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Review Paper

Targeted Nanoparticle-Based Drug Delivery Systems: Enhancing Therapeutic Efficacy in Cancer Treatment

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ABSTRACT

Cancer remains a significant cause of illness and death globally, regardless of the level of human development. One key strategy in cancer treatment is the targeted delivery of drugs directly to tumor sites. Recent advancements in nanotechnology have opened new avenues for researchers to enhance cancer therapies. Nanoparticles are defined as particles with a size smaller than 0.1 µm, or 100 nm. They play a crucial role in improving the delivery and uptake of medications in targeted cells. There are two primary methods for synthesizing nanoparticles: the bottom-up method and the top-down method. When it comes to delivering therapeutic nanoparticles to targeted areas, two main strategies are utilized: passive targeting and active targeting. Passive targeting relies on the natural accumulation of nanoparticles within solid tumors, while active targeting enhances the binding of nanoparticles to specific antigens.

INTRODUCTION

Cancer comprises a range of disorders characterized by atypical cell proliferation, often leading to metastasis in different regions of the body. Globally, cancer-associated death rates come second after the deaths related to cardiovascular system diseases and are considered the most critical global health issue. Consequently, the discourse surrounding cancer treatment has become a collaborative effort among healthcare professionals and researchers[1,2]. Currently, there are very few treatment options available for cancer, primarily limited to therapies like chemotherapy. One of the widely used treatments

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for cancer faces an issue: its lack of specificity for tumor cells, which results in challenges and restrictions. Additionally, the intricate nature of tumor microenvironments and structures can complicate the development of new, effective treatment alternatives[3,4]. Transporting pharmaceutical substances to their intended locations poses a significant challenge in various cancer treatments. To address this issue, there has been remarkable advancement in research and application within the fields of nanoscience and nanotechnology. These technologies are utilized for both the diagnosis and treatment of health conditions[5]. Nanoparticles are defined as particles with dimensions smaller than 0.1 µm or 100 nm[6]. In the context of drug delivery, larger nanoparticles (greater than 100 nm) might be required to carry an adequate quantity of the drug. Furthermore, in drug delivery systems, not only can engineered particles serve as carriers, but the drug itself can also be designed at the nanoscale, effectively acting as its own "carrier"[7]. The makeup of these engineered nanoparticles can differ. Source materials can originate from biological sources such as phospholipids, lipids, lactic acid, dextran, or chitosan. Alternatively, they can possess more industrial characteristics, including various polymers, carbon, silica, and metals[8,9]. Nanoparticles (NPs) serve as effective radiosensitizers in medical fields, particularly in drug delivery and cancer treatment[10]. Depending on the nanoparticle's overall shape, these can be classified as 0D, 1D, 2D or 3D [11] For instance, gold nanoparticles (Au NPs) are noted for their effectiveness in enhancing radiation therapy in these medical applications[12]. In this article, we explore the application of nanoparticles as a method for delivering drugs in the treatment of cancer. The goals of using nanoparticles to encapsulate drugs include improving delivery to and absorption by target cells, as well as minimizing the toxicity of the unbound drug to non-target organs[13]. Achieving these objectives will enhance the therapeutic index, which is the difference between doses that provide therapeutic benefits, such as killing tumor cells, and those that cause damage to other organ systems. To accomplish these goals, it is essential to develop nanoparticles that are long-lasting and specifically targeted [7].

Method of nanoparticles synthesis:

The nanoparticles vary in shape, size, and structure. To create them, various synthesis techniques are used, which can be primarily grouped into two main categories: 1) the bottom-up approach and 2) the top-down approach. Each of these methods can be further divided into different subclasses depending on the specific reaction conditions [14] and processes involved listed in Table No. 1 The top-down approach involves shaping larger materials using either subtractive or additive techniques to create nano-sized structures. Various methods exist for producing nanostructures via this approach [15]. Conversely, the bottom-up method constructs nanostructures by assembling single atoms or molecules. This technique allows for the controlled arrangement of atoms or molecules as they form the desired nanostructures, typically in the range of 2 to 10 nanometres [16]. Material design and size serves as the foundation for nanotechnology, aiming to develop drug delivery systems specifically for tumor treatment [17]. We have broadly classified the materials currently being developed into several categories: polymeric nanoparticles (both natural and synthetic), liposomes, micelles, hydrogels, exosomes, and other extracellular vesicles. This includes natural membrane-coated nanoparticles, such as blood cell nanoparticles, leukocyte-based carriers, and platelet-derived materials, as well as viruses and inorganic nanoparticles, like mesoporous silica, gold nanoparticles, and carbon nanomaterials [18,19]

Polymeric nanoparticles:

Polymeric nanoparticle are largely used type of nanoparticle due to their small size ranging from 10 to 100 nm [20]. These nanoparticles offer several advantages as drug delivery systems, including the ability to enable controlled release, safeguard therapeutic agents and biologically active molecules from environmental degradation, enhance bioavailability, and improve the therapeutic index [21,9]. Typically, polymeric nanoparticles can be categorized into three main types: synthetic polymers, natural materials, and hybrid combinations that integrate both synthetic and natural elements to full-fill diverse functionalities [22].

Liposomes:

Liposomes are spherical structures that form spontaneously and feature membranes made of phospholipid bilayers. Their size can vary from 25 nm to 10μm, depending on the method of preparation [23]. Investigated as potential drug delivery vehicles for over five decades since their discovery by Bangham, liposomes have shown promise [24]. However, conventional liposome-based drug delivery systems face limitations due to their brief circulation time in the bloodstream, largely because of rapid clearance by macrophages in the reticuloendothelial system (RES) [25]. Innovations in the form of second-generation polymer-coated liposomes have significantly extended blood circulation times, enhancing them from just a few minutes to as long as three days [24,25].

Table No. 1 Categories of Bottom-Up and Top-Down Types of Nanoparticle Synthesis [26,27]

Nanoparticls Synthesis	Bottom-Up	1) Chemical	chemical reduction Co-precipitation Sol-Gel Electrochemistry Photochemical Reduction Reverse Micelles
		2) Biological	Bacteria Ex. Fusarium acidovorans fungi Ex. Fusarium oxysporum Plant Plant Ex. Acalypha indica Yeast Ex. Saccharomyces pombe Virus Ex. TMV (Tobacco Mosaic Virus) Algae Ex. Chlorella vulgaris
	Top-Down	1) Physical	Vaporization Lithography Laser Ablation Spray Pyrolysis Photoirradiation Ultrasonication

Polymeric Micelles:

Polymeric micelles arise from the self-assembly of amphiphilic di- or tri-block copolymers into nanosized core/shell structures in aqueous environments. Recent research has highlighted the potential of certain micelle-based anticancer treatments as effective drug carriers in oncology [28,29]. Genexol-PM (PEG-poly (D, L-lactide)

paclitaxel) represents the inaugural polymeric micelle formulation of paclitaxel. Notably, it is free from Cremophor, a component found in other paclitaxel formulations containing polyethoxylated castor oil. Additionally, there is ongoing development of multifunctional polymeric micelles that incorporate targeting ligands, as well as imaging and therapeutic agents [30,31].

Nanogels (Hydrogels):

Nanogels (Hydrogels): Nanogels are three-dimensional hydrogel substances at the nanoscale created through cross-linked, swellable polymer networks [32]. They impressively retain water without dissolving in the surrounding liquid. These nano gels merge the properties of nanoparticles and hydrogels, with sizes ranging between 20 and 200 nm [33]. Hydrogels are renowned for their outstanding biocompatibility, biodegradability, and capabilities in drug loading and controlled drug release [34]. Consequently, they find extensive application in treatments such as radiotherapy, chemotherapy, immunotherapy, hyperthermia, photodynamic therapy, and photothermal therapy [35].

Delivery of Therapeutic Nanoparticles at Targeted Site:

Passive Targeting:

The term "passive targeting" is frequently utilized in nanomedicine to refer to the observation of nanoparticle accumulation in solid tumors. In contrast to passive targeting nanoparticles, active targeting nanoparticles are engineered with specific nanoparticle surface ligands [36]. As tumors expand and begin to exceed the available oxygen and nutrient supply, they emit cytokines and various signaling molecules that stimulate the formation of new blood vessels in a process known as angiogenesis [37]. The blood vessels formed during angiogenesis in tumor tissues have gaps ranging from 600 to 800 nm between neighboring endothelial cells, unlike the tightly connected vessels found in normal tissues [38,36]. This flawed vascular structure, combined with inadequate lymphatic drainage, leads to an enhanced permeability and retention (EPR) effect. The EPR effect occurs due to the fact that tumors have a high demand for blood flow to provide the necessary nutrients and oxygen for their uncontrolled cell growth [12,39]. They tend to accumulate preferentially in the tumor interstitium. Generally, the degree of NP accumulation in tumor tissues is influenced by several factors, including the properties of the nanoparticles size, surface properties, circulation half-life, and the level of angiogenesis present in the tumor[40]. It is believed that nanoparticles sized between 10 and 100 nm are most effective for tumor accumulation. Proper surface properties and extended circulation times of nanoparticles can enhance their uptake by tumors, as previously noted. The unmodified phospholipid surface of liposomes tends to attract plasma proteins, leading to their identification by the mononuclear phagocytic system (MPS) and resulting in quick removal from the bloodstream. This characteristic hinders the effective distribution of drugs carried by liposomes to solid tumors[41,42]. Surface-modified (stealth) liposomes address the issue of rapid clearance, resulting in liposomes with a notably longer half-life in circulation and reduced clearance rates [43]. Passive targeting leverages the natural size of nanoparticles along with the distinct characteristics of tumor blood vessels [44].

Active Targeting:

Active targeting plays a crucial role in the effective delivery of drugs. This process utilizes affinity ligands to enhance the binding of nanoparticles (NPs) to antigens that are overexpressed on the membranes of diseased cells or to extracellular matrix proteins present in disease tissue [52]. Actively targeted NPs can be applied in scenarios where drug release occurs either outside or inside the cells. This approach markedly increases the

amount of drug that reaches the target cells compared to free drugs or passively targeted nano systems. The first instances of targeted NPs appeared in the 1980s, focusing on modifying the surfaces of liposomes with monoclonal antibodies (mAbs) that specifically recognized antigens on target cells. To date, 30 mAbs have received clinical approval, with Muromonab-CD3 (OKT3), an immunosuppressive agent, being the first to be authorized in 1986[53]. Although targeted nanoparticles may not consistently enhance drug accumulation in tumors relative to non-targeted nanoparticles, they do offer improved intracellular drug delivery to cancer cells, resulting in a significant boost in antitumor effectiveness [54].

The nanoparticles listed in Table No. 2, which have been utilized clinically, primarily leverage the enhanced permeability and retention (EPR) effect of tumors and their microenvironments for selective delivery [55]. Various targeting elements have been integrated into drug delivery systems, including antibody fragments, peptides, phage display-identified sequences, small molecules, or aptamers. Below, detailed descriptions of some actively targeted NPs are provided to illustrate the ligands involved [55].

Table No.2 List of some Nanoparticles which use clinically

Type of Nanoparticle	Name and Refs	Therapeutic agent
Liposomes	DaunoXome[45,24]	Dox
Polymeric micelles	Genexol-PM[46,24]	Paclitaxel
Polymer-drug conjugate based nanoparticles	Xyotax[47,48,49]	Paclitaxel
Albumin-based nanoparticles	Abraxane[50,51]	Paclitaxel

Antibodies:

Monoclonal antibodies (mAbs) or their fragments, such as Fab' and single-chain Fv (scFv), have been extensively employed as ligands to target cancer cells that express specific receptors. Poly (lactic-co-glycolic acid) (PLGA) NPs linked with mAbs were targeted specifically to MCF10A neo T cells, while uncoated NPs dispersed randomly [56]. In another study, mAb 2C5-modified PEGylated liposomes exhibited a three- to eight-fold increase in binding and uptake across various cancer cell lines from different origins, demonstrating higher cytotoxicity toward multiple cancer cells and significant therapeutic advantages compared to control liposomes (those modified with a nonspecific IgG). Nonetheless, to reduce immunogenicity and avoid clearance through Fc receptor-mediated processes, fragments like Fab' and scFv are often preferred over whole mAbs. Kou et al. created PLGA NPs coated with the SM5–1 monoclonal antibody (scFv), which improved in vitro cytotoxicity against human hepatocellular carcinoma cell lines and led to significant tumor growth inhibition and regression [57,58]. Herceptin® is a therapeutic antibody designed to target the human EGF receptor-2 (HER2), which is often found in excess on the surfaces of breast cancer cells [59,60]. Research involving anti-HER2 immunoliposomes, which are created by linking anti-HER2 antibody fragments to PEGylated liposomes, has indicated that these immunoliposomes can effectively deliver drugs into cells through mAb-mediated endocytosis. In contrast, nontargeted liposomes tend to be mainly located in the extracellular stroma or within macrophages [59]. Additionally, DOX-loaded anti-HER2 immunoliposomes demonstrated a considerable antitumor effect in comparison to nontargeted liposomes [61]. Nevertheless, despite the reported high uptake of these immunoliposomes, the significance of active targeting remains uncertain. Indeed, the same study presented evidence of similar high accumulation levels in tumor tissue between anti-

HER2 immunoliposomes and nontargeted liposomes in HER2-overexpressing breast cancer xenografts (BT-474). As a result, targeted nanocarriers did not enhance tumor accumulation when compared to their nontargeted counterparts. One factor that may explain the minimal accumulation observed relates to the model utilized in the study, which focused on tumor cells rather than tumor endothelial cells, the intended target. Another possible reason is the high density of ligands present on the nanoparticle (NP) surface. The excessive presence of active ligands can inhibit the long-circulation capabilities of PEG, resulting in a quicker removal of NPs from the bloodstream. Furthermore, several considerations must be addressed when using antibodies as targeting agents [62,63], including:

• The method of conjugation for attaching antibodies to nanocarriers

• The impact of freely circulating antibodies [62].

Advantages of Nanoparticles in Cancer Therapy

The application of nanotechnology in cancer diagnosis, treatment, and management has ushered in a transformative era. Nanoparticles (NPs), whether through active or passive targeting methods, enhance the concentration of drugs within cells while minimizing toxicity to healthy tissues. These targeted NPs can be engineered to be pH-sensitive or temperature-sensitive, allowing for controlled drug release. The pH-sensitive delivery system is particularly effective in delivering drugs within the acidic tumor microenvironment (TME). Likewise, temperature-sensitive NPs release drugs at the target site due to temperature changes induced by methods like magnetic fields and ultrasound [64,65]. Moreover, the "physicochemical properties" of NPs—such as their shape, size, molecular weight, and surface chemistry—play a critical role in drug delivery targeting. NPs can be customized to suit specific targets and direct themselves towards particular molecules. Traditional chemotherapy and radiation treatment come with several limitations, particularly concerning their effectiveness and side effects stemming from uneven distribution and cytotoxicity. Consequently, careful dosing is necessary to kill cancer cells while keeping toxicity to a minimum [66,67]. To reach their target, drugs must navigate through various barriers. Drug metabolism is complex; under physiological conditions, a drug must traverse the TME, the reticuloendothelial system (RES), the blood-brain barrier (BBB), and undergo kidney filtration. The RES, which includes "blood monocytes, macrophages, and other immune cells," reacts with drugs in the liver, spleen, or lungs, activating macrophages and leukocytes that swiftly eliminate the drug, resulting in a shortened half-life. To address this, NPs with "surface modification," such as polyethylene glycol (PEG), can circumvent this mechanism, extending the "drug half-life." Additionally, kidney filtration plays a vital role in reducing NP-related toxicity [68,69]. The blood-brain barrier (BBB) serves as a specialized protective structure designed to shield the central nervous system (CNS) from harmful substances [70]. It comprises "brain capillary endothelial cells" that form a barrier ensuring essential nutrients reach the brain while limiting access to toxic agents. As a result, current chemotherapy options for brain cancer are primarily limited to intraventricular or intracerebral infusions. In contrast, NPs have the ability to cross the BBB. Various techniques, including the enhanced permeability and retention (EPR) effect, focused ultrasound, peptide-modified endocytosis, and transcytosis, are utilized for NP delivery. For instance, glutathione-PEGylated liposomes loaded with methotrexate demonstrated improved methotrexate uptake in rats. Gold NPs (Au-NPs) are commonly employed due to their effectiveness in drug transport and the induction of apoptosis [71,72]. Additionally, NPs

as carriers enhance drug stability by preventing the degradation of the loaded substances, allowing for a larger volume of drugs to be encapsulated without chemical reactions. Dry solid dosage forms are generally more stable compared to nano liquid formulations. Stabilizers can further enhance this stability, and utilizing porous NPs is another strategy for improving stability [14,73]. Tumors exhibit distinct pathophysiological features, such as significant angiogenesis, irregular vascular structures, and poor lymphatic drainage [74]. Nanoparticles (NPs) take advantage of these characteristics to effectively target tumor tissues. Because of reduced venous return and ineffective lymphatic clearance in tumor regions, NPs are more readily retained, a phenomenon known as the EPR effect. Additionally, focusing on nearby tissues can enhance tumor localization [39]. NPs can be delivered via various methods, including oral, nasal, parenteral, and intraocular routes. With their high surface-to-volume ratios and capability for cellular uptake, NPs have shown superior effectiveness compared to microparticles when used as drug carriers [75].

Significant Challenges in the Clinical Application of Nanoparticles:

It is widely recognized that the tumor microenvironment (TME) contributes significantly to the unsatisfactory outcomes observed in nanomedicine therapies [76]. The TME, which comprises malignant cells, tumor-associated fibroblasts (CAFs or TAFs), various immune cells, and the stroma (including blood vessels and the extravascular matrix), plays a crucial role in the resistance of cancer to treatment [77]. Currently, with the rapid advancement of nanotechnology, there has been a dramatic increase in the knowledge and research surrounding nanoparticles. However, only a limited number of these nanoparticles progress to clinical trials, with most remaining at the in vivo and in vitro phases [78]. The approval rate for new nano-drugs is below 10%, and concerns regarding biosafety are rising. Each unique nano formulation encounters specific hurdles in clinical translation, yet many nanoparticles face common obstacles that can be classified into biological, technological, and study-design-related categories [79]. Additionally, one intricate challenge is bypassing the “mononuclear phagocytic system (MPS).” In biological fluids, nanoparticles adsorb proteins, forming a protein corona that facilitates uptake by the MPS. To avoid this, nanoparticles have been coated with substances intended to prevent protein corona formation, yet these methods have not yielded substantial results [80]. Developing nanoparticles that specifically target macrophages and utilizing them as novel drug carriers may help address this issue. Presently, strategies such as preventing macrophage recruitment, depleting and reprogramming tumor-associated macrophages (TAMs), and blocking the “CD47-SIRPα pathways” are commonly employed [14]. Another concern includes the production of nano drugs, as large-scale synthesis of nanomedicines continues to pose a significant challenge. While these obstacles may seem daunting, with focused efforts, progress can be achieved [81,82].

CONCLUSION:

In conclusion, the use of nanomedicine for cancer treatment is on the rise, as nanotechnology offers numerous benefits that align well with the needs of tumor therapy. Ideally, therapeutic vectors based on nanotechnology should precisely transport their payloads directly into tumors and then safely degrade without causing side effects. To make better use of nanotechnology in the fight against cancer, several efforts are necessary, including establishing foundational principles, designing suitable materials, creating animal models, and gaining a deeper understanding of the biological characteristics of tumors

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