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REVIEW ARTICLE

NANOCARRIER SYSTEMS FOR TARGETED CANCER THERAPY: RECENT ADVANCES AND TRANSLATIONAL PERSPECTIVES

Egno Gerald Komba[1], Said Salim Said*[2], Febronia Mkama Alphonce[2]
[1]*Jagiellonian University Medical College, Kraków, Poland.*
[2]*Zanzibar Food and Drug Agency, Zanzibar, Tanzania.*

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***Address for Correspondence:**
Said Salim Said, Zanzibar Food and Drug Agency, Zanzibar, Tanzania.
Tel: +255-777594 373
E-mail: *saidalriyamy67@gmail.com*

Abstract

Cancer is one of the major concerns in the world today, and it accounts for almost 20 million new cases and 10 million deaths annually, leading to significant disability-adjusted life years lost. The total incidence of lung, breast, colorectal, prostate, and stomach cancer accounts for almost half of the total cancer incidence cases worldwide. The burden of cancer is high in low- and middle-income countries, where the mortality and incidence rate is high due to delayed diagnosis and lack of access to efficient treatments. The burden of cancer is expected to rise in the future due to the increasing population and the aging population in the world, and cancer incidence rates are expected to rise in the year 2040 in resource-constrained countries. The burden of cancer is related to cancer types and their association with certain preventable factors and infecting agents; however, the incidence rate of cancer types is escalating, and hence, precise and efficient cancer therapies are the need of the hour. The limitation in traditional cancer therapies, such as chemotherapy, is systemic toxicity, lack of specificity of drugs, and low drug bioavailability, and hence, cancer therapies using nanotechnology show immense promise, especially drug delivery systems such as liposomes, polymeric nanoparticles, dendrimers, micelles, solid lipid nanoparticles, and inorganic nanoparticles. The review aims to critically discuss the construction of nanocarriers, cancer cell targeting, and cancer therapy, and the challenges in cancer nanotherapy.

Keywords: Cancer therapy, polymeric micelles, stimuli-responsive nanoparticles, targeted drug delivery.

INTRODUCTION

Cancer, a significant global health issue, still ranks as one of the leading causes of morbidity and mortality. According to the most recent available statistics, nearly 20 million new cancer cases are diagnosed annually, and mortality from cancer reaches as high as 9.7 to 10 million, or approximately 14 to 15% of total deaths worldwide, contributing substantially to Disability-Adjusted Life Years (DALYs)[1-3]. A small number of cancer types are responsible for a significant number of cancer cases. Breast cancer in women, lung, colorectal, prostate, and stomach cancer combined account for nearly half of all new cancer cases. In terms of cancer mortality, lung cancer leads, followed by colorectal, liver, breast, and stomach cancer, in that order[4]. Although incidence rates are higher in high-income or "transitioned" countries, the outcomes are worse in low- and middle-income countries, where mortality-to-incidence ratios and DALY rates are higher, indicating a lag in diagnosis and a lack of comprehensive medical care. Because of the size of the population and the incidence of gastrointestinal cancer, Asia carries the greatest burden of cancer. Meanwhile, countries that are "transitioning" socially and economically, such as those in Africa, Latin America, and South-Central Asia, are witnessing a rapid increase in colorectal and breast cancer[5,6]. The growth of the world population and the aging of populations are expected to fuel this growth, and predictions are that there will be a 47% increase in cancer cases by the year 2040, or approximately 28 to 29 million, and as high as 35 million by the year 2050, especially in resource-constrained countries[1,4,7]. A significant percentage of cancer cases are associated with modifiable risk factors. Tobacco, obesity, diet, inactivity, and alcohol, as well as oncogenic infections, such as Helicobacter pylori, hepatitis B and C, and human papillomavirus, are estimated to be responsible for 40 to 45% of cancer deaths[8,9].

Despite all the preventive measures, the incidence of cancer is on the rise worldwide[10]. The therapeutic

options that are currently available for the treatment of cancer include surgery, radiotherapy, cytotoxic chemotherapy, molecularly targeted therapy, immunotherapy, and endocrine therapy. Among these options, chemotherapy is believed to be the mainstay in the treatment of cancer[11]. However, the efficacy of chemotherapy is limited because of the high toxicity, low bioavailability, and low specificity of the drugs that are used in the treatment of cancer[12]. The low water solubility of the drugs used in chemotherapy has also restricted the optimal use of the drugs in the treatment of cancer. In addition, the problem of multidrug resistance is also an impediment in the treatment of cancer[13]. Recently, the application of nanotechnology has opened up new avenues in the treatment of cancer[14]. This has led to the development of nanoscale drug delivery systems that have provided precise targeting of the drugs[15]. This has led to an enhancement in the pharmacological effects. In addition, nanotechnology has opened up new avenues in the diagnosis and treatment of various diseases. The unique physicochemical properties of these particles allow them to be preferentially taken up in the tumor tissues, which in turn can be used for the targeted therapy of cancer[16]. In comparison to free drug formulations, it has also shown better therapeutic index/safety profiles in some cases[17]. Drug delivery systems with the help of nanocarriers have shown promise as an innovative tool to overcome the limitations of conventional drug delivery systems by directly addressing the limitations of conventional therapies. These include solubility, circulation time, and bio-distribution, which can be achieved through passive or active targeting[18]. Anticancer drugs can stay in systemic circulation for a long time before being retained in the tumor tissues, which can be taken up by cancer cells through receptor-mediated endocytosis[19]. This review is based on the current advances in nanocarrier-based drug delivery systems for cancer therapy, which includes targeting, surface engineering, and stimuli-responsive approaches, biological barriers, production, safety, and regulatory considerations, which are of utmost importance in developing intelligent nano medicine for cancer therapy in the future.

METHODS

An extensive literature search was conducted using online databases, including PubMed, Science Direct, Web of Science, SpringerLink, and Google Scholar. Key literature was identified by combining the following keywords: “nanocarriers”, “nanomedicine”, "targeted drug delivery”, “cancer therapy," “stimuli-responsive nanoparticles”, “polymeric micelles”, “liposomes”, “tumor targeting”, and “drug delivery systems”. Boolean operators, specifically “AND” and “OR”, were also used to refine the search strategy; for example, “nanocarriers AND cancer therapy”, and “polymeric micelles AND tumor targeting”. Literature was selected according to its relevance to the nanocarriers, targeting, stimuli-responsive nano-systems, and challenges in cancer therapy, with emphasis on the therapeutic performance and mechanism of action.

Targeted delivery strategies

Targeted drug delivery systems play an important role in cancer therapy. The aim is to achieve the highest possible effect from the drug and at the same time reduce its adverse effects on normal tissues. Nanocarriers can be engineered to carry various targeting ligands like antibodies, peptides, and aptamers that have the ability to bind to overexpressed targets on cancer cells[20]. Active targeting of nanoparticles involves surface functionalization of nanoparticles that carry targeting ligands that have the ability to specifically target specific targets on cancer cells, thus facilitating receptor-mediated endocytosis and delivery of the drug inside the cancer cells[21]. This will result in direct delivery of the drug to cancer cells and exclude normal tissues, thus reducing adverse effects. The pharmacokinetics and pharmacodynamics of drug-delivery particles will be influenced by parameters like particle size, chemistry, and surface charge[22]. Targeting agents that have the ability to bind specifically to targets that are overexpressed on cancer cells are crucial for targeting cancer cells[23]. Passive targeting utilizes the increased permeability and retention effect due to poor lymphatic drainage in cancer tissues, thus enhancing the accumulation of nanoparticles in cancer tissues[24]. Nanocarriers take advantage of the variations in the physiological microenvironment in the tumor area[25]. In addition, the passive targeting approach can be supported by the application of active targeting methods that make the most of the unique selectivity of the cancer cells[26].

Various factors influence the application of the most appropriate targeting methods in cancer therapy. The factors include the type of cancer, tumor micro-environment conditions, chemo- and/or radiation therapy modalities, and the degree of effect desired[27]. Combination targeting methods are becoming popular in cancer therapy. Combination targeting methods make the most of the benefits of various targeting methods and take it a step further. Combination targeting methods can be either passive or active targeting methods[28]. The application of either passive or active targeting methods will be beneficial in increasing the accumulation of the drug at the tumor site and off-target effects. The application of dual-targeted nanocarriers will be beneficial in increasing the specificity and avidity of the nanocarriers to the cancer cells[29]. The application of dual-targeted nanocarriers will be beneficial in the delivery of drugs to the tumor site[30]. The application of stimuli-responsive nanocarriers will be beneficial in the control of the release of the drugs at the tumor site.

Nanoparticle formulations

Nanoparticles in drug delivery systems vary in composition, size, and shape. Each nanoparticle will have its own benefits in the treatment of cancer. Several nanocarriers have been developed and studied for the targeted treatment of cancer. These nanocarriers are but a few: liposomes, polymeric nanoparticles, micelles, dendrimers, gold nanoparticles, and carbon nanotubes[30,31]. Of all the nanocarriers developed and

studied for the targeted treatment of cancer, liposomes are the most studied. Liposomes are small vesicles made up of lipid bilayers. The lipid bilayers are made up of natural and synthetic lipids. Liposomes are the most studied nanocarriers because they are bio-compatible and biodegradable and can encapsulate both hydrophilic and hydrophobic drugs[32,33].

Liposomes are one of the most developed nanocarriers in the clinical setting. In the clinical setting, several liposomal formulations have been developed and are FDA-approved for the treatment of cancer and infectious diseases. The development and approval of these formulations are evidence of the biocompatibility and biodegradability of liposomes and the ability of liposomes to encapsulate both water-soluble and water-insoluble drugs[34]. However, conventional liposomes are known to have the drawback of low drug encapsulation efficiency, leakage of the encapsulated drugs during storage, and rapid clearance[35]. The mechanical and chemical instability of the membrane also make it difficult to produce liposomes in the industrial setting[36]. In the clinical setting, liposomes have been reported to cause activation of the complement system that results in pseudoallergy and accumulation in the liver and spleen[37]. The accumulation of liposomes in the liver and spleen and the disruption of the membrane have been reported to be harmful and require careful optimization of the composition of the liposomes[38].

Polymeric nanoparticles: can be made from natural or synthetic polymers and in the form of different sizes, shapes, and surface functionalization that is able to have preferential or targeted drug release. Polymeric nanoparticles are usually made from biodegradable polymers and can deliver a drug in a controlled way and at a controlled delivery rate. So, the polymeric nanoparticles' release can be designed to release the drug in a sustained manner, extending the therapeutic window[39]. They can incorporate targeting ligands and stealth coatings to exploit passive and active tumor targeting[40,41]. Nonetheless, only a small subset has reached clinical trials, largely because rapid uptake by the reticuloendothelial system (RES) depletes circu-lating dose before tumor accumulation, constra-ining efficacy[41,42]. Stealth strategies (e.g., PEGylation) reduce but do not abolish RES sequestration and can introduce anti-PEG immunity[40]. Additional barriers include complex, multi-step syntheses, batch-to-batch variability, scale-up difficulties, and lingering concerns over polymer degradation products and long-term safety[42,43].

Polymeric micelles: are self-assembled aggregates of amphiphilic copolymers that significantly improve the solubility and systemic delivery of hydrophobic drugs. They consist of a hydrophobic core that encapsulates poorly soluble therapeutics and a hydrophilic shell that enhances stability and prolongs circulation in the bloodstream, and several micellar formulations have progressed into clinical trials[36,40,44]. Stimuli-responsive designs (pH, redox, light) enable controlled release at tumor sites[43]. However, micelles often exhibit limited kinetic and thermodynamic stability in the bloodstream, leading to premature disassembly and drug release upon dilution and interaction with serum components[36,45]. Their nanoscale size favors renal clearance and RES uptake, which together reduce tumor deposition[36,46]. Restricted tumor penetration, potential polymer related cytotoxicity, and manu-facturing challenges in achieving uniform, stable assemblies further constrain robust clinical translation[43,45,46].

Similarly, dendrimers are mono-disperse, hyperbra-nched macromolecules with precisely controllable size and dense surface functionality, enabling high drug/ligand loading and sophisticated architectures such as conjugates, Janus structures, and linear dendritic hybrids[47,48]. They improve solubility, enable multivalent targeting, and can be engineered for BBB penetration[47,49]. Yet, despite decades of research, clinical translation remains limited, with very few formulations progressing beyond early phase trials[50,51]. The key barriers include synthetic complexity and cost, regulatory discomfort with heterogeneous surface conjugation, and toxicity associated with cationic surfaces, including hemolysis and complement activation, which necessitate extensive surface shielding (e.g., PEGylation)[50]. Industrially, low drug to carrier mass ratios and challenges in scalable, reproducible multi functionalization reduce comer-cial attractiveness[50,51].

Gold nanoparticles: (AuNPs) are attractive for chemical stability, straightforward synthesis, and facile surface modification, with applications in photothermal therapy, imaging, and theranostics[36,40]. Their high atomic number affords strong contrast in CT imaging, and dense surface chemistry supports multivalent ligand display. Clinically, however, AuNPs exemplify the broader concerns with inorganic carriers: they are non-biodegradable and prone to long-term accumulation in organs, especially the liver and spleen, raising chronic toxicity concerns[40]. Size and surface chemistry strongly influence RES uptake and clearance, but complete elimination is rarely achieved. Unresolved issues regarding long-term fate, potential immunotoxicity, and regulatory caution toward persistent inorganic materials significantly limit broad therapeutic deployment, particularly for non-life-threatening indications[36,40].

Quantum dots: (QDs) offer exceptional fluorescence brightness, photostability, and tunable emission, enabling multiplexed imaging and theranostic designs[52]. Surface modification improves aqueous dispersibility and targeting capability. Nonetheless, most QDs contain heavy metals (e.g., Cd, Pb), and are non-biodegradable, leading to concerns about cytotoxicity, oxidative stress, and long-term tissue retention. Toxicity to lung cells and induction of oxidative damage have been documented, even with coated structures[36]. These safety issues, coupled with stringent regulatory scrutiny and availability of safer organic or inorganic imaging alternatives, mean that the clinical prospects of QDs as systemic nanocarriers are currently limited, with use largely confined to preclinical imaging and *ex vivo* diagnostics[36,40].

Carbon nanotubes: cylindrical structures composed of rolled-up graphene sheets, possess high surface area and mechanical strength, enabling efficient drug loading and targeted delivery to cancer cells[53]. Carbon nanotubes (CNTs) possess extraordinary surface area, mechanical strength, and ability to traverse cell membranes, enabling high drug loading and potential use in photothermal/photodynamic applications[36,40]. Their one-dimensional geometry and modifiable surfaces make them attractive multifunctional platforms. However, pristine CNTs display poor aqueous solubility, low biodegradability, and significant toxicity, including inflammation, fibrosis, and asbestos like pathology in some *in vivo* models[36]. Functionalization can improve dispersibility and reduce acute toxicity, but does not fully address bio-persistence and long-term accumulation, particularly in lungs and reticuloendothelial organs[36,40]. These safety and bio-persistence concerns, combined with manufacturing heterogeneity (length, diameter, residual catalysts), have sharply constrained clinical translation, relegating CNTs largely to exploratory research rather than near-term pharmaceutical development[40] .

Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers have been recognized as an innovative approach in cancer therapy. Stimuli-responsive nanocarriers respond to stimuli that are present in the tumor microenvironment. The stimuli include pH levels, redox potential, and enzyme activity[54]. They respond either to internal stimuli, which include reduced pH levels in tumor tissues, or external stimuli, which include light or temperature. The utilization of external stimuli enables the development of an accurate and precise drug delivery system[55]. The release of drugs is carefully controlled in order for them to be delivered at appropriate times in appropriate locations in the tumor microenvironment[56]. For example, pH-responsive nanoparticles respond to the acidic nature of tumor tissues. The release of drugs is carried out in response to reduced pH levels in tumor tissues in comparison with normal tissues[57]. Moreover, redox-responsive nanoparticles respond to the high levels of glutathione in cancer cells. Glutathione is known to have the ability to cleave disulfide bonds, which enables the release of drugs. Enzyme-responsive nanoparticles respond to enzymes that have been upregulated in tumor tissues. They ensure that there is a localized release of drugs in tumor tissues[58]. The release of drugs is carried out using conditions that prevail in tumor tissues. This approach is beneficial in that it is not associated with systemic toxicity. Moreover, it is a phenomenon that is more likely in anti-cancer therapy[59]. Thermosensitive liposomes, which are temperature-sensitive nanoparticles, release drugs at appropriate temperatures. This is carried out using an external heat source, which is high-intensity focused ultrasound or near-infrared light[60]. The on-site release of drugs in response to temperature is beneficial in that it is likely to increase the therapeutic index. This is carried out by increasing the concentration of drugs at sites where they are needed. Moreover, thermosensitive nanoparticles have an advantage in that they allow for the modulation of release using external magnetic fields. This is carried out using magnetic nanoparticles[61]. Following this line of development, the use of stimuli-responsive nanomaterials in combination with external triggers, such as photothermal or hyperthermia induced methods, is proposed as a new avenue for the development of improved tumor-targeting systems with enhanced therapeutic effects[62]. Among such systems, bio-responsive nanogels are receiving increasing attention for their potential to efficiently encapsulate and release chemotherapeutic and biotherapeutic drugs, thus showing improved antitumor effects *in vitro* and *in vivo*[63]. Another type of nanosystem, namely, hydrogels, with their high water content and mechanical properties, is also emerging as a promising tool for tumor treatment, particularly due to their stimuli-responsive properties, which enable them to react to various stimuli in the tumor environment[64]. These complex nanosystems, such as those using phase-change materials and copper sulfide nanocrystals, can be used for both endogenous and external stimuli-induced drug release, as well as for synergistic chemo- and photothermal treatments for enhanced tumor inhibition[65]. The versatility of such nanosystems, which can be externally regulated using a magnetic field for their accumulation in the tumor area, is proposed as a new avenue for the development of a versatile drug delivery system using cytostatics for tumor treatment[66]. This method is particularly useful, as the nanoparticles are not affected by the blood flow in the vessel, thus enabling their immobilization in the desired area[67]. Magnetic implants, in particular, can be incorporated in areas of tissues that are affected, providing localized treatment of cancer in bones through the provision of a driving force for drug delivery[68]. These are considered an advanced form of drug delivery systems, moving beyond conventional means of drug delivery. The discovery of smart materials, especially those with an ability to sense internal and external triggers, has greatly impacted drug delivery systems[69]. These materials allow for the spatially and temporally controlled release of drugs, which are encapsulated in these systems. This is considered an improvement in drug delivery systems, enhancing their efficacy and reducing systemic toxicity. These systems should allow for controlled mechanisms of drug uptake and release to function as efficient drug delivery systems. Ideally, these systems should also have theranostic properties. Further advancements in this field include the discovery of magnetic nanogels, which can be used to turn drug delivery systems on and off rapidly using oscillating magnetic fields[70]. This is considered an improvement in drug delivery systems, providing precise control of drugs. In addition, these systems can be used to overcome multidrug resistance in cancer cells[71]. This is considered an advantage of these advanced systems of drug delivery. Various nanocarriers, such as dendrimers, organic micelles, metal oxide nano-particles, quantum dots, and inorganic mesoporous silica, have been used to overcome these challenges. Nanomedicines are considered an attractive option for cancer therapy[72]. These are considered an improvement

in drug delivery systems, enabling dynamic adjustments in therapeutic interventions in real-time[73].

Externally triggered smart materials show promise for precise therapy, but there are fundamental challenges. Delivering external stimuli to deep tissues is complex. Light-responsive and photothermal systems are limited by scattering and absorption, often restricting activation to superficial or endoscopically accessible areas unless invasive light guides are employed[74,75]. Magnetic fields, RF and ultrasound can reach deep sites, yet they require sophisticated applicators, real-time imaging and patient-specific modeling to achieve adequate field strength at the target while avoiding off-target heating or mechanical damage[76,77]. In hyperthermia-responsive systems, the therapeutic window is narrow: temperature-sensitive carriers must switch sharply within a few degrees around clinically achievable mild hyperthermia (39 to 43 °C), and their release kinetics must match feasible clinical heating protocols[78]. This demands careful integration of material design with realistic thermal dosimetry and stringent temperature constraints for normal tissues. In parallel, toxicological and stability issues of smart materials remain major translational bottlenecks. Different findings consistently underline that nano-platforms based on polymers, lipids, metals/metal oxides, and MOFs can show size-, composition, and surface-dependent organ accumulation, immunogenicity, and long-term uncertainty, and that the absence of standardized toxicity assessment and clear preclinical-clinical correlations is a key reason why complex stimulus-sensitive DDS have not yet reached routine clinical use[79,80]. Many smart hydrogels, nanogels, and thermo-responsive polymers also struggle with long-term physicochemical and functional stability: crosslinking density, degradation, and protein corona formation can alter swelling, mechanical integrity, responsiveness, and release profiles over time, especially in complex biofluids[74-81]. Dual- or multi-stimulus systems add further design and manufacturing complexity and may amplify failure modes if one component loses activity[82] .

Polysaccharide-based nanocarriers

Polysaccharide-based nanocarriers such as hyaluronic acid, chitosan, and alginate have been found to be of considerable interest in targeted cancer therapy because of their biocompatibility and biodegradability[83]. In addition, these materials have the ability to target the disease site. For instance, hyaluronic acid is a natural polysaccharide that binds with the CD44 receptor. CD44 is overexpressed in various cancer cells[84]. Therefore, this property of hyaluronic acid makes it useful in targeted cancer therapy and gene therapy[85]. Chitosan is another polysaccharide-based nanocarrier that is derived from chitin. Chitosan has mucoadhesive properties that make it useful in the permeation of drugs. Therefore, it can be used in the development of drugs that are intended for oral and transdermal delivery[86]. Alginate is an anionic polysaccharide that is obtained from brown algae. Alginate has the ability to form hydrogels under mild conditions. Therefore, it can be used in the encapsulation of drugs and cells[87]. The nanocarriers can be engineered in such a way that the release of the drugs is tailored. In this way, the dissociation of the drug and the nano-shell is prevented. This helps in the prevention of the dissociation of the drug from the nano-shell before it reaches the tumor site. In this way, the drugs are prevented from accumulating in the healthy tissues. This approach is quite useful in the enhancement of the therapeutic index because the concentration of the drugs is maximized at the tumor site[88]. In addition, the development of the nanocarriers with the appropriate size is quite useful in the enhancement of the therapeutic efficacy. The inherent characteristics of these polysaccharide-based nanocarriers, such as their low immunogenicity and their easily modifiable physicochemical properties, also render them suitable for diverse surface functionalization strategies to further enhance their specificity and drug loading capacity[67,89]. Biodegradable polyelectrolyte microcapsules, for example, are supramolecular structures that can be degraded by enzymes in viable cells under physiological conditions and thus present a highly potent strategy for targeted drug delivery of antineoplastic agents[90]. The potential of these polysaccharide-based nanocarriers also extends to their integration into intelligent drug delivery systems that can respond to tumor-specific cues and thus facilitate drug release in an ‘on-demand’ fashion[91]. Chitosan nanoparticles, for example, owing to their excellent biocompatibility and biodegradability, are now being explored as suitable platforms for the oral delivery of challenging therapeutic macromolecules and exhibit sustained and controlled release profiles[92]. These polymeric systems can be further optimized to include responsive elements that trigger drug release in response to tumor microenvironmental cues, such as pH, temperature, and concentration of enzymes[93].

To ensure the successful translation of these polysaccharide-based nanocarriers into the clinic, it is essential to consider the inherent heterogeneity of natural polysaccharide materials and their inherent complexity in drug delivery systems. Chitosan, alginate, fucoidan, hyaluronic acid, and pectin are examples of natural polysaccharides that exhibit source-dependent variability in molecular weight, degree of substitution, and charge density[94]. Such variability in their inherent properties can manifest as significant differences in nanoparticle size, drug loading capacity, and drug release characteristics, which can be problematic in large-scale production and drug approval[95]. In physiological media, many polysaccharide-based systems face colloidal instability under neutral pH and ionic strength; for example, chitosan nanocarriers may lose surface charge and aggregate or prematurely disassemble, necessitating stabilization strategies such as chemical modification, ionic or covalent crosslinking, or hybridization with synthetic polymers or inorganic components to preserve structural integrity and controlled release *in vivo*[96,97]. At the same time, polysaccharides are not pharmacologically inert excipients: marine and terrestrial polysaccharides can interact with immune cells and receptors, conferring valuable immunostimulatory or immunomodulatory properties that are

exploited in cancer immunotherapy, but also raising the possibility of unintended complement activation, cytokine release, or off-target immune responses, which depend sensitively on structure, dose, and formulation context[98,99].

Polymeric micelles as drug delivery systems

Polymeric micelles have surfaced as multifunctional nanoparticles and hold immense potential in various scientific domains[100]. Micelles are widely employed to enhance the efficacy and mitigate the harmful side effects of drugs, owing to their ability to extend circulation time and promote uptake via the enhanced permeability and retention effect[101]. Polymeric micelles, self-assembling nanostructures formed by amphiphilic polymers, present a unique platform for drug delivery due to their core-shell architecture, biocompatibility, and ability to solubilize hydrophobic drugs[102]. The hydrophobic core serves as a reservoir for drug encapsulation, while the hydrophilic shell stabilizes the micelle in aqueous environments and prevents opsonization by the immune system. Stimuli-responsive micelles can be designed to release their drug cargo in response to specific triggers, such as pH, temperature, redox potential, or enzymatic activity, enabling precise control over drug release at the tumor site. This targeted release mechanism can significantly improve therapeutic indices by concentrating drug delivery at pathological sites while minimizing systemic exposure and associated toxicities[103]. Despite these advantages, the *in vivo* stability of many micelle systems remains a challenge, often leading to premature drug release and non-specific tissue accumulation[104].

Moreover, Conventional self-assembled micelles are only thermodynamically stable above the CMC; after intravenous injection, strong dilution and interaction with serum proteins can drive dissociation, premature drug release, and loss of targeting advantages[105]. Achieving reproducible large-scale manufacturing with consistent drug loading, long-term colloidal stability, and well-characterized *in vivo* behavior remains difficult, especially for complex cross-linked or multi-stimuli responsive systems[106]. However, innovations in block copolymer design and cross-linking strategies are actively addressing these limitations, enhancing micellar integrity and prolonging systemic circulation (107). The physical entrapment of water-insoluble small molecules into the micelle core represents a highly feasible pathway for clinical translation[102]. For instance, polymeric micelles formed from amphiphilic block copolymers can significantly improve the solubility and bioavailability of hydrophobic anticancer drugs, facilitating their effective delivery to tumor tissues[108]. These nano scale carriers also exhibit prolonged circulation times and reduced systemic toxicity, contributing to improved therapeutic outcomes[109,110]. Specifically, doxorubicin-loaded mixed micelles have shown promise in enhancing anticancer sensitivity, demonstrating how tailored micellar formulations can augment therapeutic efficacy[111]. Furthermore, the precise control over drug release kinetics and the ability to selectively accumulate at diseased sites underscore the advanced capabilities of polymeric micelles in modern nanomedicine.

Surface modification and targeting ligands

Surface modification of nanocarriers with targeting ligands, such as antibodies, peptides, aptamers, or small molecules, enables selective recognition and binding to cancer cells, enhancing drug delivery and therapeutic efficacy[112]. Antibody-conjugated nanoparticles can target specific tumor-associated antigens, triggering receptor-mediated endocytosis and the subsequent release of intracellular drugs. Peptide-modified nanocarriers can bind to overexpressed receptors on cancer cells, facilitating targeted drug delivery and imaging. Aptamer-functionalized nanoparticles can recognize and bind to specific molecular targets on cancer cells, enabling targeted drug delivery and gene therapy. This active targeting approach, combined with the inherent benefits of nanocarriers, offers a pathway to significantly improve therapeutic outcomes and reduce systemic side effects in cancer treatment[113]. However, despite surface functionalization, nanocarriers still struggle with autonomous navigation to the target, necessitating further advancements in self-propelling and navigational functionalities for precise intracellular delivery and deep tissue penetration[114]. Further research is focusing on integrating microfluidic systems and external magnetic fields to guide these nanocarriers with enhanced precision, enabling real-time localization and release at the cellular level within complex biological environments[115]. This integrated approach promises to overcome current limitations in targeted therapy by ensuring optimal drug concentration at the diseased site, thereby maximizing therapeutic impact and minimizing off-target effects[116,117].

Clinical trials and translational studies

The clinical translation of drug delivery systems using nanocarriers has also witnessed considerable progress. Several formulations have been approved for cancer therapy[118]. Doxil, which is a liposomal doxorubicin formulation, was the first nanotechnology-based formulation that was approved for cancer therapy. It has been reported that Doxil shows improved efficacy with reduced cardiotoxicity in comparison with the conventional doxorubicin formulation. Abraxane, which is an albumin-bound nanoparticle formulation of paclitaxel, shows improved efficacy with reduced toxicity in metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer[119]. Among the liposomal formulations, Doxil/Caelyx, which is PEGylated liposomal doxorubicin (80-90 nm), was approved by the FDA in 1995 and by the EMA in 1996 for HIV-associated Kaposi's sarcoma, ovarian cancer, metastatic breast cancer, and multiple myeloma. DaunoXome, which is non-PEGylated liposomal daunorubicin (45 nm), was approved by the FDA in 1996 for HIV-associated Kaposi's sarcoma. Lipo-Dox, which is another formulation of doxorubicin in liposomes (180 nm), was approved in Taiwan in 1998 for Kaposi's sarcoma, breast cancer, and ovarian cancer[120]. DepoCyt, which is a liposomal cytarabine with larger particles (10-20µm), was approved by the FDA in 1999 for neoplastic meningitis. Subsequently,

Myocet, which is non-PEGylated liposomal doxorubicin (190 nm), was approved by the EMA in 2000 for breast cancer therapy. Abraxane, which is an albumin-bound nanoparticle formulation of paclitaxel (130nm), was approved by the FDA in 2005 and by the EMA in 2008 for non-small cell lung cancer, metastatic pancreatic cancer, and metastatic breast cancer[121]. For instance, in 2006, the FDA approved Oncaspar, a PEGylated L-asparaginase conjugate (50-200nm), for leukemia treatment[122]. Genexol-PM, a PEG-PLA polymeric micelle encapsulating paclitaxel (20-50 nm), was approved in 2007 in South Korea for the treatment of breast, lung, and ovarian cancers[123,124]. Other emerging nanomedicine platforms include MEPACT (mifamurtide) – a non-PEGylated formulation of a liposome – which was approved by the EMA in 2009 for osteosarcoma. NanoTherm, iron oxide nanoparticles of 15-20 nm, was approved by the EMA in 2010 for use in the treatment of glioblastoma multiforme through magnetic thermal ablation[125]. The FDA subsequently approved Marqibo, a non-PEGylated formulation of a vincristine liposome (100 nm), in 2012 for Philadelphia chromosome-negative acute lymphoblastic leukemia[126]. More recently, MM-398, a PEGylated formulation of a liposome encapsulating irinotecan (80-140 nm), was approved by the FDA in 2015 for the treatment of metastatic pancreatic cancer in the second-line setting[125]. In 2017, NU-0129, a formulation of gold nanoparticles encapsulating gold cores and siRNAs, was used in clinical trials for glioblastoma multiforme[127]. In the same year, MM-398, a formulation of a liposome encapsulating irinotecan (80-140 nm), was used in Phase I-III clinical trials for small cell lung cancer, metastatic pancreatic adenocarcinoma, and pediatric solid tumors[128-130]. Polymeric nanocarriers are also well represented in the drug delivery field. For instance, Genexol-PM, a polymeric micelle formulation of paclitaxel, with a particle size of <50 nm, was used in Phase I/II clinical trials for gynecologic cancers, hepatocellular carcinoma, advanced breast cancer, and non-small cell lung cancer[129-133]. Similarly, CRLX101, a formulation of a polymer conjugate of camptothecin, with a particle size of 30 The silica-gold nanoparticles (150 nm) system, AuroLase was tested in Phase I clinical trials for prostate, head and neck, and lung cancer[136,137]. Gold-based systems like these are commonly studied for photothermal therapeutic applications. There are many liposomal formulations that are at the forefront in clinical trials. A liposome injection for vincristine sulfate (100 nm) is in Phase I/II clinical trials for Kaposiform hemangioendothelioma, Kasabach-Merritt syndrome, tufted angioma, rhabdomyosarcoma, recurrent adult acute myeloid leukemia, lymphoblastic leukemia, various lymphomas (non-Hodgkin's, follicular, mantle-cell, small-cell, and B-cell marginal zone), and Waldenstrom's Macroglobulinemia[126,138]. An anti-EGFR immuno-liposome for delivering doxorubicin (130-200 nm) is in phase II clinical trials for breast cancer[139].

Another liposomal formulation, mitoxantrone HCl liposome injection (plm60-s) (60nm), is in Phase II clinical trials for breast cancer, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, and peripheral T/NK lymphomas[140]. Earlier-stage liposomal candidates include CPX-351 (2014), a liposomal formulation assessed in Phase I trials for acute myeloid leukemia[141], and Lipocurc, a liposomal curcumin formulation evaluated in Phase I/II studies for advanced cancers refractory to standard therapy[142]. Gene-based nanomedicine is represented by SGT-53, a liposomal vector delivering plasmid DNA encoding wild-type human p53, investigated in Phase I/II trials for glioblastoma, other neoplasms, and metastatic pancreatic cancer[143-145]. LiPlaCis, a liposomal cisplatin formulation, advanced to Phase I/II trials for advanced or refractory solid tumors, including metastatic breast cancer[146]. In 2012, PROMITIL, a liposomal mitomycin-C (~90 nm), entered Phase I trials for solid tumors[147]. Additionally, in 2011, Abraxane, a protein–drug conjugate consisting of albumin-bound paclitaxel (130nm), was evaluated in Phase II trials for breast cancer[148].

Despite the clinical success of several nanocarrier-based drugs, challenges remain in terms of scalability, reproducibility, and regulatory approval[149,150]. Most research remains limited to *in vivo* and *in vitro* studies[151]. Translational hurdles persist, primarily due to the complex biological barriers, tumor heterogeneity, and systemic clearance mechanisms that still challenge optimal drug accumulation at target sites[152]. A major translational barrier is the variability and context-dependence of the EPR effect in humans. While preclinical xenograft models and rodent tumors often display strong and relatively homogeneous EPR, human tumors show highly heterogeneous, sometimes transient EPR that varies between tumor types, primary versus metastatic lesions, and even between lesions in the same patient[153,154]. Clinical and comparative imaging data indicate that only a subset of human tumors (e.g., some carcinomas) exhibits robust EPR-mediated accumulation, and the magnitude of uptake is far lower and more variable than in mice[155]. This mismatch between animal models and human pathophysiology is widely regarded as a key reason for clinical failures.

Nano medicines relative to expectations based on preclinical studies. Inadequate modeling of tumor heterogeneity, metastasis, and human-like vasculature further limits predictive value and contributes to disappointing trial outcomes[155,156]. Beyond limited efficacy, toxicity and long-term biosafety remain central concerns. Nanoparticles can induce oxidative stress, damage membranes, organelles, and DNA, and engage cell-surface receptors to trigger unintended immune and inflammatory responses[152]. Toxicological profiles are highly dependent on size, shape, composition, surface charge, and coating, which are often modified during scale-up or functionalization, complicating risk assessment[153,157]. For inorganic and metal-containing systems, nanoscale manipulation can fundamentally alter toxicology compared with bulk materials, raising concerns about chronic accumulation and delayed organ toxicity, particularly under repeated dosing regimens typical of oncology[157]. These uncertainties contribute to conservative clinical trial

designs and slow regulatory acceptance, and help explain why most approved cancer Nano drugs are relatively simple liposomes or albumin nanoparticles with well-characterized materials[158].

Immunogenicity and off-target immune effects are critical concerns in nano-immunotherapy and RNA or biologic delivery. Exogenous nano carriers may activate complement and innate immune pathways, causing hypersensitivity, cytokine release, or immune suppression, while repeated dosing can induce anti-carrier antibodies that alter pharmacokinetics and efficacy. Ensuring selective antitumor immune-stimulation without systemic immunotoxicity, there-fore, remains a major challenge[159]. In the blood-stream, nanocarriers rapidly form a protein corona that alters their biological identity, masking targeting ligands, promoting opsonization, and increasing uptake by the mononuclear phagocyte system, particularly in the liver and spleen[153]. This reduces tumor delivery and can modify toxicity profiles. Controlling corona formation is challenging due to patient-specific plasma composition and dynamic *in vivo* conditions, while rapid macrophage clearance, hepatic and splenic filtration, renal excretion, and potential long-term tissue accumulation further limit circulation time and intratumoral exposure[152,159,160]. Clinical translation of advanced nanocarriers is limited by challenges in robust, scalable, and reproducible manufacturing. Complex multi-component systems require precise control of size, surface chemistry, and drug loading, increasing batch variability and complicating GMP scale-up[152,157,161]. Difficulty in preserving critical quality attributes during industrial production raises costs, favoring simpler liposomal and polymeric formulations with more tractable process control [152,153,158]. Therefore, there is emphasis placed on the need for further research to develop new strategies that can overcome these challenges, including the development of new targeting ligands, drug release systems, and pharmacokinetic profiles for the improvement of the clinical utility of these nanocarriers[152]. In addition, the application of artificial intelligence in conjunction with machine learning may greatly improve the development of new nanocarrier designs and their interactions in complex biological systems, thereby promoting the clinical translation of these nanocarriers[162]. Furthermore, the immunological effects of nanocarriers are important in the long-term safety and efficacy of these nanocarriers. Therefore, immunogenicity studies are important in the development process of these nanocarriers. In addition, quality control of nano medicines is important in the production of these nanocarriers to make them safe and effective in the clinical utility process[163].

Overcoming biological barriers for targeted delivery

The nanocarriers have the ability to cross physiological barriers such as the blood–brain barrier, tumor microenvironment, and drug resistance, thereby enhancing the efficiency of drug localization[164]. The localization of anticancer drugs in tumor tissues with minimal localization in other parts of the body could be responsible for enhancing the efficacy of anticancer drugs while minimizing toxicity[165]. The dynamics of tumor microenvironment have been significant in enhancing the efficient design of nanoparticles, thereby ensuring effective drug delivery[166]. The application of nanotechnology in cancer therapy is a dynamic field with tremendous potential for cancer therapy[167]. Engineered nanoparticles have been effective in protecting anticancer drugs from early degradation, extending the half-life of anticancer drugs, and accumulating anticancer drugs in tumor tissues using the EPR effect[168-170]. The rationale behind targeted drug delivery is targeting anticancer drugs specifically in cancer cells, thereby minimizing the impact of anticancer drugs on normal cells[171].

Targeted drug delivery is an approach that uses nanoscale drug delivery vectors, which may be derived from organic compounds, that target anticancer drugs specifically in cancer cells[172]. The drug delivery vectors may also be engineered in a manner that they release anticancer drugs in response to tumor-specific stimuli, thereby enhancing effective release of anticancer drugs[173]. The advancement in biotechnology has been significant in synthesizing effective drug delivery vectors, including liposomes, dendrimers, metal nanoparticles, and magnetic nanoparticles. Beyond therapy, such platforms offer opportunities for simultaneous diagnosis and disease monitoring[174]. Passive targeting strategies exploit the abnormal architecture of tumor vasculature and deficient lymphatic drainage, characterized by vascular fenestrations typically ranging from 100 to 780 nm[175]. Nanoparticles engineered within this dimensional window can preferentially accumulate in tumor tissues, thereby enhancing local drug concentration and therapeutic response[176].

Targeted therapeutic strategies are aimed at achieving the optimal concentration of drugs that are delivered directly to the target tissues where the disease manifests, while ensuring that the optimal concentration of drugs is maintained for a long time[177]. The introduction of nano-based drug delivery systems has resulted in a significant increase in attributes such as drug bioavailability, *in vivo* stability, intestinal absorption pattern, solubility, and the targeted and long-lasting distribution of drugs, as well as the therapeutic efficacy of a number of anticancer drugs[178]. The efficacy of a number of drugs, including anticancer drugs, is improved by nano-based drug delivery systems, which enhances drug bioavailability/ biodistribution[179].

By enabling more accurate localization of drugs at pathological sites, nanotechnology has significantly advanced precision medicine approaches[180]. Due to their small dimensions, nano drugs are capable of traversing narrow capillary networks and lymphatic endothelium, which may contribute to prolonged systemic circulation and improved interaction with target tissues. Once accumulated at the tumor site, nanocarriers can facilitate efficient cellular internalization and induce cytotoxic effects within malignant cells[181]. A central objective of nanotechnology in oncology is to concentrate therapeutic action at the intended site while minimizing adverse systemic

reactions commonly associated with conventional chemotherapy[182]. Recent progress in cell-mediated nanoparticle delivery systems has further strengthened tumor-targeting strategies[183]. Such biomimetic platforms provide advantages such as enhanced biocompatibility, extended circulation time, intrinsic homing capacity, and the ability to overcome physiological barriers. Additionally, localized hyperthermia applied to solid tumors can stimulate vascular permeability and cellular responses, thereby improving nanomedicine penetration and retention[184]. Nanocarriers also enable the transport of diverse therapeutic payloads, including small-molecule drugs, genes, and proteins, directly into cancer cells, improving treatment outcomes while reducing collateral toxicity[173]. This is particularly relevant given the well-recognized limitations of traditional chemotherapeutics, such as poor aqueous solubility, limited tumor selectivity, and susceptibility to multidrug resistance. Nano formulations of natural anticancer compounds have similarly demonstrated improved stability, biodistribution, targeting efficiency, and therapeutic potency[185]. Overall, nanoparticle-based systems offer versatile solutions to many of the constraints associated with conventional cancer treatment modalities[186].

Application of Nanocarriers in Cancer Therapy

In targeting multiple biological levels

Nanocarriers can be engineered to act hierarchically at the level of tumor tissue, cancer cells, and specific organelles, thereby improving therapeutic precision. Fan *et al*., showed that size, surface ligands, and charge can be tuned to first promote tumor accumulation, then receptor-mediated uptake by cancer cells, and finally subcellular targeting (e.g., mitochondria or nuclei) to maximize drug action while limiting off-target toxicity[161]. Cell-membrane–coated systems further extend this concept: by cloaking nanoparticles with cancer cell or immune cell membranes, Li *et al*., achieved prolonged circulation, homotypic binding to tumor tissue, and improved intracellular delivery across several biological barriers[187]. These strategies illustrate how nanocarriers can be designed to sequentially navigate blood, stroma, cell membrane, endosomal compartments, and organelles, rather than acting at a single biological level[161,187].

In overcoming multidrug resistance

A second key application is the reversal of multidrug resistance (MDR) through nano-enabled delivery. Yao *et al*., summarized how nanoparticles can circumvent efflux transporters (e.g., P-gp) by favoring endocytic uptake and high intracellular payload concentrations, which restored sensitivity to doxorubicin and paclitaxel in resistant cell lines and xenografts[164]. In addition to bypassing pumps, nanocarriers can co-deliver chemotherapeutics with P-gp inhibitors or siRNA targeting resistance-related genes, leading to more sustained MDR reversal[164]. TME-responsive nano drug delivery systems also address microenvironment-driven resistance: Shao *et al*., reported platforms that respond to acidic pH or hypoxia in the tumor, releasing drugs and adjuvants precisely where physicochemical conditions promote resistance, thereby improving cytotoxic efficacy in MDR models[188].

In enhancing radiotherapy with smart platforms

Nanocarriers are increasingly used as radiosensitizing platforms that modify both tumor cells and their microenvironment. Feng *et al*., constructed a ZIF-8–based nanoplatform co-loading indocyanine green and rapamycin, designed to disassemble in the tumor microenvironment and provide photothermal therapy together with radiotherapy sensitization[189]. Rapamycin inhibited mTOR signaling, enhanced DNA damage, and promoted immunogenic cell death, while the photothermal effect further compromised tumor viability, resulting in marked radiosensitization and tumor growth inhibition in HepG2 xenografts[189]. TME-responsive carriers that alleviate hypoxia or modulate redox status have similarly been shown to improve radiotherapy outcomes by increasing reactive oxygen species generation and reducing DNA repair capacity in tumor cells[188,189].

Supporting and potentiating cancer immunotherapy

Nanocarriers also act as powerful tools to potentiate cancer immunotherapy by delivering immune modulators to specific immune or stromal cell populations. Lu *et al*., reported nanoparticles designed to repolarize tumor-associated macrophages from an M2- to an M1-like phenotype, promote dendritic cell maturation, and enhance T-cell infiltration, which together remodeled an immunosuppressive TME into an immune-permissive niche. Such systems were able to synergize with immune checkpoint blockade by increasing intratumoral effector T cells and reducing regulatory populations[190]. Peng *et al*., showed that TME-responsive nanomedicines, triggered by acidity or high ROS, can confine the release of immunostimulatory agents to tumors, amplifying local immune activation while minimizing systemic immune related adverse events[191]. These examples highlight how nanocarriers can orchestrate multi-cellular immune networks within the TME to improve the depth and durability of immunotherapy responses.

Exploiting and remodeling the tumor microenvironment

Finally, nanocarriers are increasingly designed to exploit and actively remodel the tumor microenvironment itself. Aldhubiab *et al*., described multiple platforms that regulate hypoxia, pH, and redox balance, degrade dense extracellular matrix, and interfere with immunosuppressive mediators, thereby improving drug penetration and sensitizing tumors to therapy[159]. For instance, oxygen-generating or hypoxia-responsive nanoparticles can relieve hypoxia-induced resistance and enhance both chemo- and radiotherapy, while matrix-degrading carriers improve the intratumoral distribution of payloads[159,188]. In lung cancer, Sarma *et al*., showed that bio functionalized nanocarriers equipped with ROS-modulating inorganic components and TME-targeting ligands could modulate cancer-associated fibroblasts, suppress TAM and MDSC activity, and normalize vasculature, leading to improved penetration and antitumor effects in non-small-cell lung cancer models[192]. Collectively, these studies demonstrate that nanocarriers can be rationally

designed not only to survive the hostile TME but to reprogram it into a more treatment-sensitive state[190].

CONCLUSIONS

Nanocarrier based drug delivery systems have greatly contributed to the development of targeted cancer therapies by overcoming the major drawbacks of conventional chemotherapy. The conventional chemotherapy methods have been plagued by issues such as systemic toxicity, lack of tumor selectivity, low bioavailability of drugs, and the development of multidrug resistance. The nanocarriers have been able to address these issues by improving the solubility and stability of drugs, increasing the circulation time of drugs in the body, and providing the ability to control the release of drugs. The nanocarriers have also been able to improve the ability of drugs to reach the tumor sites. The nanocarriers that have been developed and tested in cancer therapy include liposomes, polymeric nanoparticles, dendrimers, micelles, and inorganic nanoparticles. The development of these nanocarriers has been highly beneficial in addressing the issues that have been experienced with conventional chemo-therapy. However, despite the benefits that the nanocarriers have provided in the development of targeted cancer therapies, there are several issues that need to be addressed. For instance, the long-term safety and accumulation of these nanocarriers in the body are issues that need to be addressed. In the future, the development of nanocarriers should be focused on the development of multifunctional nanocarriers that can be tailored to respond to different stimuli. The nanocarriers should be designed in such a way that they can be tailored to the patient. The nanocarriers should be optimized in terms of their size and surface characteristics.

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AUTHOR'S CONTRIBUTIONS

Komba EG: writing the original draft, methodology, investigation. **Said SS:** literature survey, data processing. **Alphonce FM:** literature survey, critical review. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

None to declare.

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