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Targeted drug delivery via nanoparticles for cancer treatment

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Abstract

This review paper addresses the latest techniques for treating cancer as well as the numerous recent studies conducted on nanoparticles as delivery vehicles for anticancer medication. Numerous chemical and structural formulations of nanoparticles have been investigated for their ability to selectively bind to certain targets and to function as a drug delivery system. The surface characteristics and size of nanoparticles are key factors that impact the bio distribution of chemotherapy medications in the body as well as the efficiency of Nano carriers. For targeting cancerous cells and transporting anticarcinogenic drugs in a controlled way, numerous scientific researchers have been led to investigate the usage of magnetic nanoparticles in the cure of oncogenic breast cancer and brain tumor cells. Other drug delivery systems that have been tested include liposomes, magnetic nanoparticles, polymeric micelles, ceramic nanoparticles, and colloidal gold nanoparticles. The application of ceramic nanoparticles in photodynamic therapy for the cure of cancer is also covered in this article. Thus, the article provides a brief overview of the topic with suitable references to review articles and original research articles that describe previous and ongoing research findings related to different types of nanoparticles for drug delivery in cancer treatment.

Keywords: Targeted drug delivery; Nanoparticles; Cancer nanotechnology; Liposomes; Polymeric nanoparticles; Tumor targeting

1. Introduction

There is a solid petition for ground-breaking delivery system fit for delivery of many pharmacological agents, particularly those with high efficacy, low charges, low risk and harmfulness [1]. Some therapeutic agents can be improved via Nano-sized drug delivery systems to advance the supply of active pharmaceutical ingredients who have poor pharmacokinetics and tissue distribution [2]. For example, the common chemotherapeutic agents have poor pharmacokinetic profiles and disseminate indiscriminatingly throughout the body, leading to general toxicity and severe side effects [3]. Therefore, structure-based Nano-sized pharmaceutical preparations, for example, polymeric nanoparticles, liposomes [4], Nano suspension [7], polymeric nanoparticles [5], and electro sprayed particles [6] have confirmed improved therapy of the medicinal agents [8].

These particles have the capability to penetrate tissues deeply by passing through the aperture in the epithelial tissue of small blood vessels. They can access the systemic bloodstream without creating blood platelet clumps. The smaller size of their particles results in an amplified surface area, which leads to a system for quicker medication release. Drug delivery speeds and particle structure can be adjusted by designing carriers to respond to changes in pH [9], magnetic fields, chemo stimuli [10] or heat sources [11]. Therapeutic and diagnostic agents can be encapsulated, covalently bonded, or absorbed into Nano carriers while suitable ligands and synthetic polymers can be added to the surface of the nanoparticle [12].

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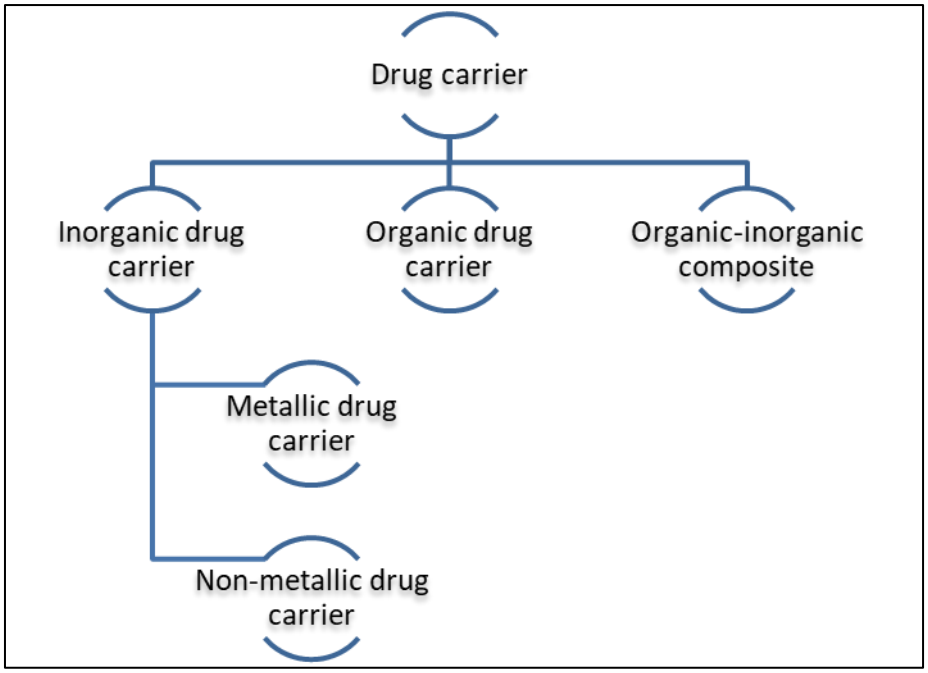

Figure 1 Classification of Drug Carrier

Different types of nanoparticles being researched for drug delivery systems include biodegradable polymeric nanoparticles like dendrimers, liposomes, polymeric micelles, Ceramic Nano particles, Nano spheres and Nano capsules. The carrier could alternatively be a silica nanoparticle or a carbon nanotube, with drug molecules attached to its surface. Structural attachment of biological molecules such as antibodies, enzymes, hormones, and pharmaceutical drugs to nanoparticles enables them to be effective drug delivery systems [13].

Gold nanoparticles can be easily prepared, exhibit low toxicity, and can be linked to biologically significant molecules. The wavelength of the laser light that is used to visualize the particles cause only a little damage to biological tissues. This technique could possibly permit observing a single drug molecule within a cell or other biological specimens. This is employed as a carrier for targeted drug delivery to tumors [14]. Lipid coated nanoparticles permit vital membrane proteins to solubilize while conserving their complete organizational shape which is crucial factor in assay development. It has best lead selection and optimization to enhance targeted drug delivery by targeting on tumor blood vessels. It is utilized as a carrier for delivering a lipophilic antitumor medication to hepatoma cells. It is beneficial in passive tumor targeting, gene delivery, targeting to cell surface ligands, vaccine adjuvants etc. in diverse fields of pathology [15]. MNPs are extensively utilized in thermotherapy, In vivo imaging rapid screening, Loco-regional delivery of anticancer drugs in cancer treatment [16].

Ceramic nanoparticles can be created readily at ambient temperatures with the required porosity shape and size. It is employed as DDS in photodynamic cancer chemotherapy [17].Synthetic or natural polymeric nanoparticles are synthesized simply with little or no toxicity. It is utilized in antibody-targeted therapies, targeted therapy of cancer, delivery through bypassing the reticuloendothelial system and targeting delivery via angiogenesis [12].

2. Different delivery system

2.1. Liposomes

Liposomes are Nano-sized transporters made up of lipid bilayers and containing an empty center. The medications or substances are enclosed within the core of nanoparticles and transported to the specified site [18]. Liposomes consist of a lipid bilayer with a hydrophilic interior that can transport hydrophilic molecules [19], Additionally, hydrophobic particles can be incorporated into liposomes, allowing them to deliver both types of molecules to the desired site. The way in which liposomes deliver drugs is by merging with the cell's lipid bilayer, allowing the drug to be transported to the cell's cytoplasm. Liposomal systems offer many benefits compared to traditional drug delivery methods for targeting drug molecules to inflammatory lesions, whether through active or passive means. Lipid nanoparticles (LNPs) like

liposomes, Nano-structured lipid carriers, solid lipid nanoparticles, Nano lipid-drug conjugates, Nano emulsions and mixed micelles and have displayed promising outcomes in oral anticancer drug delivery using Nano technology [20].

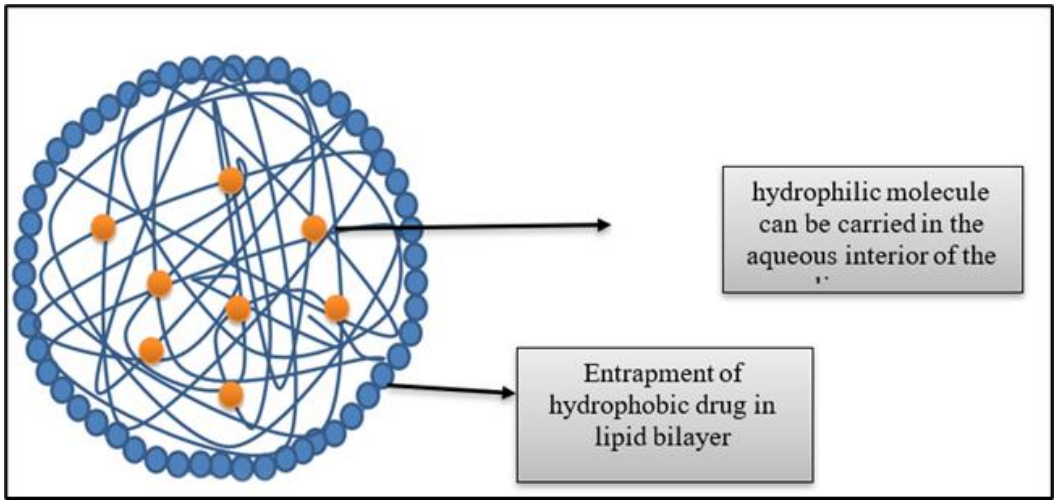

Figure 2 Liposomal Carrier Structure

Liposomes containing tamoxifen/raloxifene are utilized for treating breast cancer orally. The reverse-phase evaporation method was used to prepare the liposomes [21]. 3 mg of tamoxifen or raloxifene in 0.5 ml of methanol was mixed, and dissolved 30 mg of DPPC in 4.5 ml of ethyl acetate in a round bottom glass flask. The absorption enhancers sodium taurocholate (NaTC) or dimethyl-β-cyclodextrine (DM-β-CD) were included in the flask for enhanced absorption. A 1 mg/ml chitosan solution was made in a 0.02 M acetate buffer/0.1 M NaCl (pH 4.5) solution, and 100 µl of this solution was slowly dripped into the flask while under an ultrasonic bath. Next, the rotary evaporator was utilized to eliminate the organic phase at a temperature of 30–35 °C. Subsequently, a gelatinous, desiccated lipid layer was produced and it was rehydrated with 5 ml of physiological saline (PS) while being sonicated for an hour. The liposome suspensions were spun at 20,000 g for 15 minutes at room temperature to separate the liposomes from the supernatants. The specified combinations (tamoxifen + DM-β-CD liposomes, raloxifene + DM-β-CD liposomes and tamoxifen + DM-β-CD solution, raloxifene + DM-β-CD solutions) were given orally to 300 ± 10 gr tumor-carrying female rats of the Sprague Dawley breed. To induce tumor growth, female Sprague Dawley rats were given a 50 mg/kg dose of nitroso methyl urea (NMU) through intraperitoneal administration. Untreated rats with tumors were used as a control for comparison. Administration of liposome formulations (dosage of 1200 µg/ml for raloxifene and tamoxifen) were carried out. Formulations were administered weekly for duration of eight weeks, while weights and tumor sizes were assessed on a weekly basis. A measuring tool, known as a caliper, was utilized for determining the sizes of tumors and for computing their areas. Studies correlating in vitro findings with in vivo results were conducted as documented in prior research. Consequently, the cytochrome C protein is released by the mitochondria, initiating the caspase cascade that ultimately results in cell death. DOX moves from the cytosol into the nucleus where it inserts between double-stranded DNA helices and hinders the enzymes topoisomerases I and II.DNA damage results in the generation of free radicals, activation of the p53 pathway, and alkylation, ultimately hindering cell growth and initiating cell death. DOX can also overstimulate the nuclear enzyme PARP-1, leading to cellular energy depletion and inducing autophagy. Due to the risk of cardiotoxicity, the therapeutic benefits of DOX may be limited, which has been clearly associated with its overall cumulative dosage. To address this issue, researchers developed liposomal DOX (L-DOX) to reduce DOX-related cardiac toxicity while preserving its efficacy against tumors [22].

At the moment, different sorts of antineoplastic medications have been incorporated into this liposomes through various preparation techniques such as liposomal versions of the anthracyclines, daunorubicin and doxorubicin authorized for management of HHV-8 and metastatic breast cancer [23].

Doxorubicin (DOX) is a highly effective antineoplastic agent for both initial and late-stage breast cancers when used in anthracyclines-based chemotherapy. Doxorubicin mechanism on cancer cells starts with it dispersion across the phospholipid bilayer membrane of cancerous cells into the cytoplasm where Doxorubicin undergoes oxidation leading to the formation of unstable molecules. Doxorubicin infiltrates the mitochondria and causes the destruction of DNA. Therefore, the mitochondria release cytochrome C protein, beginning the flow which results in apoptosis. From the cytosol, DOX translocate into the nucleus where it intercalates between double-stranded DNA helices and inhibits the enzymes topoisomerases I and II. The resulting damage to DNA leads to free radical generation, alkylation, and

activation of the p53 pathway, hence inhibiting cell proliferation and inducing apoptosis. DOX can also hyper activate the nuclear enzyme poly ADP ribose polymerase (PARP)-1, hence depleting the cell's energy, thereby resulting in autophagy. the potential therapeutic benefits of DOX are limited by the risk of cardiotoxicity, which has been evidently related to its lifetime cumulative dose. To overcome this hurdle, the liposomal DOX (L-DOX) formulation was developed in order to reduce DOX-associated cardiotoxicity while preserving its antitumor efficacy[24]. PEGylated liposomal doxorubicin is the only liposomal anthracycline with significantly reduced uptake by the mononuclear phagocyte system, thanks to an additional polyethylene glycol layer on the liposome containing doxorubicin, resulting in a longer plasma half-life compared to other liposomal anthracyclines. The liposomes can traverse through leaky neoplastic blood vessels due to the size of the drug-filled vesicles [25].

The Estrogen Receptor (ER), a nuclear hormone receptor, is predominantly present in various cancer types in estrogen-responsive organs like the ovary, uterus, breast, skin, prostate, and brain. It plays both genomic and non-genomic roles. It is widely recognized that ER is present in gynecological organs during early stages of neoplastic transformation, making ER a viable target for drug development against ER-positive cancers of gynecological origin for many years. This becomes even more relevant considering the identification of membrane-bound ER receptors (mER) like GPR30. 17β Estradiol, a form of estrogen, is a naturally occurring steroid hormone and the primary molecule that binds to ER. Therefore, to enhance precision in targeting and delivery to ER-positive cancer cells, specific targeting ligands such as estradiol or estradiol-derived molecules are preferred in delivery systems to minimize non-specific drug toxicity. ER plays a crucial role in gynecological cancers and is a major focus in the treatment of ovarian, breast, and endometrial cancers. Anti-estrogens were incorporated into the oily core of liposomes containing high levels of RU58668 or 4-HT (4-hydroxy tamoxifen). This combination was used in the treatment of multiple myeloma, since the cancer cells possess estrogen receptors and are particularly significant in treating estrogen-dependent breast cancer [13].

2.2. Gold nanoparticles

Nanoparticles range in size between 1-100 nm, and are gaining the attention and huge interest of researchers due to their unique biomedical applications. This is because nanoparticles possess unique magnetic, electrical, thermal, and catalytic properties. Different sizes and shapes of metal nanoparticles have different applications and may also depend on chemical composition. Size and shape of nanoparticles are crucial because these characteristics decide the interaction between metal nanoparticles and membrane proteins of a cell, enzymes, and other components [28].

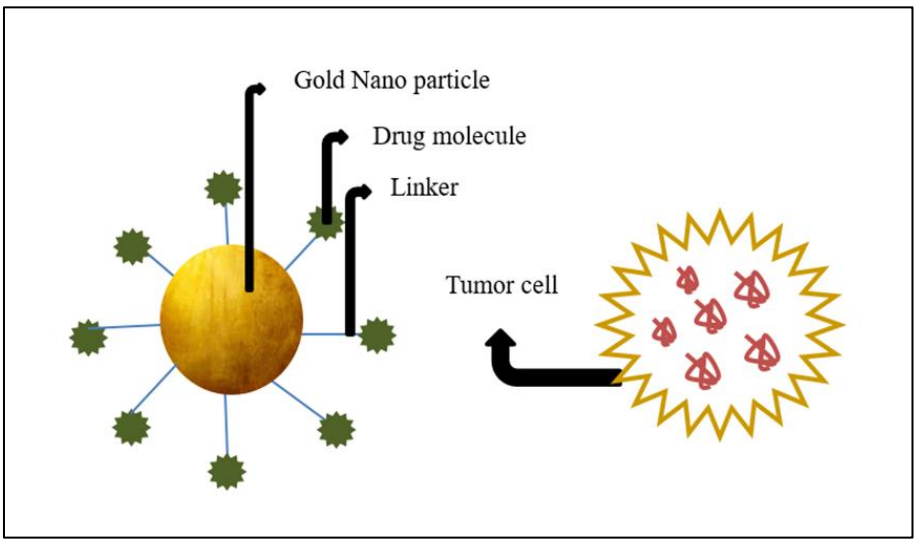

Figure 3 Colloidal Gold Nanoparticle

Among the various types of nanoparticles, colloidal gold is the most broadly originated nanoparticles for the delivery of anticarcinogenic drugs. In relation to other nanoparticles, these gold nanoparticles are more biocompatible. The chemical or physical properties of colloidal gold nanoparticles allow the attachment of one or more protein molecules to a colloidal gold's single particle [13]. Paciotti et al. have reported that tumor necrosis factor-alpha (TNF) can be delivered to solid tumors using colloidal gold nanoparticles [29].

Colloidal gold nanoparticles have been used as a drug delivery vehicle of TNF in mice with a growing tumor [30]. Despite the fact that TNF is scrutinized in treating cancer, it may cause some side effects like hypotension and in some situations

cause organ failure and can result in mortality. Recent researches have demonstrated that therapeutic levels of TNF, when linked with colloidal gold nanoparticles, can be safely delivered to cause tumor cell death in animal models. A method known as selective nanothermolysis that employed self-assembled gold nanoparticles was devised to destroy human breast cancer tissue's tumor cells using laser light. These nanoparticles were attached to secondary antibodies, named as goat anti-mouse IgG. The above arrangement of structure had a unique localization in the adeno-carcinomatous breast cells, which were particularly targeted through the application of primary antibodies. Colloidal gold nanoparticles can also be used as an efficient and safe vector for delivering genes in immunotherapy and gene therapy for cancer. The plasmid DNA assembled with gold particles. In contrast to other gene delivery vehicles, gold nanoparticles presented remarkably enhanced transfection efficiency and cellular delivery[13]. Gold Nano-conjugated cetuximab and gemcitabine have exhibited tremendous potential for targeting pancreas cancer cells with increased EGFR expression. Jiang et al. synthesized AuNPs with dimensions ranging between 2 and 100 nm and then conjugated them with trastuzumab employing the citric acid reduction method. Results showed that (HER-2)- positive SK-BR-3 breast cancer cells were targeted by AuNPs, enhanced targeting was demonstrated, and cells responded strongly to AuNPs with a diameter between 40 and 50 nm by endocytosis, whereas smaller diameter AuNPs are more likely to undergo cell membrane dissociation [31]. Chen et al. utilized a carrier conjugated with methotrexate (MTX) with an estimated size of 14 nm AuNPs in order to elucidate anticarcinogenic effects within the body and adverse effects outside the body. The outcomes show that coupling MTX with AuNPs can be efficiently or rapidly concentrated in tumor cells, which considerably lessens the dose-dependent effect of efficacy [32].

2.3. Magnetic nanoparticles

Magnetite nanoparticles have garnered significant interest previously owing to their distinct physicochemical, electronic, optical, and magnetic characteristics [33]. The sizes of MNPs mark them appropriate for creating functional nanostructures and surface Nano-engineering [34]. Through the alteration of MNPs, they can be utilized in diverse medical and pharmaceutical contexts ranging from diagnostics to drug delivery, showing particular promise in cancer treatment [35, 36]. Currently, several MNPs are undergoing initial clinical trials with certain formulations already approved for therapeutic and medical imaging purposes. Examples of these include GastromarkVR for examining the bowel and LumirenVR as well as EndoremVR for imaging the liver and spleen and Feridex I.V.VR, among other options [37] [38]. Magnetic nanoparticles have been the center of much interest as a means of drug delivery because their ability to address the issue of a deficient transport mechanism in the body for delivering medication to the target area. Particles with sizes less than 10 nm, displaying superparamagnetic or single domain state [39], exhibit magnetic properties only when subjected to an external magnetic field and become non-magnetic upon removal of the field. Superparamagnetic materials can be advantageous for targeting therapeutics to specific areas using an external magnetic field, as they can be demagnetized for excretion when the field is removed[40]. Over the last 30 years, researchers have created different magnetic nanoparticles (MNPs) and micro particle carriers for targeted drug delivery in living organisms [41, 42]. Iron oxide nanoparticles are extensively utilized in various biomedical fields because of their great biocompatibility as well as affordability, including tasks like cell separation, cell transportation, and enhancing contrast in MRI[43]. In recent years, significant work has been carried out in synthesizing iron oxide nanoparticles as their composition, distribution of size, and morphology are influenced by the synthesis process [44]. These factors directly influence the physical characteristics, rate of clearance, and clearance pathway of nanoparticles [45, 46]. Various types of functional MNPs are utilized, such as iron oxide (e.g. MFe2O4 and Fe3O4 (M1=4Mn, Zn and Co)), alloys (e.g. Fecor PtCo and FePt,), and multifunctional MNPs having core/shell, multicomponent hybrid structure or dumbbell. Magnetizable materials are increasingly valuable in producing essential components for a variety of devices and machines in current usage, drawing considerable technological, industrial, and scientific interest. Hexaferrite materials such as M-Type SrFe12O19, BaFe12O19, and PbFe12O19 are commonly used as high-density magnetic recording materials, permanent magnets, and microwave components due to their chemical stability, great saturation magnetization, corrosion resistance, curie temperature, and exceptional affordability [47]. The use of various ion doping in Ba-Sr hexaferrite powders is commonly studied for creating materials for electromagnetic attenuation and magnetic recording media due to their high electrical resistivity, low density, and ability to absorb microwaves [48]. Recently, significant progress have been made in the synthesis of barium hexaferrite utilizing various methods, but the primary challenge remains the elevated melting point of BaFe12O19 (1580 ± 50 C). Recent advancements involve creating strontium and barium hexaferrite by reducing gas in CO (carbon monoxide) followed by recalcination, or by using a blend of boron oxides and antimony for glass crystallization. The challenge lies in finding a solvent or flux that can decrease the melting point while promoting the crystallization of barium hexaferrite phases. Carbonate fluxes [50], Borate fluxes [51], and lead oxide fluxes [52] stand out as particularly intriguing and have shown promising outcomes. Nonetheless, limited information has been provided on the use of PbO solvent. Examining how varying levels of lead oxide impact both the solution's homogenization temperature and the characteristics of the subsequent barium hexaferrite crystals. A comparison was made between the outcomes of crystals formed using carbonate and borate fluxes and those formed through solid-state sintering with no flux present. It comes as no surprise that PbO flux causes the partial substitution of Ba2þ with Pb2þ, given that the

material's crystal structure is similar to the Pb-containing mineral PbFe12O19, which is the eponym of the structure. In cancer treatment using magnetic nanoparticles, there are two main goals in optimizing these carriers: to lower the systemic exposure of the cytotoxic agents, thus decreasing side effects, and to lessen the necessary dose through better targeting of the drug. In the last decade,, significant advancements have been achieved in studying MNPs to fulfill the typical necessities for DDS including (i) evading capture by the reticuloendothelial system (RES), (ii) delivering drugs to the desired site in high amounts with safety, (iii) having minimal toxicity with decreased side effects and simple excretion after function and (iv) precisely releasing and targeting effective drug doses to reach the required concentration [53].

MNPs are a significant class of NPs, usually made from pure metals such as Ni, Co, Fe, and few rare earth metals, or a combination of polymers and metals [54]. The use of Magnetic NPs has grown in various medical fields, such as bio sensing, controlled drug delivery, hyperthermia for cancer treatment, and MRI. Furthermore, the effectiveness and magnetic properties of MNPs in the body can be modified by adding a safe and biocompatible coating to improve their appropriateness for a particular target within the body. This layer offers chemical properties that assist in incorporating useful ligands. Changing the surface chemistry of MNPs can lead to their multi-functional properties. For example, altering chemicals offers several functions like combined multiple imaging methods and hyperthermia-drug delivery [55] **.**

Current cancer chemotherapies often struggle to differentiate between cancerous and healthy cells when administered systematically, leading to the destruction of healthy cells as well. As a result, many studies have focused on finding ways to target drug delivery specifically to cancer cells without harming nearby healthy cells. MNPs have been recognized as a possible answer to this significant issue, as they have the ability to alter the pharmacokinetics of medications in order to reduce toxicity and extend the duration and half-life of drugs. Furthermore, MNPs can be equipped with high-affinity ligands, such as peptides and antibodies, to enhance their selectivity [57] in detecting cancer cells, in addition to being able to be localized at cancerous sites by a magnetic field [56].

The use of magnetic-drug targeting presents a distinct chance to locally treat malignant tumors. Alexiou et al. 56 used magnetic nanoparticles (Ferro fluids) coupled with mitoxantrone to treat squamous cell carcinoma in living organisms, concentrating the chemotherapeutic agent locally with a magnetic field. The MRI can also show the particles accumulating within the tumor [29].

The MNP called MF66, which combines magnetic hyperthermia and drug delivery for breast cancer xenograft treatment, was produced using the co-precipitation technique. Coating with dimercaptosuccinic acid (DMSA) was carried out. In short, the MNP were first covered with oleic acid and spread in toluene before introducing a DMSA solution in DMSO to switch the ligand from oleic acid to DMSA. The coated MNP with DMSA precipitated and went through multiple washes with water. Ultimately, the MNP were suspended in distilled water, the pH was modified, and sterile filtration was performed [58]. The magnetic properties of the characterized MF66 MNP used in this research have already been studied. The Z-average size of the MNP dispersed in water was determined using dynamic light scattering to assess the hydrodynamic diameter. The MNP discussed in this research are suitable for hyperthermia therapies. An in vitro study showed that N6L modification enhanced internalization and DOX modification resulted in more cell death compared to unmodified MNP. In live animals, the MNP caused a significant decrease in tumor size and near-total regression in numerous instances. The newly introduced functionalized MNP provides new possibilities for improving cancer treatment through magnetic hyperthermia using MNP with strong heating capabilities. The extra electrostatic interaction between N6L and DOX may potentially enhance the uptake of MNPs in cells and enhance their ability to deactivate cells. Improved radiology techniques can now effectively treat early stages of breast cancer that have single tumors and negative lymph nodes, which are being detected more frequently due to advances in diagnostic methods [59].

2.4. Ceramic nanoparticles

The ceramic drug delivery systems have gained more interest due to advancements in pharmaceutics, medicine, and material science. Commonly used bio ceramics consist of mesoporous silica, beta tricalcium phosphate (β-TCP), hydroxyapatite-zirconia composite, etc. Bio ceramics also play a vital role in certain organic-inorganic composites utilized as drug transporters. Ceramic-based drug transporters offer adjustable structure and size for filling Nano-sized drugs, along with reduced toxicity. Additionally, they exhibit great biological stability, biocompatibility, and biodegradability. Some ceramics are responsive to environmental factors like heat, light, or magnetism, allowing for precise targeted delivery. Therefore, drug carriers made from ceramics have gathered significant attention from researchers in numerous fields such as biomaterials, biochemistry, biophysics, pharmaceutics, bioengineering, and medicine. These include hydroxyapatite, silica, zirconia, zeolite, and tricalcium phosphate. Bio ceramics are valued as

effective drug reservoirs or matrix in DDS [60, 61]. For example, β-TCP can be formed into a hollow arrangement of a specific shape and size. In a physiological environment, they have the ability to degrade in the biological environment because of the presence of body fluids, enzymes, or cells. The release of pharmaceuticals through ceramics pores is regulated by the drug solubility and concentration gradient, while the penetrability of the ceramics drug carrier affects drug dispersion. Drugs can be placed on or within the carriers using different techniques, such as a simple sono-chemical technique[62]. Certain ceramic drug carriers have drawbacks like expensive cost, limited encapsulation, and unpredictable dose. Therefore, controlled release, targeted delivery, and enhancing the loading capacity of drug delivery systems (DDS) are crucial in order to optimize drug effectiveness and reduce toxicity to healthy tissues and cells. Additionally, optimizing the synthetic process is crucial in reducing the expenses associated with ceramic-based carriers.

2.4.1. Common ceramic drug carriers

Hydroxyapatite

HAP, a key inorganic component in hard tissues like teeth and bone of vertebrates, makes up around 60-70% of the inorganic content in the human body. Therefore, HAP has been extensively used in the area of bone healing. It can be produced naturally in living organisms, withstand moisture, prevent shrinking, and have varying levels of hardness[63]. Nanostructured HAP possesses advantageous characteristics such as high biocompatibility, degradability, potent biological activity, osteoconductivity, non-toxicity, simple in-vivo metabolism, and a hollow mesoporous assembly. Therefore, it has been viewed as a favorable option in lieu of the prolonged and controlled delivery of genes, medications, and proteins in the field of Drug delivery system [64, 65]. Traditionally, drugs are taken 1-3 times a day via oral intake, however it is difficult to take drugs on schedule, especially for patients with depression, cancer and other chronic illness. In contrast, conventionally medications are usually consumed orally 1-3 times daily, but adhering to a schedule can be challenging for patients dealing with conditions like cancer, depression, and other chronic illnesses. On the other hand, prolonged DDS can deliver medication over a span of days or even weeks. Qiao and colleagues produced four types of CHAM microspheres with hollow mesoporous carbonation by blending CaCO3 and SDS using a hydrothermal process. Adjusting the amount of SDS can regulate the shape, dimensions, and thickness of CHAM. The research revealed that the level of SDS had a positive impact on enhancing drug entrapment efficiency, as well as sustaining release, biocompatibility, and osteoconductivity. The release of drug was reliant on pH due to the pH-sensitive degradation of CHAMs. The HAP crystal morphology is crucial for protein and drug adsorption, sustained release and enhancing drug entrapment effectiveness by reducing crystallinity in Hydroxyapatite. Overall, the C group of CHAM appears to be the top choice for managing and gradually releasing cis-diaminedichloroplatinum (CDDP). The research recommended this system as a perfect choice for cancer treatment due to its high effectiveness on human squamous cell in laboratory settings and its ability to trap CDDP. Moreover, this system could potentially be utilized in the treatment of cancer due to its effectiveness [66].

Tricalcium phosphate (TCP, Ca3(PO4)2)

There are two types of TCP: α-TCP is an elevated temperature phase, while β-TCP is a lower temperature phase. β-TCP shows superior biocompatibility, biodegradability, and thermodynamic stability compared to α-TCP [67-70]. In this scenario, β-TCP is utilized as a highly appealing carrier in the field of DDS, featuring capabilities for controlled, prolonged, and targeted drug delivery. By using a regulator (sodium dodecyl benzene sulfonate), it is possible to adjust the size, shape, and distribution of β-TCP.

Silicon based ceramics

Mesoporous SiO2 nanoparticles (MSNs) possess the favorable characteristics of being cost-effective, having a significant pore volume and surface area, adjustable and uniform pore sizes, a mesoporous structure, a high drug loading capability, favorable compatibility with biological systems, non-toxicity, stability, biodegradability. Therefore, they possess great potential in the area of Drug Delivery System for continuous and controlled release of medications along with precise delivery. Typically, the synthesis process involves hydrolyzing tetraethyl orthosilicate (TEOS, Si(OC2H5)4) [71, 72]. Zhang and colleagues created MSNs/hyaluronic acid for use as hyaluronidase-responsive drug delivery systems. This system showed a higher rate of DOX release, induced more efficient cell death in cancer cells compared to free DOX, and inhibited cancer cell growth with lesser cytotoxicity to the individual. Thus, the HAase-responsive system had the ability to serve as a DDS for specifically targeting cancer cells that produce HAase, like those found in colon cancer [73].

Liu et al created a near-infrared responsive drug delivery system using MSNs-ZOL (zoledronic acid) combined with IR-780 iodide and phospholipid bilayers. The research demonstrated that the drug release was influenced by NIR and

resulted in a decrease in cytotoxic effects, while also displaying excellent dispersion stability. The research proposed that this method could be utilized in areas of NIR-responsive drug delivery systems for cancer cells [74].

Dong et al created CD-MSN/UP38 by combining chemical synthesis and nanotechnology to incorporate BBD (4-Benzylamino-7-nitro-2,1,3-benzoxadiazole) as a thermal responder, with a temperature resolution of up to 0.2°C. Particularly noteworthy was the ability of this system to be activated by the thermal energy of a malignant tumor [75]. This system exhibited potent therapeutic benefits as well as reduced cytotoxicity, making it suitable for use in thermal-sensitive DDS cancer therapy.

Zeolitic Imidazole Framework (ZIFs)

ZIFs have rapidly become a new variety of flexible porous biomaterial for use in DDS due to their distinct structural variety, large surface area, satisfactory thermodynamic and chemical stability, favorable biocompatibility, and lack of toxicity [76-78]. Adhikari and colleagues [79] studied how well ZIF-7 and ZIF-8 carriers performed in releasing DOX. It was demonstrated that both carriers easily encapsulated DOX, with ZIF-7 taking 10 hours and ZIF-8 taking 3 hours for delivery of the drug. In addition, the stiffness of ZIF-7 resulted in a 10-hour duration of controlled drug release. Additionally, ZIF-8 displayed pH sensitivity and could release DOX in acidic conditions commonly found in tumor cells, a trait not observed in ZIF-7. Hence, the release of the drug could be managed by utilizing distinct traits of various ZIFs. This reference serves as a starting point for future research on using DDS for treating conditions like cancer [80].

2.5. PEG polymeric micelles

Micelles are amphiphilic copolymers that self-assemble into Nano size varying from 1 to 20 nm. These copolymer structures are basically built of two distinct functional domains: inner core and outer shell, known commonly as the corona. In general, the outer shell is built of blocks of hydrophilic segments like PEG, and the block forming the core is hydrophobic and varies widely. The outer layer governs pharmacokinetic properties within the body, whereas the central part is accountable for the envelopment of the drug, its stability, and the features of the release of the drug. Polymeric micelles are unique due to their feature of encapsulating poorly water-soluble drugs inside the core while the outer layer can be adjusted to present some specific attributes. In the context of the above, drug delivery and targeting using polymeric micelles may seem both promising and opportunistic.

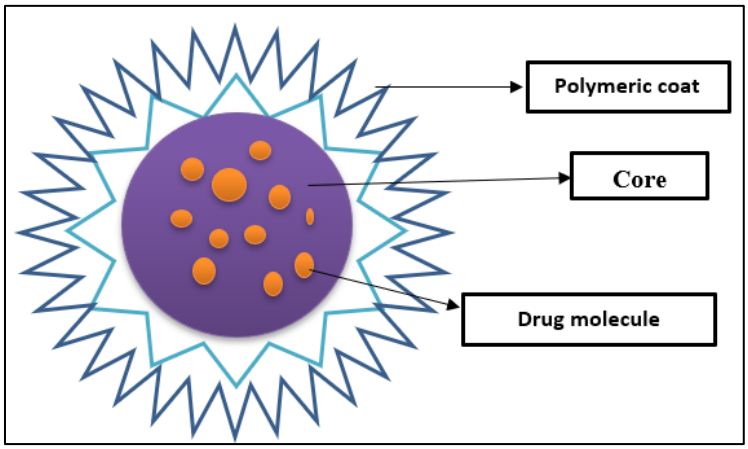

Figure 4 Structure of peg polymeric micelle

Paclitaxel is otherwise simply known as Taxol or PTX. It has been used as an effective medication over the last few decades, in the chemotherapy treatment of breast cancer, lung cancer, neck, head and ovarian cancers and even more progressive types of Kaposi's sarcoma [81, 82]. Paclitaxel is a diterpenoid naturally extracted from the Taxus brevifolia bark. It binds to mitotic dividing cells microtubules. This binding stabilizes kinetics, culminating in mitotic arrest of cell division [83]. Reduced water solubility of paclitaxel, approximately 0.6 microgram per milliliter, is the main formulation development challenge because it has to ensure safe and effective delivery of paclitaxel [84]. In commercial practice, PTX is co-suspended in a 50:50 volume/volume ratio of absolute ethanol and Cremophor® EL (polyethoxylated castor oil). However, this vehicle, Cremophor EL, has been implicated as the cause of numerous side effects, for Thus, aqueous-based formulations of Taxol have received much attention from research workers. Recently, Taxol has been delivered through a variety of systems such as nanoparticles, dendrimers, liposomes, and other polymeric carriers like Nano emulsions and niosomes [87, 88]. Instead, recent attention is paid to polymeric micelles that have unique characteristics favoring the solubilization of poorly soluble pharmaceuticals. Such a biodegradable copolymeric micelle system

employing mPEG–PLA and in US and Korea encapsulated PTX (Genexol®-PM) is recently under phase II clinical trials [89].

2.5.1. Polymeric micelles used in the anticancer drug delivery

PEG-PLA

In the majority of studies that have been documented, PEG is mainly used as a hydrophilic component of polymeric micelles. Nevertheless, there was a wide range of options for using the hydrophobic block (core). While different block copolymers have been utilized as the central component, only a small number of polymers, like PBLA and PLA, have been consistently employed as the hydrophobic block. In a report by Yasugi et al., Poly (ethylene glycol) -poly (D, L-lactide) block copolymers (PEG-PLA) were synthesized at room temperature by open ring polymerization in an argon atmosphere. The synthesized PEG-PLA copolymers were utilized to transport a hydrophobic medication. PEG served as the external barrier due to its hydrophilic nature, while PLA acted as the inner core shielding the drug from the aqueous environment. The micelles measured 50 nanometers, leading to a high extravasation efficacy due to the EPR effect [90]. Hami et al. (2014) combined PEG-PLA polymeric micelles with folate as a targeting agent to deliver DOX. They synthesized PEG-PLA block copolymer through ring-opening polymerization of lactide with carboxylic acid present. In short, vacuum - dried carboxylated PEG and lactide underwent a reaction in anhydrous toluene tin (II) 2-ethylhexanoate utilized as a catalyst at its reflux temperature. After the reaction solvent was evaporated, the PLA-PEG copolymer was isolated using chloroform. Folic acid is small in size, is non-immunogenic, has increased stability, and a low molecular weight. Thus, drug delivery systems of micellar have been altered with ligands that are target-specific such as folate to increase specificity of tumors and enhance tumor absorption through folate receptor-mediated endocytosis [91].

PEG-PLLA

PEG-PLA, derived from poly (L-lactic acid) -b-poly (ethylene glycol), has been studied in research for its ability to transport anticancer drugs and other medications. In 1996, Zhang et al. discussed the formation of polymeric micelles using MePEG-PDLLA di-block copolymer produced through ring-opening polymerization [92]. PEG-PLA, a type of polymeric micelles made from poly (L-lactic acid) -b-poly (ethylene glycol), is commonly used in research for delivering drugs, including anticancer medications. Bae and Yin (2009) discussed pH-responsive micelles made from poly (L-histidine) -b-poly (ethylene glycol) and poly (L-lactide) -b-poly (ethylene glycol). PH above 7.4, PEG-PLLA micelles were highly stable; however, they became unstable when the pH dropped below 6.8 due to greater electrostatic repulsion from the gradual protonation of the imidazole rings on the poly (L-histidine) blocks. Poly (L-histidine) (polyHis) is recognized for its ability to disrupt endosomal membranes through a B-proton sponge mechanism involving the imidazole groups. Therefore, the use of the polymeric micellar system with the polyHis core resulted in a more efficient method for delivering anticancer drugs into the cytosol [93].

PEG-PBLA

Poly (b-Benzyl-L-aspartate) produces AB block copolymer-based polymeric micelles, serving as an additional polymeric block. Yokoyama et al. (1998) documented that PEG-PBLA demonstrates the capacity to form micelles. Researchers conducted the polymerization of benzyl L-aspartate N-carboxyanhydride using the terminal amino group of α-Methoxy-ω-aminopoly (ethylene glycol) to create the block copolymer. [94]. In the year 2000, Kataoka and colleagues synthesized PEG-PBLA polymeric micelles by conducting ring-opening polymerization of α-Benzyl-L-aspartate. Under an argon atmosphere in chloroform, N-carboxyanhydride was generated from the terminal primary amino group of α-Methoxy-ω-amino poly (ethylene glycol) using Nippon Oil and Fats. Micelles capture both DOX dimer derivatives and DOX molecules. The dimer derivatives are assumed to slightly improve the stability of these micelles due to their low aqueous solubility and possible π–π-stacking-type interaction with benzyl residues of PBLA segments. PEG–PBLA micelles increased the blood circulation of DOX remarkably, and that may possibly be because of decreased uptake of the micelles by RES by a mechanism of steric stabilization [95]. Opanasopit et al. built PEG-PBLA micelles and worked on the delivery of camptothecin [96, 97].

2.6. Dendrimers

Dendrimers are compact, extensively branched polymers with a distinct core, a central area, and numerous terminal groups. The dendrimers have ideal properties like uniform size, capability to encapsulate, ability to dissolve in water, and numerous functional groups, making them promising for drug delivery. Multiple previous studies have discussed the initial research on utilizing dendrimers for drug delivery [98, 99]. At present, there are three approaches to utilize dendrimers in DDS: (a) create dendrimer prodrugs by covalently linking a drug to dendrimer's outer edges, (b) through ionic interactions, binding a drug to an external functional group, or (c) the dendrimer functions as a single-molecule micelle via trapping a drug within a dendrimer drug supramolecular complex through encapsulation. The latter method

is intriguing for several causes and allows for the containment of pharmacologically active substances and the exploration of the supramolecular structures created in these systems. For instance, polyamidoamine dendrimers and polypropylene imine have been used to encapsulate rose bengal and acetylsalicylic acid through noncovalent interactions. The internalized dye molecules in the example of rose bengal were restrained within the dendrimer as a result of steric congestion at the periphery of the dendrimer. Pyrene was placed inside unimolecular micelles made from PEGylated Fre´chet-type dendrites as well as polypropylene imine dendrimers. Moreover, 4-(dicyanomethylene)-2-methyl-6-(4-dimethylaminostyril)-4H-pyrane and phenol blue are examples of fluorescent dyes that have been encapsulated. Poly(amidoamine) dendrimers were utilized to improve ibuprofen delivery to A549 lung epithelial cells in another instance [29].

Dendrimers are being studied as incredible transporters for serious illnesses like cancer, tuberculosis, and AIDS [100]. Research has been conducted on dendrimers for the purpose of encapsulating and regulating the release of different anticancer medications owing to the simple production process, their capacity to hold high amounts of drugs, ability to pass through the skin, stability, and potential for delivering medication orally [101]. Dendrimers have shown to be effective drug carriers due to their high functionality three-dimensional arrangement and minimal disparity in size. Dendrimers could enhance the stability of bioactives, extend the residence time, and shield them from the biological surroundings [101]. Moreover, in gene therapy, dendrimers have been utilized to deliver genetic material inside target cells [102]. Dendrimers have been commendably studied for transporting anticancer medication and for theranostic uses in cancer treatment. Dendrimeric drug conjugates of anticancer agents have demonstrated the capacity to evade efflux transporter, enhance the bioavailability of loaded molecular cargo, and deliver the drug intracellularly. Dendrimer complexes with cisplatin have demonstrated decreased toxicity while displaying prominent anti-proliferative effects. In addition to delivering chemotherapy drugs directly to specific targets, dendrimers are being studied for delivering diagnostic agents to enable targeted imaging of cancerous tissues [103].

2.6.1. Methods for synthesis of dendrimer

Various methods such as divergent growth, hyper core, convergent growth branched, mixed growth, and double exponential are typically employed for dendrimer synthesis [104].

Divergent growth method

This method initiates dendrimer growth at the core, expanding outward. The technique was initially presented by Newkome and Tomalia, and the term divergent was derived from the method of dendrimer growth around the central core. Different methods of growth that diverge create a 3D structure in dendrimers by adding generations to a core, leading to an increase in surface functional groups, generation, and molecular weight [104].

Convergent growth method

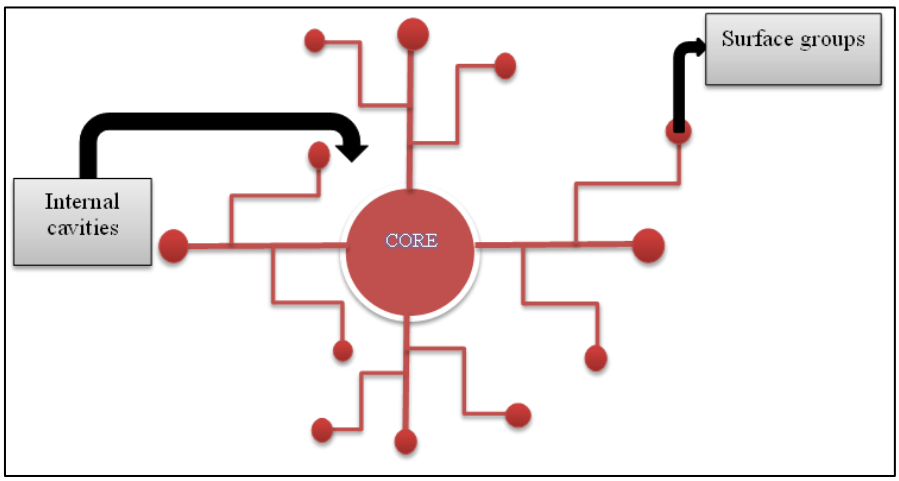

Figure 5 Dendrimer Structure

Primarily, this approach starts at the center and advances towards the inside. The branching segments are developed and linked to additional groups. Once reached to a certain size, these branches are connected to the central molecule [104].

Hyper core and branched method

In this process, oligomers are assembled beforehand and then combine to form the desired dendrimer structure in a small number of steps. This method is more suitable than the convergent method as it requires fewer steps for synthesizing of dendrimers higher generation [104].

Double exponential and mixed growth

According to this technique, both convergent and divergent growth methods are used to produce dendrimers [104]. It is the most innovative technique for dendrimer production, utilizing both convergent and divergent approaches to create a triangle known as the 'Dendrimer'. The growth process can be restated using the triangle [105].

2.6.2. Types of dendrimers

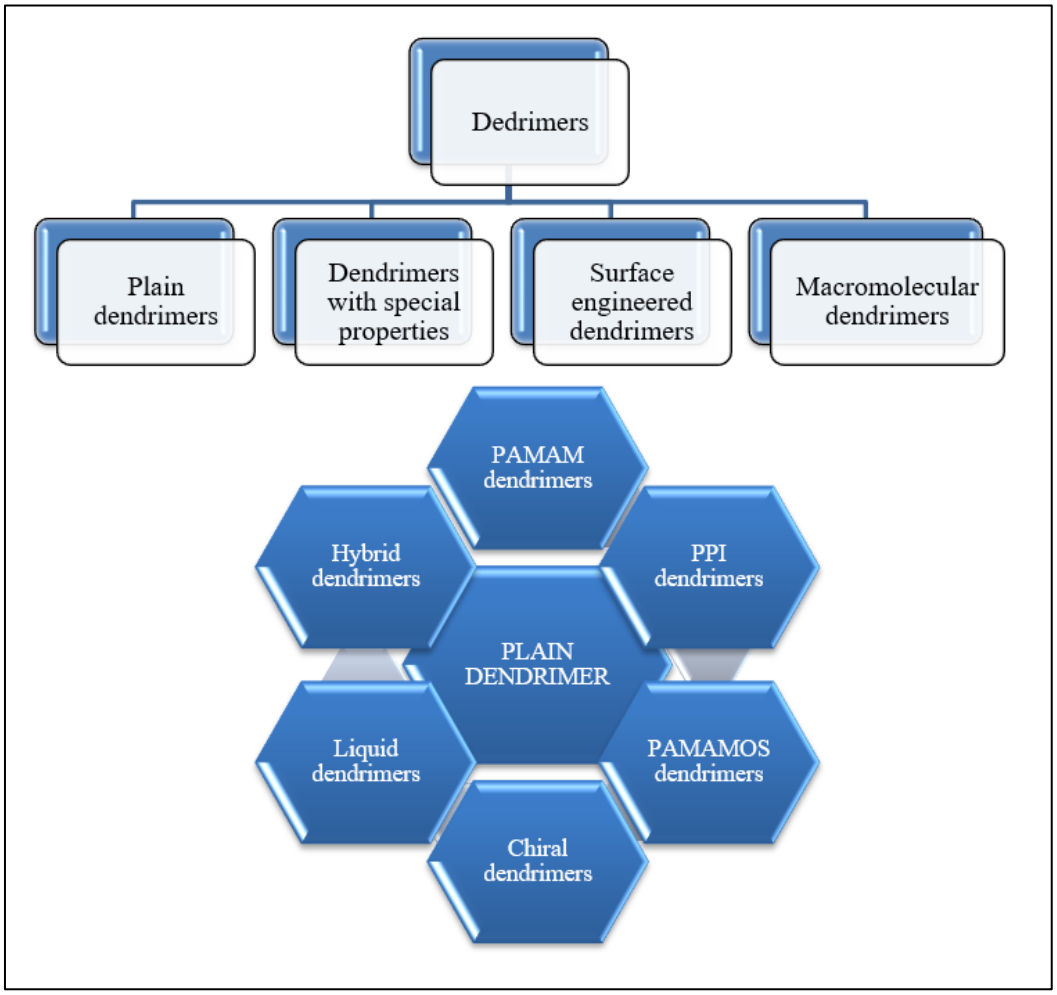

Figure 6 Classification of Dendrimer

2.6.3. Mechanism of dendrimer–drug interactions

Drug molecules can be linked to the dendrimer's end group through covalent bonds or trapped within the core through hydrophobic interactions, electrostatic interactions or hydrogen bonding [106]. The drug loading capability is affected by the number of generations, with higher generations offering more space for drugs and on the surface more functional groups for drug conjugation. PLL, PAMAM, PPI, polyether dendrimers, polyesters, polypeptide, and dendrimers based on carbohydrates or PEG have been primarily studied for delivering anticancer medications [107][108]. Because they have a high density of amine functional groups located on their outer surface, these dendrimers are extensively explored as carriers for drugs. Furthermore, the cationic charges of PLL, PPI, and PAMAM dendrimers assist in the transportation of genetic material. The discharge of drugs from dendrimers is determined by the specific interactions between the dendrimer and the drug. The anticancer medication interacts with dendrimers through three distinct processes: physical encapsulation, covalent conjugation, and electrostatic interaction [108].

Physical encapsulation

Because of their spherical shape, empty internal spaces, and structure, dendrimers are able to encapsulate drug particles within the interior of the macromolecule. Through hydrophobic interactions, the hydrophobic empty spaces within dendrimers interact with less soluble drugs. [99]. The interaction between drug molecules and oxygen or nitrogen atoms within dendrimers' internal spaces can occur through hydrogen bonding [109]. Drug molecules and the inner spaces of dendrimers could include interactions such as hydrophobic bonding, physical encapsulation, or hydrogen bonding. Because of their specific structure, drugs can be inserted into dendrimers through hydrophobic interactions, electrostatic interactions, or hydrogen bonding, with charged dendrimer surfaces. Physical encapsulation of drugs offers the benefit of simple and quick preparation with no alteration of the pharmacological activity of the drug, in contrast to chemical conjugation. Some drawbacks are the lack of stability in storage, early drug release, inconsistency in drug concentration between batches, and limited drug loading capacity [110].

Electrostatic interactions

The high concentration of carboxyl and amine groups present on dendrimers' surface offers potential in improving hydrophobic drug solubility through electrostatic interaction [111]. Dendrimers have formed complexes with drugs containing carboxyl groups, such as ibuprofen, diflunisal, indomethacin, and naproxen, through electrostatic interactions. By means of electrostatic interactions, different ionizable medications create complexes by versatile surfaces of dendrimers containing numerous ionizable surface groups. In PAMAM dendrimers, the primary amine group on the surface has titrable pKa values of 10.7 and tertiary amine group has pKa values of 6.5 within the core. Therefore, they contain ionizable groups at the end and also within their core, providing potential locations for drug interactions. Several drugs, including ibuprofen, benzoic acid, piroxicam, and indomethacin, have been found to create strong complexes via electrostatic interactions [112].

Covalent conjugation

The surface of dendrimers contains many functional groups, making them ideal for covalently bonding numerous drugs with the necessary functional groups [113]. When a drug is attached to dendrimers through covalent bonding, its release is triggered by breaking either chemically or enzymatically the hydrolytically unstable bonds [113]. Additionally, dendrimers can be linked to drugs using various spacers like p-amino hippuric acid, PEG, and p-amino benzoic acid, etc., as well as biodegradable bonds like ester or amide linkages. This method of using prodrugs has been discovered to enhance drug stability and greatly impact their release rate. Multiple researchers have effectively attached naproxen, penicillin V, 5-aminosalicylic acid, venlafaxine, and propranolol to PAMAM dendrimers. The findings indicate controlled drug release and improved drug solubility from these complexes when compared to the drug on its own. In addition, dendrimers have been used to conjugate various anticancer drugs for example cisplatin, methotrexate, epirubicin, doxorubicin, and paclitaxel, resulting in promising drug targeting effects [114].

2.7. Silver nanoparticles

Metal NPs like gold, silver, and platinum NPs possess a large surface area and are typically tiny, around 50 nanometers. Their small size enables them to move through capillaries in cells and tissues. Their large surface area, in addition to being able to chemically alter their surfaces, enables nanoparticles to transport a reasonable amount of drugs. Metal nanoparticles have been employed for regulating drug release in cancer treatment [115]. Although it is desired for these metals to be inert, there may still be potential for toxicity and bioaccumulation. Conversely, a significant benefit of metal nanoparticles is their capacity to absorb light energy effectively and transform it into heat. So, they can be utilized in hyperthermic tumor treatment, where thermal energy is delivered through photo stimulation, to increase the specificity of this therapy [116]. Silver nanoparticles (AgNPs) are being more widely utilized in various industries such as food, pharmaceuticals, microelectronics, and aerospace, as well as in medicine, because of their unique biological, physical, and chemical intrinsic properties [116].

The unique features of silver nanoparticles, including their optical, biological qualities, and high electrical conductivity, contribute to their broad potential for use in various therapies such as anti-fungal, antibacterial, anti-viral, anti-inflammatory, anti-angiogenic, and anti-cancer treatments. AgNPs are commonly employed in the manufacturing of detergents, cosmetics, and hygiene products. Recent research suggests that in diluted concentrations, AgNPs are harmless to humans but still effective at killing bacteria, viruses, and other eukaryotic microorganisms[117]. Numerous researches have indicated that silver nanoparticles are being used in cancer therapy as anti-cancer agents [118]. Multiple experiments conducted in a laboratory setting have shown that silver nanoparticles can be ingested by the cells through endocytosis and are typically found in the perinuclear region of the cytoplasm and within the endolysosomal compartment [119] [120]. Additionally, silver nanoparticles are able to penetrate the mitochondria and generate reactive oxygen species (ROS) by impacting cell respiration. In short, the toxic effects of AgNPs can cause mitochondrial

damage, DNA damage, apoptosis induction, and oxidative stress in cancer cells [121].]. The process by which silver nanoparticles affect cancer cells is depicted in a diagram. Additionally, research has shown that AgNPs impact the activity of VEGF (vascular endothelial growth factor). It is also denoted as vascular permeability aspect and has a significant impact on angiogenesis in tumors [122]. These findings suggest that AgNPs possess anticancer effects and may serve as a substitute for angiogenesis inhibitor therapy and cancer therapy [123]. Theranostic uses of green-synthesized nanoparticles were studied for their potential in the biomedical field, including activities such as anti-nociceptive, antimicrobial, anticancer, anti-inflammatory, and enzyme inhibition. Theranostic refers to the combination of both diagnostics and therapy. The AgNPs produced through biological methods have potential uses in theranostic applications such as anti-cancer treatments, bio imaging vehicles, and drug delivery [124]. Green silver nanoparticles have the capability to function as advantageous theranostic agents for the exploration of diverse biomedical uses. AgNPs, synthesized biologically for various uses, were evaluated in diverse cancer cell lines [125].

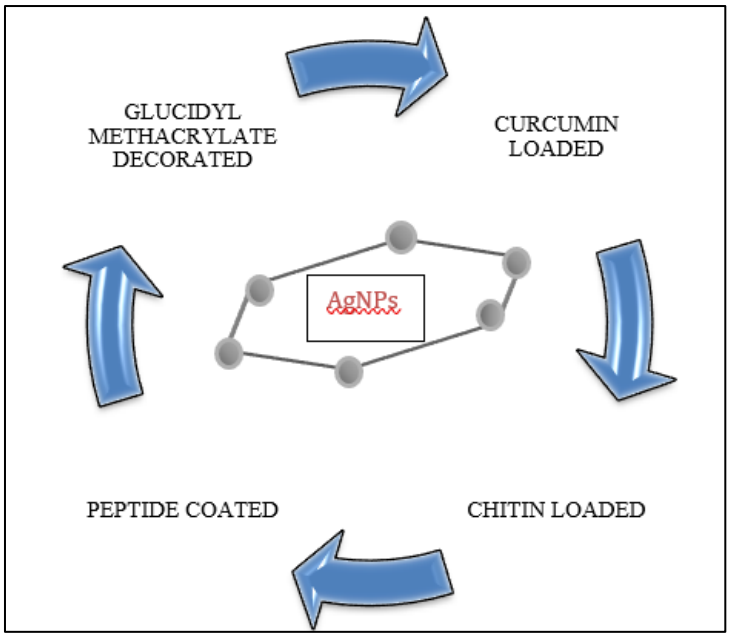

Figure 7 Various Types Of Silver Nanoparticles

Methotrexate, an anionic anticancer medication from the antimetabolites class, is a folic acid analogues employed for the treatment of various cancer forms like lung and breast cancer. It exhibits a brief half-life of 03–17 hours and experiences rapid removal from cells, necessitating high treatment amounts of 15–20 mg/m2, administered twice weekly. Some adverse reactions that may be caused by this medication include hair loss, reduction in blood cell count, harm to the liver, harm to the lungs, and more[126]. In 2020, Rozalen and colleagues[126] created AgNPs with an average size of 11.13 ± 2.3 nm and combined them with methotrexate to form AgNPs-MTX. The AgNPs-MTX was synthesized chemically with the use of sodium borohydride and citrate as reducing agents, with citrate also serving as a capping agent. Sodium borohydride and trisodium citrate solutions were combined in water and then heated at 60 °C with intense stirring, keeping a dark environment. Next, silver nitrate solution was gradually dropped into the mixture. By adding sodium hydroxide, the pH was adjusted to 10.5, and the temperature was raised to 90 degrees Celsius. The solution that was obtained was stirred for 30 minutes continuously. Afterward, the AgNPs that were prepared were cooled to 25°C, centrifuged at 12,000 rpm for 15 minutes, and then kept at −80 ◦ C for 48h in order to undergo additional freeze-drying. Eventually, varying amounts of solutions of methotrexate in potassium carbonate were slowly dripped into newly prepared suspensions of silver NPs. The resulting colloids were then stirred for an additional 30 minutes, leading to the creation of AgNPs-MTX 400, AgNPs-MTX 200, and AgNPs-MTX 300, depending on methotrexate concentration. Once more, the suspensions were air-cooled, spun at 12,000 rpm for 15 minutes, and then retained in a freezer at −80 ◦ C for 2 days before undergoing lyophilization. At first, nanoparticles are covered by citrate, which acts as a cap, and later, it is substituted with methotrexate molecules. The anticancer effectiveness of AgNPs-MTX, AgNPs, and free MTX was tested on lung cancerous cell line (A-549) and colorectal carcinoma cell line (HTC-116) after assembling AgNPs-MTX. Toxicity testing was done on zebrafish, with free MTX showing pronounced toxic effects, leading to higher rates of phenotypic alterations, pericardial edema, or embryonic mortality (13-20%). Nonetheless, the combination of AgNPs-MTX exhibited decreased side effects: mild pericardial edema, which vanished within 48 hours, and a reduced mortality rate (below 5%). The findings suggest a reduction in the toxicity of the Nano system compared to the administration of MTX alone. Hence, due to the combined AgNPs-MTX synergism and reduced cytotoxicity, the

utilization of AgNPs as a vehicle for methotrexate in chemotherapy must be further investigated. Epirubicin, a medication from the anthracycline class, is utilized for the treatment of breast, lung, and liver cancer. Having multiple hydroxyl groups allows it to have beneficial reducing characteristics [127]. This drug was another example found in the literature, which was assessed for its anticancer effect when in conjugation with AgNPs acting as Nano carriers. In the literature, this medication was also an example evaluated for its anti-cancer impact when combined with AgNPs functioning as Nano carriers. Ding et al.(2019)[127], chemically created silver NPs linked with epirubicin by introducing the anticancer drug to the heated solution of $AgNO_3$, held at 120°C for 60 minutes. In order to purify, Nano conjugate was subjected to dialysis in ultra-pure water for 48 hours (to get rid of unbound Epirubicin), then centrifuging at 10,000× g for 0.5 hours. The AgNPs, when produced, had a mean diameter of 36 nanometers. The drug was utilized for its reducing properties. This study showed that when epirubicin is exposed to 120°C for 1 hour it did not result in any alterations to the drug that would affect its effectiveness when synthesized with EPI-AgNPs. The nature of interaction among the nanoparticles and the drug was not specified by the authors in the study. Nonetheless, because of the resemblance between epirubicin and doxorubicin, it is possible to infer that the drug formed coordinated covalent bonds with silver NPs, likely using the hydroxyl groups that remained unoxidized during the reduction of silver NPs. In order to evaluate the anticancer effects of EPI-AgNPs, the HepG2 cell line was selected and MTT assays showed that the IC50 of the epirubicin-coated nanoparticles (1.92 μg/mL) remained greater in comparison to the free drug (0.11 μg/mL). Nevertheless, theoretically, this Nano carrier has the potential to decrease the occurrence of negative consequences by remaining in close proximity to the malignant tumor because of the EPR (enhanced permeability and retention) effect, ultimately minimizing the contact with healthy tissues. The authors asserted that the Nano system had significant benefits compared to the high doses of epirubicin used in treatment due to its toxicity and serious adverse effects. Because of the enhanced permeability and retention effect of the silver NPs, merely the tumor would be primarily targeted via the Nano system, resulting in decreased toxicity on healthy cells [128].

3. Drug delivery and toxicity related issues

In delivering drugs, the diffusion of nanoparticles and large molecules is a critical concern. The movement of microscopic substances across cells is influenced by various factors like tissue type, extracellular matrix composition, anatomical location, and more. The arrangement and concentration of decorin, collagen, and hyaluronan can hinder the diffusion of nanoparticles and large molecules in tumors [129]. Variations in blood flow within solid tumors also hinder the perfusion of nanoparticles, leading to unpredictable and uneven dispersion. Jain showed that problems in blood and lymphatic vessels can hinder the transport of macromolecules and nanoparticles in solid tumors [130]. Even though nanoparticles are perfect for addressing and resolving solubility and stability problems in drug delivery, concerns have been raised about their potential toxicity. Indeed, in recent years, several toxicology studies have shown that being exposed to specific particles derived from nanotechnology can present significant dangers to biological systems [131]. For example, when human keratinocytes are exposed to unsolvable single-wall carbon nanotubes, it can lead to oxidative stress and apoptosis[132]. Toxicity concerns are frequently overlooked in this intriguing area of study. For example, what happens to Nano carriers and their components in the body, specifically non-biodegradable ones like coating agents like poly (ethylene glycol) and functionalized carbon nanotubes? Is it possible for polymeric vectors and other polymer-based biomaterials to disrupt cellular processes or cause changes in gene expression when used for gene delivery? What are the potential impacts in the distant future? How much can we apply findings of immunological and cellular toxicity from animal studies to humans? The problem of toxicity is especially concerning when it comes to nanoparticles injected intravenously, as the likelihood of incorrect targeting is significantly increased due to the widespread circulation within the body. Delivery of nanoparticles directly to a specific region could be a reasonable method if intravenous administration is seen as risky, but what if non-biodegradable items build up in the local area.

4. Conclusion

Researchers worldwide are exploring Nano drugs as a potential method for drug delivery and effective treatments. The distinctive features of nanoparticles, such as their small size and surface properties, are being utilized to treat and target specific areas efficiently. Nano medicine, with advancements in molecular medicine, biochemistry, immunology, and artificial intelligence, is likely to emerge as the preferred option for cancer diagnosis and treatment management. The significant potential of nanotechnology has led to substantial scientific investment in this field. The NIH (National Institute of Health) strategic plan 'Nano medicine Initiatives' predicts that nanoscale techniques will offer increased medical benefits in the next decade. However, technologists must address concerns about the impact of nanomaterials on biological systems and any safety risks to ensure the successful and efficient application of these technologies. The future of Nano medicine depends on the strategic development of nanotechnology tools and materials, guided by a comprehensive understanding of biological mechanisms, instead of the current trend of using certain materials without proper consideration.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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