The small size and surface properties of nanoparticles enable them to extravasate through leaky tumor vasculature and accumulate within the tumor microenvironment via the enhanced permeability and retention (EPR) effect. This improved tissue distribution ensures more uniform drug exposure throughout the tumor, enhancing treatment outcomes.

5.3.4. Enhanced Cellular Uptake: Nanoparticles can facilitate cellular uptake of drugs by cancer cells through various mechanisms, including receptor-mediated endocytosis and passive diffusion. Surface functionalization with targeting ligands enhances the specificity of nanoparticle-cell interactions, promoting selective uptake by cancer cells while minimizing uptake by healthy cells. This targeted approach increases drug concentrations within cancer cells, leading to improved therapeutic efficacy.

5.3.5. Increased Bioavailability: Nanoparticle-based drug delivery systems can improve the bioavailability of poorly soluble drugs, enhancing their absorption and distribution in the body. Nanoparticles can solubilize hydrophobic drugs within their core or enhance their dispersibility in aqueous media, facilitating their transport across biological barriers and increasing their bioavailability. This enhanced bioavailability ensures that a higher proportion of the administered dose reaches the systemic circulation, maximizing therapeutic efficacy.

5.4. Overcoming multidrug resistance in cancer cells:

Multidrug resistance (MDR) poses a significant challenge in cancer therapy, leading to treatment failure and disease progression. Cancer cells can develop resistance to multiple chemotherapeutic agents through various mechanisms, including drug efflux pumps, alterations in drug targets, and dysregulation of apoptosis pathways. Overcoming MDR is crucial for improving treatment outcomes and enhancing the efficacy of chemotherapy. Nanoparticle-based drug delivery systems offer innovative strategies to circumvent MDR mechanisms and restore sensitivity to chemotherapeutic agents. Shapira, A. et al., (2011) have explored how nanoparticle-based approaches overcome multidrug resistance in cancer cells as follows:

5.4.1. Bypassing Drug Efflux Mechanisms: One of the primary mechanisms of MDR involves the overexpression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp), which actively pump drugs out of cancer cells, reducing intracellular drug concentrations. Nanoparticles can bypass these drug efflux mechanisms by shielding encapsulated drugs from recognition by ABC transporters or modifying their surface properties to evade efflux pump recognition. Additionally, nanoparticle-mediated drug delivery can promote intracellular drug accumulation by facilitating endocytic uptake pathways that bypass efflux pumps, thereby overcoming MDR.

5.4.2. Selective Targeting of Drug-Resistant Cells: Nanoparticle-based drug delivery systems can be engineered to selectively target drug-resistant cancer cells while sparing sensitive cells. Surface functionalization of nanoparticles with targeting ligands, such as antibodies or peptides, that specifically recognize drug-resistant phenotypes or biomarkers can facilitate selective uptake by resistant cells. By delivering therapeutic agents directly to drug-resistant cells, nanoparticle-based approaches circumvent resistance mechanisms and enhance the efficacy of chemotherapy.

5.4.3. Combination Therapy and Synergistic Effects: Nanoparticle-based drug delivery systems enable the co-delivery of multiple therapeutic agents or combination therapies targeting different signaling pathways implicated in MDR. By encapsulating synergistic drug combinations within nanoparticles, it is possible to overcome resistance mechanisms and potentiate the cytotoxic effects against drug-resistant cancer cells. Furthermore, nanoparticles can facilitate the intracellular co-delivery of drugs with distinct mechanisms of action, leading to synergistic interactions and overcoming cross-resistance to individual agents.

5.4.4. Stimuli-Responsive Drug Release: Stimuli-responsive nanoparticles can overcome MDR by releasing therapeutic agents in response to specific cues present in the tumor microenvironment, such as pH, temperature, or enzymatic activity.

By exploiting the differences between drug-resistant and drug-sensitive tumor cells, stimuli-responsive nanoparticles can selectively release drugs within drug-resistant cells while sparing sensitive cells. This targeted drug release approach enhances therapeutic efficacy against drug-resistant cancer cells and minimizes off-target effects.

5.4.5. Overcoming Apoptosis Dysregulation: Nanoparticle-based drug delivery systems can restore apoptotic pathways dysregulated in drug-resistant cancer cells by delivering pro-apoptotic agents directly to the intracellular compartments. By promoting apoptosis in drug-resistant cells, nanoparticles can overcome resistance mechanisms that evade cell death and enhance the sensitivity of cancer cells to chemotherapy. Additionally, nanoparticles can encapsulate inhibitors of anti-apoptotic proteins or signaling pathways implicated in MDR, further sensitizing drug-resistant cells to cytotoxic agents.

6. Design and Synthesis of Nanoparticle-Based Drug Delivery Systems.

Nanoparticle-based drug delivery systems offer a versatile platform for the targeted delivery of therapeutic agents, with precise control over drug release kinetics and tissue distribution. The design and synthesis of these systems involve careful consideration of nanoparticle properties, drug incorporation strategies, and surface functionalization for optimized therapeutic outcomes (Zhang, R. X. et al., 2017). Here we explored the various aspects of designing and synthesizing nanoparticle-based drug delivery systems:

6.1. Overview of Synthesis Methods for Nanoparticles.

Nanoparticles can be synthesized using a variety of methods, each offering unique advantages in terms of scalability, reproducibility, and control over nanoparticle properties as follows (Jamkhande, P. G. et al., 2019):

6.1.1. Chemical Synthesis: Chemical methods, such as sol-gel synthesis, precipitation, and thermal decomposition, involve the reduction of precursor materials to form nanoparticles in solution. These methods offer precise control over nanoparticle size, shape, and composition and are widely used for synthesizing metallic, semiconductor, and oxide nanoparticles.

6.1.2. Physical Methods: Physical methods, including laser ablation, evaporation-condensation, and sputtering, involve the physical transformation of bulk materials into nanoparticles through techniques such as vapor deposition or laser irradiation. These methods are suitable for producing nanoparticles with narrow size distributions and high purity but may require specialized equipment and controlled environments.

6.1.3. Green Synthesis: Green synthesis methods utilize natural sources, such as plant extracts, microorganisms, or biomolecules, as reducing or stabilizing agents for nanoparticle synthesis. These environmentally friendly approaches offer sustainable and cost-effective routes to nanoparticle production and are gaining popularity due to their low toxicity and biocompatibility.

6.2. Strategies for Incorporating Drugs into Nanoparticles:

Once nanoparticles are synthesized, therapeutic agents can be incorporated using various strategies, including:

6.2.1. Encapsulation: Drugs can be encapsulated within the core of nanoparticles during synthesis or post-synthesis. This encapsulation provides protection against degradation, controlled release kinetics, and enhanced drug stability. Common encapsulation materials include lipids, polymers, and inorganic matrices (Peer, D. et al., 2007).

6.2.2. Conjugation: Drugs can be covalently attached to the surface of nanoparticles through chemical conjugation techniques. This approach allows for precise control over drug loading and release and enables targeted delivery to specific tissues or cells (Patra, J. K. et al., 2018).

6.2.3. Physical Adsorption: Drugs can be adsorbed onto the surface of nanoparticles through physical interactions, such as electrostatic interactions or hydrophobic interactions. While simple and versatile, physical adsorption may result in premature drug release and lower drug loading capacities compared to encapsulation or conjugation (Aggarwal, P. et al., 2009).

6.3. Importance of Surface Functionalization for Targeting and Controlled Drug Release:

Surface functionalization plays a crucial role in nanoparticle-based drug delivery systems, enabling targeted delivery to specific tissues or cells and controlled release of therapeutic agents Kolishetti, N et al., have discussed the importance of surface functionalization for targeting and controlled drug (Kolishetti, N et al., 2010):

6.3.1. Targeting Ligands: Surface functionalization with targeting ligands, such as antibodies, peptides, or aptamers, facilitates selective recognition and binding to receptors overexpressed on the surface of target cells or tissues. This targeted approach enhances nanoparticle accumulation at the site of action and minimizes off-target effects.

6.3.2. Responsive Coatings: Responsive coatings, such as pH-sensitive polymers or stimuli-responsive nanoparticles, enable controlled drug release in response to specific environmental cues, such as pH changes, enzymatic activity, or temperature variations. This spatiotemporal control over drug release enhances therapeutic efficacy and minimizes systemic toxicity.

6.3.3. Stealth Coatings: Surface modification with hydrophilic polymers, such as polyethylene glycol (PEG), creates a stealth effect that reduces nanoparticle recognition by the immune system and extends circulation times in the bloodstream. This stealth coating improves nanoparticle biocompatibility and enhances their ability to evade clearance mechanisms, thereby improving drug delivery efficiency.

7. Targeting Strategies in Cancer Therapy:

Targeted drug delivery represents a promising approach in cancer therapy, aiming to deliver therapeutic agents selectively to tumor tissues while sparing healthy cells (Figure 6). Various targeting ligands have been explored for active tumor targeting, including antibodies, peptides, aptamers, small molecules, and more (Huang, P. S., & Oliff, A. 2001).

7.1. Review of Various Targeting Ligands:

Ligand-targeted strategies facilitate effective delivery of intravenously administered photosensitizers (PSs) to tumor microenvironment cells (Van Straten, D et al., 2017). Upon injection, ligand-targeted PSs circulate sufficiently to extravasate through tumor blood vessel fenestration (Table 3). Upon tumor accumulation, PSs attached to targeting moieties are internalized via receptor-mediated endocytosis. If the carrier has fusogenic properties, PSs are released into the cell cytosol, accumulating in organelles. Illumination with an appropriate laser after a drug-to-light interval (DLI) triggers PS activation, generating singlet oxygen and reactive oxygen species (ROS) (Figure 7). This oxidative stress induces cancer cell death via various mechanisms (Gierlich, et al., 2020).

7.1.1. Antibodies: Monoclonal antibodies (mAbs) are highly specific targeting ligands that recognize and bind to antigens overexpressed on the surface of cancer cells. Antibodies can be engineered for high affinity and selectivity, making them ideal candidates for targeted drug delivery in cancer therapy (Uhlén, M., & Pontén, F. 2005).

7.1.2. Peptides: Short peptide sequences can serve as targeting ligands by selectively binding to receptors or proteins expressed on the surface of cancer cells. Peptides offer advantages such as low immunogenicity, rapid tissue penetration, and ease of synthesis, making them attractive for targeted drug delivery applications (Yokosaki, Y. et al., 1999).

7.1.3. Aptamers: Aptamers are short, single-stranded DNA or RNA molecules that fold into unique tertiary structures and bind to specific targets with high affinity and selectivity. Aptamers can be selected against a wide range of targets, including proteins, nucleic acids, and small molecules, making them versatile targeting ligands for cancer therapy (Keefe, A. D., Pai, S., & Ellington, A. D. 2010).

7.1.4. Small Molecules: Small molecules, such as small organic compounds or natural products, can serve as targeting ligands by binding to receptors or enzymes overexpressed on cancer cells. Small molecules offer advantages such as high stability, low immunogenicity, and ease of synthesis, making them attractive for targeted drug delivery strategies (Wang, Y et al,., 2017). .

7.2. Examples of Targeting Ligands and Their Receptors Overexpressed on Cancer Cells.

7.2.1. Epidermal Growth Factor Receptor (EGFR): EGFR is overexpressed on the surface of various cancer cells, including breast, lung, and colorectal cancers. Antibodies targeting EGFR, such as cetuximab and trastuzumab, have been developed for the treatment of EGFR-positive tumors (Normanno, N et al., 2006).

7.2.2. Human Epidermal Growth Factor Receptor 2 (HER2): HER2 is overexpressed in a subset of breast cancers and other solid tumors. Trastuzumab, a monoclonal antibody targeting HER2, has been approved for the treatment of HER2-positive breast cancer (Siena, S et al., 2018)..

7.2.3. Vascular Endothelial Growth Factor Receptor (VEGFR): VEGFR is overexpressed on the surface of endothelial cells in tumor vasculature. Bevacizumab, a monoclonal antibody targeting VEGF, has been approved for the treatment of various cancers, including colorectal, lung, and kidney cancers (Swann, R., et al., 2010).

7.2.4. Integrins: Integrins are cell adhesion receptors that play a crucial role in tumor angiogenesis and metastasis. Peptides targeting integrins, such as RGD peptides, have been developed for targeted drug delivery to tumor cells and tumor vasculature (Zhang, C et al., 2016).

7.2.5. Prostate-Specific Membrane Antigen (PSMA): PSMA is highly expressed on the surface of prostate cancer cells. PSMA-targeting ligands, such as antibodies and small molecules, are being investigated for the selective delivery of therapeutic agents to prostate cancer cells (Ghosh, A., & Heston, W. D. 2003).

8. In vitro and In vivo Evaluation of Nanoparticle Drug Delivery Systems.

Nanoparticle drug delivery systems undergo rigorous evaluation to assess their efficacy, safety, and therapeutic potential before clinical translation. Both in vitro and in vivo experimental techniques are utilized to comprehensively characterize nanoparticle behavior, biodistribution, and therapeutic outcomes (Hałupka-Bryl, M. et al., 2014). Here we provide an overview of the experimental techniques and parameters assessed in the evaluation of nanoparticle-based drug delivery systems:

8.1. Cell Culture Studies: In vitro cell culture studies are essential for evaluating the cellular uptake, internalization mechanisms, and cytotoxicity of nanoparticle formulations. Various cell lines representing different cancer types are utilized to assess nanoparticle-cell interactions and therapeutic effects (Lanza, G. M. et al., 2002).

8.2. Animal Models: In vivo animal studies are conducted to investigate the pharmacokinetics, biodistribution, tumor accumulation, and therapeutic efficacy of nanoparticle drug delivery systems. Animal models, including mice, rats, and xenograft models, are used to simulate human physiology and assess the translational potential of nanoparticle formulations. (Hałupka-Bryl, M. et al., 2014).

8.3. Imaging Techniques: Advanced imaging techniques, such as fluorescence imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT), are employed to track the biodistribution and tumor targeting of nanoparticle formulations in real-time. These imaging modalities provide valuable insights into nanoparticle behavior in vivo and facilitate the optimization of drug delivery strategies (Ito, A., et at., p2005). .

9. Clinical Translation and Challenges.

Nanoparticle-based drug delivery systems hold immense promise for revolutionizing cancer therapy by improving drug efficacy, minimizing side effects, and enabling targeted delivery. While several nanoparticle formulations have progressed to clinical trials or clinical use, their translation from preclinical studies to clinical applications presents various challenges and limitations.

9.1. Nanoparticle-Based Drug Delivery Systems in Clinical Trials or Clinical Use.

9.1.1. Doxil (Doxorubicin Liposomal): Doxil, a liposommal formulation of doxorubicin, was one of the first nanoparticle-based drug delivery systems approved for clinical use. It is indicated for the treatment of various cancers, including ovarian cancer, multiple myeloma, and Kaposi's sarcoma (O'Brien, M et al., 2004).

9.1.2. Abraxane (Albumin-bound Paclitaxel): Abraxane is a nanoparticle formulation of paclitaxel bound to albumin nanoparticles. It is approved for the treatment of breast cancer, non-small cell lung cancer, and pancreatic cancer (Yamada, K. 2009).

9.1.3. Onivyde (Irinotecan Liposomal): Onivyde is a liposomal formulation of irinotecan indicated for the treatment of metastatic pancreatic cancer in combination with fluorouracil and leucovorin (Milano, G. et al., 2022).

9.1.4. VYXEOS (Liposomal Daunorubicin and Cytarabine): VYXEOS is a liposomal formulation of daunorubicin and cytarabine approved for the treatment of certain types of acute myeloid leukemia (AML)(Deutsch, Y. E. et al., 2018).

9.2. Challenges and Limitations in Clinical Translation.

Muthu, M. S., & Wilson, B. (2012) have highlighted some of the concerns about nanoparticle-based drug delivery systems as discussed in following sections.

9.2.1. Safety Concerns: Despite the potential benefits of nanoparticle-based drug delivery systems, safety concerns related to toxicity, immunogenicity, and long-term effects on human health remain significant challenges. The accumulation of nanoparticles in vital organs, such as the liver and spleen, may lead to off-target effects and systemic toxicity.

9.2.2. Scalability: The scalability of nanoparticle manufacturing processes is a key challenge in clinical translation. Achieving reproducible production of nanoparticles at large scales while maintaining batch-to-batch consistency and quality control poses significant technical and logistical hurdles.

9.2.3. Regulatory Issues: Nanoparticle-based drug delivery systems face regulatory challenges related to their complex physicochemical properties, manufacturing processes, and characterization methods. Regulatory agencies require robust preclinical and clinical data to demonstrate safety, efficacy, and comparability with conventional therapies.

9.2.4. Cost-Effectiveness: The development and clinical translation of nanoparticle-based drug delivery systems entail significant investment in research, development, and manufacturing. High production costs, regulatory requirements, and reimbursement challenges may impact the cost-effectiveness and accessibility of nanoparticle therapies, limiting their adoption in clinical practice.

9.2.5. Clinical Trial Design: Designing clinical trials for nanoparticle-based drug delivery systems poses unique challenges, including patient selection, endpoint assessment, and treatment monitoring. Tailoring clinical trial protocols to account for nanoparticle-specific pharmacokinetics, biodistribution, and toxicity profiles is essential for accurately evaluating their therapeutic efficacy and safety.

10. Recent Advances and Future Perspectives.

Recent years have witnessed remarkable advancements in nanoparticle-based drug delivery systems for cancer therapy, paving the way for innovative treatment strategies with enhanced efficacy and reduced side effects. In this section, we highlight key recent advancements and discuss future directions and emerging trends in the field:

10.1. Recent Advancements in Nanoparticle-Based Drug Delivery Systems.

10.1.1. Smart Nanoparticles: The development of smart nanoparticles capable of responding to specific stimuli in the tumor microenvironment, such as pH, temperature, or enzymatic activity, has gained significant attention. These stimuli-responsive nanoparticles enable controlled drug release and targeted delivery, enhancing therapeutic efficacy while minimizing off-target effects (Lombardo, D et al., 2019).

10.1.2. Combination Therapies: Nanoparticle-based combination therapies, involving the co-delivery of multiple therapeutic agents with distinct mechanisms of action, have emerged as a promising strategy for overcoming drug resistance and improving treatment outcomes. Synergistic drug combinations delivered via nanoparticles offer enhanced efficacy and reduced systemic toxicity compared to mono therapy (Mokhtari, R et al., 2017)..

10.1.3. Theranostic Nanoparticles: Theranostic nanoparticles, integrating diagnostic and therapeutic functionalities within a single platform, enable real-time monitoring of treatment response

and personalized therapy. These multifunctional nanoparticles facilitate non-invasive imaging of tumors, drug delivery tracking, and targeted therapy, leading to improved patient outcomes and treatment optimization (Janib, S. M. et al., 2010).

10.2. Future Directions and Emerging Trends.

10.2.1. Personalized Medicine: The integration of nanotechnology with personalized medicine approaches holds great promise for tailoring cancer therapy to individual patients' genetic, molecular, and physiological characteristics. Nanoparticle-based drug delivery systems enable precise targeting, controlled drug release, and real-time monitoring, facilitating personalized treatment regimens and improving patient outcomes (Mura, S., & Couvreur, P. 2012).

10.2.2. Nanomedicine Platforms: Advances in nanomedicine platforms, such as lipid-based nanoparticles, polymeric nanoparticles, and inorganic nanoparticles, continue to drive innovation in cancer therapy. These versatile platforms offer tunable properties, including size, surface charge, and drug loading capacity, allowing for customized drug delivery systems tailored to specific cancer types and patient needs(Cruz, M. A. et al., 2022). .

10.2.3. Immunotherapy: Nanoparticle-based immunotherapy approaches, including cancer vaccines, immune checkpoint inhibitors, and chimeric antigen receptor (CAR) T-cell therapies, are gaining momentum in cancer treatment. Nanoparticles can enhance the delivery and presentation of immunomodulatory agents to immune cells, promoting antitumor immune responses and overcoming immunosuppressive mechanisms within the tumor microenvironment (Schumacher, T. N., & Schreiber, R. D. 2015).

10.2.4. Targeted Drug Delivery to Tumor Microenvironment: Future advancements in nanoparticle-based drug delivery systems will focus on targeting the complex and dynamic tumor microenvironment, including tumor vasculature, extracellular matrix, and immune cell populations. Engineering nanoparticles with specific ligands and surface modifications will enable precise targeting of key components within the tumor microenvironment, enhancing therapeutic efficacy and overcoming resistance mechanisms (Benoit, D. S. W., & Koo, H. 2016).

11. Conclusion

The review highlights the significant impact of nanoparticle-based drug delivery systems on revolutionizing cancer therapy and improving patient outcomes. Key findings and insights have been presented, demonstrating the versatility, efficacy, and potential of nanoparticle-enhanced drug delivery systems in addressing various challenges associated with conventional cancer treatments.

From the development of smart nanoparticles capable of targeted drug delivery to the integration of theranostic functionalities for real-time monitoring of treatment response, recent advancements in nanoparticle-based drug delivery systems have showcased remarkable progress in enhancing therapeutic efficacy while minimizing systemic side effects. Furthermore, the exploration of combination therapies and immunotherapy strategies using nanoparticle platforms has opened new avenues for overcoming drug resistance and improving treatment outcomes in cancer patients.

Looking ahead, the potential of nanoparticle-enhanced drug delivery systems in personalized medicine holds great promise for tailoring cancer therapy to individual patient needs, optimizing treatment regimens, and maximizing therapeutic efficacy. By leveraging nanotechnology platforms, researchers can continue to innovate and refine nanoparticle formulations to target the dynamic and heterogeneous nature of cancer, ultimately transforming the landscape of cancer therapy.

In conclusion, nanoparticle-based drug delivery systems represent a paradigm shift in cancer treatment, offering unprecedented opportunities to revolutionize therapy approaches and improve the lives of cancer patients worldwide. As research advances and technology evolves, the continued exploration and refinement of nanoparticle-based drug delivery systems will play a pivotal role in shaping the future of cancer care, ushering in an era of precision medicine and personalized treatment strategies.

Author contributions

M.R., K.H., D.J.L. conceptualized, reviewed, wrote and drafted the manuscript.

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