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Recent advances in nanocarrier-based targeted drug delivery: For lung, colon, and breast cancers

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ABSTRACT

For a while now, the development of research and technology has provided us with different approaches which show how cancer works and how is it possible to develop different methods of treatment. Nanotechnology and nano-carriers have shown a promising approach toward the treatment of different types of cancer. Nano-carriers based targeted drug delivery have different forms such as lipid-based, polymeric-based, inorganic-based, and hybrid-based, each of them is unique in structure, size, "function and" ability to deliver the drugs. Therapeutic substances can be used with the help of the applied modifications to the nano-carriers. These particles have shown significant benefits such as effectiveness, safety, low toxicity, biocompatibility, biodegradability and the improved quality of the treatment. The therapeutic properties of the nano-carriers can be regulated. This can help to provide an effective treatment for a patient with a specific diagnosed disease. The treatments can be administered either orally, intravenously or by combined route. The overall results of the use of nano-carriers have certainly created an interesting approach and created an opportunity for new treatments that improve the patient's profile.

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1. Introduction

Cancer, regarded as one of the most lethal diseases globally, instills fear worldwide. Considerable financial, human resources, and material have been dedicated to the realm of cancer diagnosis. Various medical imaging methods, including computed tomography, magnetic resonance imaging (MRI), and ultrasound, have proven effective in clinical settings, enhancing our knowledge, detection, and diagnosis of tumors [1, 2]. Cancer stands as the primary cause of mortality globally, resulting in approximately 7.6 million deaths each year. The most prevalent cancer types, namely lung, breast, and colorectal cancer, accounted for over a million new cases each in 2008. The incidence of cancer continues to rise due to factors like population aging, growth, and the adoption of cancer-related behaviors like smoking and alcohol consumption, particularly in economically developing nations [3, 4]. Notably, breast cancer remains a significant global health concern, especially for women, being the most frequently diagnosed cancer [5]. Unfortunately, our current medical technology has limitations when it comes to effective cancer treatment. Conventional methods like surgery, radiation therapy, and chemotherapy, though commonly used, lack specificity, often leading to side effects and harm to healthy cells [6]. Colorectal cancers, ranking as the third most prevalent cancer type worldwide, exhibit a higher occurrence in the colon compared to the rectum, particularly in industrialized countries. This discrepancy is even more pronounced among females. In Europe, around 250,000 new colon cancer cases are diagnosed annually, accounting for roughly 9% of all malignancies. The rates of colon cancer tend to increase with industrialization and urbanization and have been more prominent in high-income countries, but they are now on the rise in middle and low-income nations [7]. Lung cancer is currently the second most common cancer, making up 14% of all cancer cases in the United States for both men and women. Moreover, lung cancer is responsible for the majority of cancer-related fatalities, contributing to 28% of male cancer deaths and 26% of female cancer deaths [8]. In fact, lung cancer claims more lives than prostate cancer, breast cancer, colon cancer, and pancreatic cancer combined, presenting a significant challenge to public health [9]. Uncontrolled cell development is the cause of a group of disorders called cancers. These aberrant cells have the capacity to invade and spread throughout the body. Cancer cells exhibit changes in amino acid and lipid metabolic pathways, glycolysis, and redox homeostasis. This includes modifications in energy metabolism, increased expression of glucose transporters, disturbances in redox balance marked by elevated glutathione transferase (GST) levels, and heightened telomerase activity. These alterations serve to preserve DNA integrity, contribute to the resistance, and enable the continued replication and proliferation of cancer cells [10, 11]. Cancers are divided into blastoma, germ cell tumor, leukemia, lymphoma, sarcoma, and carcinoma depending on the alleged source of the tumor cells. A cancer that arises from epithelial cells is referred to as carcinoma and includes almost all malignancies of the colon, pancreas, lung, prostate and breast [12].

Conventional cancer treatments like chemotherapy, radiation, and surgical removal of tumors not only kill cancer cells but also damage healthy cells in cancer patients, causing a variety of unfavorable side effects such fatigue, anemia, internal bleeding, and appetite loss [13]. A drug delivery system (DDS) is a broad term encompassing a range of physicochemical technologies designed to regulate the delivery and release of biologically active substances into tissues, organs, and cells [14, 15]. The goal is to ensure that these active substances can achieve their maximum therapeutic effects while minimizing potential side effects [16]. Depending on the administration route, various methods are employed, including skin absorption, oral intake, inhalation into the lungs, intravenous injection, and mucosal delivery. Among these, the transdermal drug delivery system (TDDS) stands out as an appealing approach. TDDS have attracted more interest over the past few decades in an effort to improve therapeutic efficacy and lessen side effects. There are several instances of TDDS that are undergoing clinical trials, although TDDS clinical translation is generally delayed. To date, significant efforts have been made to find high-affinity ligands [17]. Nanocarrier-based drug delivery is a perfect example of TDDS which has various classifications [18].

A product or apparatus is termed a drug DDS when it enables the introduction of a therapeutic material into the body and enhances its safety and effectiveness by controlling the location of drug release, as well as the timing and rate [19]. This process involves administering the therapeutic product, allowing it to release the active compounds, and then enabling the active ingredients to traverse biological membranes to reach the site of action. Also known as a therapeutic substance, this term signifies an agent that triggers the in vivo production of the active therapeutic agent, as seen in gene therapy. Gene therapy can be viewed as a drug delivery system, encompassing both its fundamental and comprehensive meanings. Innovative delivery approaches might be necessary to introduce gene vectors into the human body, notwithstanding the unique regulatory constraints associated with gene therapy [20, 21]. The differentiation between the device and the drug is crucial because it serves as the standard for the drug control authorities' regulatory supervision of the delivery method. A device is subject to stringent regulations as a medical device when it is implanted inside a human body for a function other than drug administration, like achieving therapeutic effects through a physical modality, or when a drug is incorporated into the device to mitigate complications arising from its use. The differentiation between devices and drugs is extensive, and each situation will determine whether it belongs in one or the other group [22]. Herein possible use of different nano-carriers in drug delivery, and how each of the nano-carriers has unique characteristics which can provide strength in the delivery of the drug is discussed in the research.

2. Nanocarrier-based Targeted Drug Delivery

Finding ways to target and eliminate malignant cells while minimizing the impact on healthy cells is a major challenge in the therapy of cancer. Nanocarriers can circumvent the reticuloendothelial system (RES) and protect medications from being destroyed. Because of their high circulation profile, they are able to pass across biological barriers. Additionally, toxicity and other adverse effects related to traditional medications are decreased, and drugs are more easily accessible in the intracellular region. Advancements in nanotechnology have been harnessed in the medical field to address the issues related to drug delivery. Nanoparticles (NPs) have emerged as a key innovation in this context, providing effective solutions to the unique challenges associated with delivering anticancer drugs [23, 24].

NPs are described as particles with an exterior layer of different inorganic or organic coatings that influence their properties and these particles range in size from 1 to 100 nm [25]. Numerous studies have been done to take advantage of the potential benefits of NPs in drug delivery systems for cancer treatment, despite the fact that they have not yet been widely used in clinical therapies. Due to features including biodegradability, biocompatibility, and water dispersity, NPs have gained popularity as nanocarriers. The half-life and solubility of medications are increased by the use of NPs in the treatment of cancer, enhancing the bioavailability of numerous chemotherapy agents. Additionally, NPs can result in increased drug retention and permeability (EPR) in cancer tissues. However, despite these benefits, nanocarriers (NCs) have certain drawbacks. They can be rapidly cleared from the body by the RES, and they tend to have a broad distribution throughout the body [26]. In

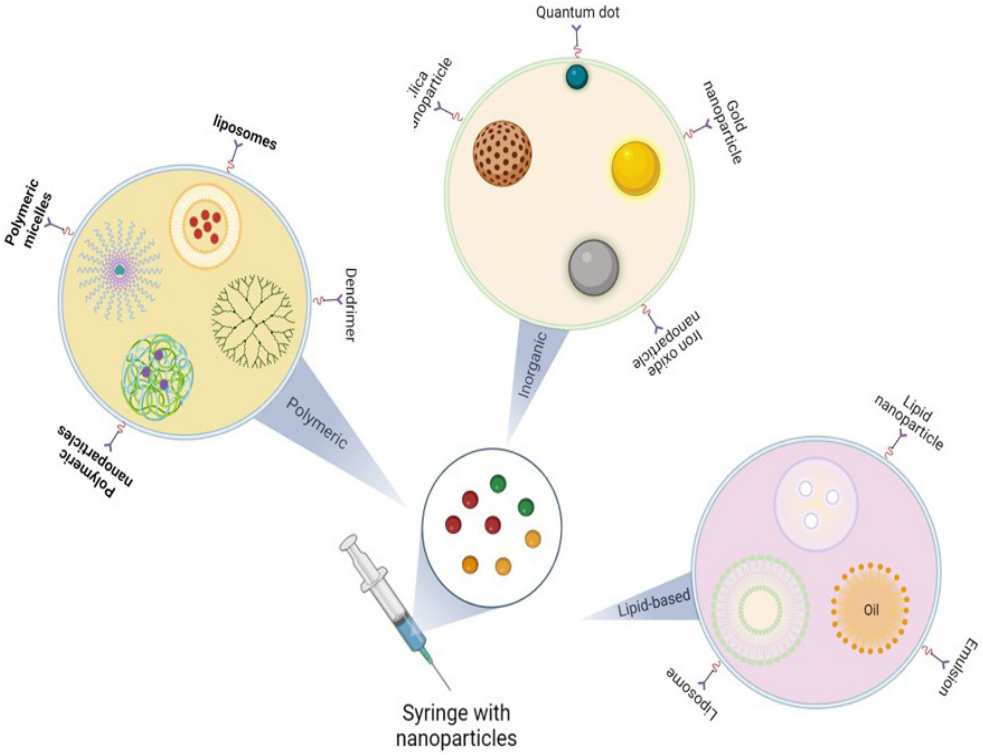

Fig. 1. different types of nanocarriers.

the end, the combination of NPs and anti-cancer drugs can increase the therapy's efficacy while minimizing adverse effects by focusing on certain cancer locations utilizing target ligands. Different NPs types have been applied to Breast Cancer-targeted DDS. These NPs can be categorized into protein, polymer-, liposomal-, carbon-, metal -based and mesoporous silica NPs [27]. Figure.1 shows the different classifications of nanocarriers which are mostly used in drug delivery systems.

2.1. Lipid-Based Nanocarrier

The most promising colloidal drug delivery systems (DDSs) currently available involve the utilization of nanoparticles (NPs) derived from natural polymers, such as polysaccharides, phospholipids, and proteins [28]. These systems have been recognized as more effective than synthetic polymers when it comes to drug loading capacity, biocompatibility, and avoiding opsonization by the RES [29]. Additionally, natural polymers have demonstrated their superiority over synthetic polymers

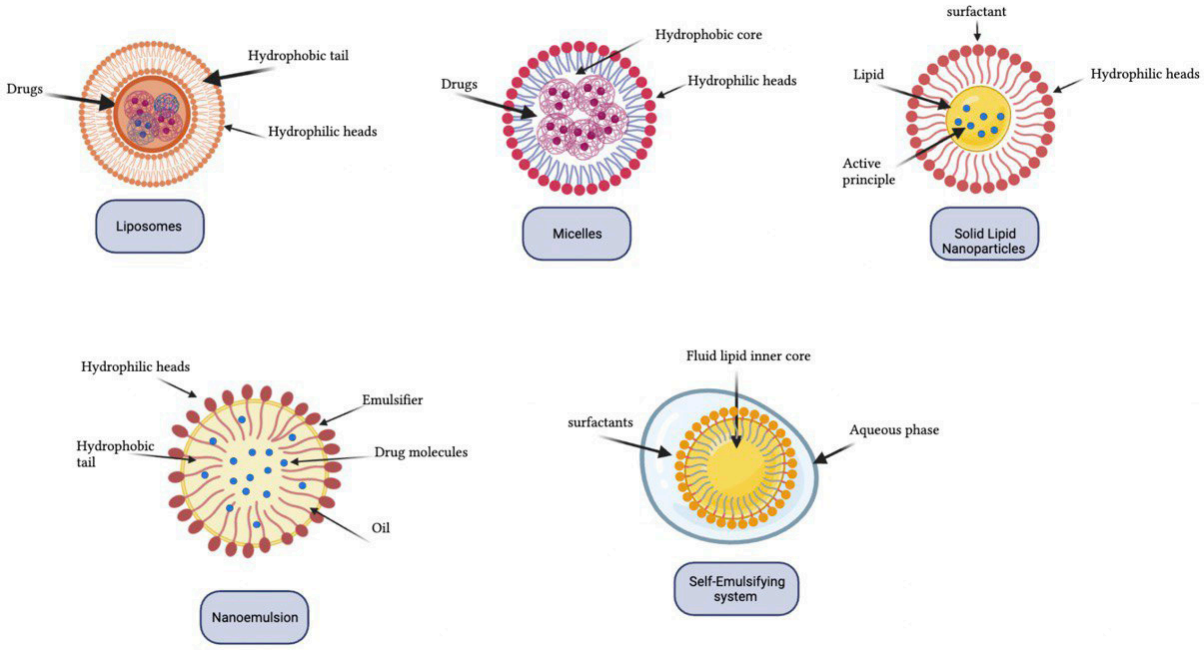

Fig. 2. Lipid based nanocarriers.

in terms of their ability to be absorbed by the human body and their production of less harmful byproducts when broken down [30]. Therefore, NPs crafted from naturally occurring polymers appear to be a more suitable choice for colloidal drug delivery intended for human use due to their reasonable safety and ease of preparation. An effective solution for addressing drug delivery challenges involves the use of a nanotherapeutic approach for administering hydrophobic chemotherapeutic drugs [21]. Lipid-based NPs are beneficial for drug delivery systems because they are biocompatible, have high drug loading efficiency, are stable in vivo, don't require organic solvents during synthesis, and have adjustable drug release modes [31, 32]. They are effective at delivering cytotoxic drugs and nucleic acids [33]. and are used in a variety of sectors, including biopharmaceuticals and food safety [34]. Various forms of lipid NPs including solid lipid NPs, vesicles, nanostructured lipid carriers, nanoemulsions, micelles, and liposomes are produced as a result of various manufacturing processes and lipid compositions, which also affect their spatial properties, chemical, and physical [35].

The liposomes are arguably the most well-known lipid-based nanostructures. A phospholipid bilayer encircles an aqueous core that may hold a variety of compounds in these spherical lipid vesicles. This characteristic is utilized in the loading of medications like gemcitabine. Additionally, liposomes are a good choice for nanocarriers since they are biocompatible, have gradual releases, and can be chemically altered to target cancer cells or prolong circulation time. Hardly surprising, liposomes make up the biggest nano platform for gemcitabine delivery.

The lipid bilayer that surrounds the hydrophilic inner core of the LNPs is hydrophobic. Hydrophobic medicinal drugs are typically enclosed in the phospholipid bilayer for delivery due to their distinct architecture. By encapsulating hydrophilic drugs in the inner core, LNPs are also widely used as therapeutic carriers for these substances. Due to non-target distribution, drug encapsulation also greatly reduces the toxicity of medications. Additionally, amphiphilic substances like doxorubicin (Dox) and vincristine, which have been demonstrated to have lower cardio-cytotoxicity than their unencapsulated forms, can be encapsulated within the LNPs aqueous inner core [36]. In figure.2 we are showing some types of lipid-based nanocarriers.

2.1.1. Lipid-based Nanocarriers for Targeted Drug Delivery to Lung, Colon, and Breast Cancers

Recent years have seen a rise in the importance of liposomes as effective anti-cancer drug delivery systems. Due to the remarkable biocompatibility of liposomes, research into them has increased over the past ten years, leading to the development of numerous novel formulations, including cationic liposomes, temperature-responsive liposomes, virosomes, and archaeosomes [37]. Liposomes are single or multiple-bilayer nanocarriers that can be created from lipids that are natural or manufactured. In 1965 Banham created phospholipid vesicles generated from liposomes, and they were soon recognized as potential drug delivery systems. These are categorized as small (300–500 Å) and big (500-1000 Å) uniflagellar vesicles, as well as multilamellar vesicles comprised of multiple concentric phospholipid bilayers from 1 to 5 um [38].

Breast cancer (BC) is a disease influenced by a variety of factors and has emerged as a significant health concern for women worldwide. Changes in lifestyle and the environment have contributed to the growing number of women diagnosed with breast cancer. This type of cancer is characterized by invasive neoplastic growth resulting from alterations in proteins and genes due to changes in the transcriptional processes within cells. Despite the availability of advanced chemotherapy and diagnostic tools, BC continues to be a highly lethal disease and presents significant treatment challenges [39]. One of the primary challenges in the treatment of breast cancer is addressing the development of multidrug resistance, which must be minimized for effective treatment [40]. In a research examining the biological response to Paclitaxel (PTX) and its encapsulation within LNPs, Marcial showed that PTX encapsulated in NLS with a size of 75 nm exhibited significantly greater effectiveness against MDA-MB-231 (IC50: 2.13±0.21 nM) and MCF-7 (half maximal inhibitory concentration, IC50: 25.33±3.17 nM) BC cells than the free drug, whose IC50 was above 500 nM. LNPs, by integrating their bilayer through the cell membrane, can build up in tumor cells. Improved targeting efficiency and longer half-lives have reportedly been achieved by employing polyethylene glycol (PEG) to modify the surfaces of LNPs. Both in vivo and in vitro, PEGylated LNPs demonstrated efficient targeting using passive techniques by encapsulating a number of medicinal agents, LNPs have also been utilized for the delivery of combination medications, aiming to achieve synergistic effects. For the treatment of BC that is insensitive to trastuzumab and hormones, Chiu and Wong presented a co-encapsulation technique which includes quercetin and vincristine in a PEGylated liposome. The results of this investigation demonstrated that co-encapsulation increased Extended drug circulation in the plasma, synergism, and achieved regulated in vivo release for JIMT- cells. In addition, when compared to the two different drugs, liposomal encapsulation has shown to be the most efficient method for inhibiting the proliferation of JIMT-1 cells [41]. For the treatment of metastatic BC, a nonPEGlyated LNPs system has also been developed to administer a mixture of cyclophosphamide and Dox. These nucleotides and peptides are prevented from degrading in the vasculature environment by being enclosed in LNPs, which also enables controlled administration using target ligands. Surface-modified LNPs with an A7R-cysteine peptide were designed to deliver PTX to MDA-MB-231 cells both in vivo and in vitro. The findings supported the significance of peptide as a targeting ligand in the PTX targeted administration by demonstrating that A7R-cysteine peptide improved vesicle uptake, enhancing accumulation and cytotoxicity in the BC xenografts. Another work used chitosan-coated LNPs to describe an in vitro co-delivery system of Small interfering RNA (siRNA). Vascular endothelial growth factors (siVEGF) and hypoxia-inducible factors (siHIF1-α) were co-delivered in this investigation to reduce cytotoxicity and increase silencing effectiveness. For the siRNA delivery to BC that expresses HER2, a carrier combination of liposomes has also been reported and bio-nanocapsules made from the antigen on the surface of the hepatitis B virus. Through the use of this strategy, protein knockdown and gene silencing were accomplished. Using siRNA and Dox, Chen et al. [42] explained an anionic and cationic liposomal method to overcome BC's multidrug resistance (MDR). This investigation demonstrated the creation of liposome-polycation-DNA (LPD) NPs utilizing a cationic lipid that contains guanidinium, which produces reactive oxygen species (ROS) and inhibits the expression of the MDR. Targeting passive metastatic BC while combining siVEGF led to an increase in Dox cell uptake. Dox was more effectively trapped by anionic-LPD NPs that had been altered to prevent Pgp-mediated drug efflux. Due to their ability to safeguard and be encapsulated until they arrive to the target cells, that is crucial for siRNAs and peptides, LNPs have become increasingly Well-known as a nanocarrier for easily biodegradable therapeutic drugs. While amphiphilic therapies can be encapsulated in LNPs, the LNPs' size is significantly greater (<50 nm), that may be a drawback for nano delivery. Additionally, LNPs are frequently with a polymer coating that increase their size and improve biocompatibility.

Many drugs that have been licensed for the treatment of lung cancer are constantly being transformed into liposomal formulations. The following drugs were created as liposomal formulations: epirubicin, cisplatin (CPPD), vinorelbine (VNB), docetaxel (DTX), erlotinib, irinotecan (IRI), paclitaxel (PTX), Dox, and etoposide (ETP). Additionally, the antimetastatic effectiveness of tretinoin and DOX-conjugated liposomes as chemotherapy treatments for tumors that have metastasized to the lungs (breast cancer, melanoma) has been investigated. Since liposomes

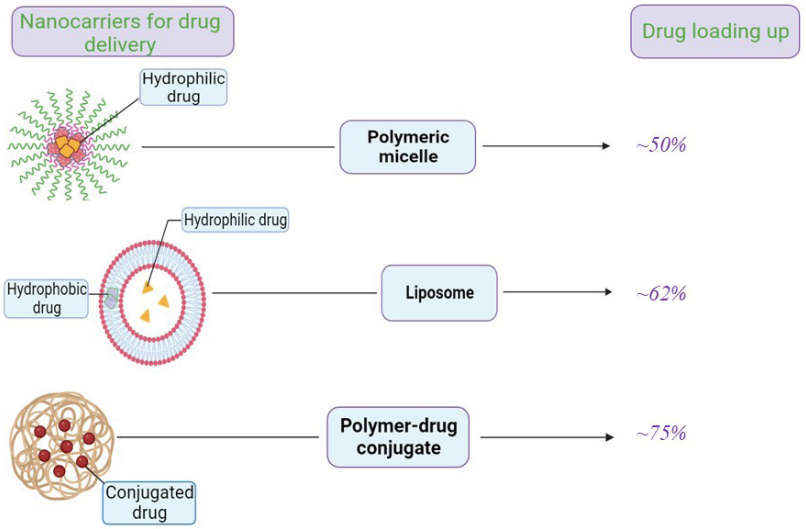

Fig. 3. Nanocarriers and drug loding.

have an extended release characteristic and a higher likelihood of administering therapeutic agents specifically to their intended targets, they are more effective and less intrusive in delivering drugs to the bronchial tissues, which is important [43].

Hydrophilic medicines like DOX, a hydrophilic weak base molecule, have been loaded via gradient techniques or remote-loading. Liposomal-based formulation reduces medication-related toxicity by acting as a water-insoluble substances like PTX, solubilizing matrix for hydrophobic. Through modifications to the surface of lipid bilayer and the addition of synthetic PEG to the mixture, PEGylated liposomes or stealth liposomes are created. Incorporating PEG into the liposomal membrane makes the liposome to circulate in the bloodstream for an extended duration, thereby reducing its uptake by the phagocytic system, especially when cholesterol is introduced into the lipoidal layer.

When the molecule of drug enters intracellular areas of action through the cellular membrane, therapeutic activities begin. As an outcome, it was suggested to use ligand-targeted liposomes to increase the delivery of liposomes with more selectivity. For use in lung cancer research and treatment, this method has attracted a lot of attention. Targeting the organelle in demand, overexpressed receptor-mediated targeting, and targeting of the tumor microenvironment (TME) are the three main targeting techniques used in lung cancer. When a liposome is created, a target-specific ligand is attached using DSPEMPEG (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[maleimide(polyethylene glycol)], this integrates the ligand with the membrane. On occasion, the ligand penetrates the lipoplasmic surface.

The EphA2 (Ephrin A-family) and EGFR receptors are significantly inhibited by cetuximab140. This ligand was connected to the DSPE-MPEG maleimide group via the liposomal bilayer's surface. Small compounds such as anisamide, that targets overexpressed sigma receptors were combined with DSPE-PEG and arginylglycylaspartic acid, that targets overexpressed integrin receptors. DOPE (1, 2-dioleoyl-sn-glycero-3 phosphoethanolamine) was shown to be associated with a CD44 receptor targeting hyaluronic acid ligand. RGD-grafted liposomes carrying siRNA were more effectively absorbed by non-small cell lung cancer (NSCLC) cells from a formulation of epirubicin liposomes that was both target-specific and multifunctional. The developed multipurpose liposomes of epirubicin outperformed non-targeted liposomes in terms of anti-cancer effect, survival time, and tumor-targeting effectiveness. Octreotide is a tumor marker that can bind specifically to the overexpressed receptors of somatostatin to attach to the liposomal membrane. Various liposomal formulations are being tested in various stages of clinical studies to treat NSCLC. Nontargeted and targeted liposomal drug delivery strategies have been found to increase therapeutic efficacy and biodistribution in a number of preclinical studies. The first nanodrug to receive FDA (U.S. Food and Drug Administration) approval was Doxil in 1995. PEGylated nanoliposomes were used, which helped to avoid RES and increase the drug's circulation time. Phase I clinical studies for To-

Table 1.
Lipid-based nanocarriers

Lipid-Based Nanocarriers					
Cancer	**Material**	**Drug**	**Method**	**Main Results**	**Ref.**
Lung	PEGylated liposomes	Hydroxyurea (HU), Nanoliposome containing HU (NL-HU), Doxorubicin	Specific method of attachment of the cytotoxic drug and linker to the antibody	elimination of breast cancer tumors with specificity in vitro and in vivo, opening the gate for further clinical evaluation in HER2-positive breast cancer.	[48]
Breast	Liposomes	PEGylated liposomal Doxorubicin (Dox)	Oligonucleotide and Peptide Synthesis	the PR_b- PEGylated nanoparticles, therapeutic payload directly to the breast	[49]
Breast	Liposomes	thermogel (DOX-Lip-Gel),doxorubicin (DOX)	open-ring polymerization	hybrid system of liposomal doxorubicin (DOX-Lip) loaded thermogel (DOX-Lip-Gel) to realize the steady sustained delivery of doxorubicin (DOX),	[50]
Breast	Liposomes	doxorubicin	Thin-film hydration method	microfluidics to produce PEGylated DSPC liposomes loaded with doxorubicin, umbelliprenin was selected as a co-therapeutic	[51]
Colon	Liposomes	Dihydroartemisinin (DHA), doxorubicin (Dox)	Multidrug resistance (MDR)	anti-MDR effect of the Man-liposomes involved preferential nuclear accumulation of the therapeutic agents, enhanced cancer cell apoptosis, downregulation of Bcl-xl, and the induction of autophagy.	[52]

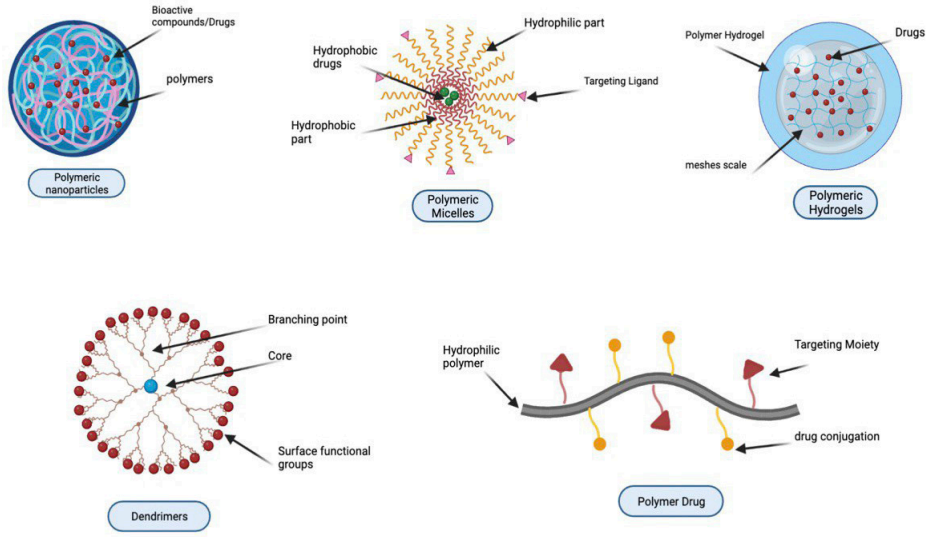

Fig. 4. Polymeric nanocarriers.

potecan and Doxil, two potential therapy options for SCLC, have begun. Nevertheless, there is no information available from this investigation.

The most often used medicine in regimens for lung cancer treatment is the chemotherapeutic agent CPPD. The first liposomal CPPD to be created, SPI-077 (Alza Corporation), included the same lipid composition as Doxil. When compared to CPPD, preclinical trials and animal studies showed promise Effectiveness in the treatment of NSCLC and a potential slow down the tumor cells proliferation and growth. Large dosages of liposome-based CPPD when delivered are safe and have reduced toxicity in patients with NSCLC, according to the data from phase I/II trials. Two clinical trials (phase II and phase III) that were randomly undertaken to compare the lipoplatin potency in NSCLC. It was discovered that lipoplatin-conjugated gemcitabine or paclitaxel was just as effective as cisplatin-conjugated versions of those drugs. These formulations have also been shown to be significantly less harmful [44]. Stimuvex showed positive outcomes in the early-stage trials in NSCLC patients (stage IV and stage III) [45]. The first cancer vaccine to progress into multiple advanced Phase III clinical trials, including START, INSPIRE, and STRIDE, was conducted globally. One issue with liposomes as drug delivery systems is the requirement for uniformity in biological fluids. Unwanted effects are consequently produced as a result of drug molecules leaking into natural tissues. At the end, by providing target-specific theranostic drugs for malignant cells, prospective investigations into liposomal-conjugated drug delivery may be structured utilizing adaptable functional platforms.

As a theranostic for lung cancer, liposomes have also demonstrated outstanding biocompatibility and biodegradability. Additionally, liposomes are superior to other NPs in that they may hold a variety of medicinal compounds and are simple to create and use to long-term drug delivery. Contrasting substances like gadolinium (Gd) are frequently used for morphological evaluation utilizing MRI [46]. Even though liposomes conjugated with Gd have been shown to have no observed toxicity or detrimental effects on normal cells, but if loaded with anticancer drugs and paired with specific ligands of interest, these complexes could be serve as a promising theranostic tool for the treatment of cancer. Table.1 shows some compact details of lipid-based nanocarriers effects on the three mentioned cancers. In order to assess shape of doxorubicin-encapsulated liposomes, drug encapsulation effectiveness, zeta potential, and the size distribution, Cheng and colleagues employed the EGFR binding properties of a novel peptide known as GE11 [47].

A 10% GE11 density was found to be ideal for A549 cytotoxicity. Using a near-infrared (NIR) fluorescence imaging system, they found that GE-11 modified liposomes aggregated and maintained 2.2-fold more than unmodified liposomes [47]. Additionally, a key objective of enhanced and modified liposome-based drugs will be to overcome therapeutic resistance. Implementing the recommendations discussed, that also seek to minimize the adverse effects on tissues and healthy cells, could advance the treatment of lung cancer through therapy [38]. Table.1 shows the details of lipid-based nanocarriers for breast, lung and colon cancer.

2.2. Polymeric Nanocarrier

Particles made of, synthetic, semi-synthetic, or natural polymers are known as polymeric NPs. Many monomer units are polymerized to form polymeric nanosystems, which can self-assemble and organize into nanometric structures with sizes between 10 and 100 nm. NPs are highly sought-after as multifunctional nanocarriers in DDSs because of the wide variety of their features. Drugs can be entrapped, bonded to polymeric NPs in the form of a nanocapsule, drug conjugate, or nanosphere, or encapsulated depending on the synthesis process. In contrast to nanocapsules, which are systems made up of a core cavity containing a polymeric shell around it and an encapsulated drug, colloidal particles known as nanospheres can physically disperse or adsorb drugs onto their surface to trap them within their matrix. Targeting ligands that enhance intracellular drug delivery, boost selectivity for cancer cells, and decrease drugs toxicity and side effects can be combined to create polymeric capsules. Antibody fragments or monoclonal antibodies (mAbs), peptides, aptamers, and tiny compounds, like folic acid, that are attached to the shell-forming block, are frequently the targeting ligands of polymeric capsules. In figure.3 we are showing nanocarriers for drug delivery and drug loading.

These ligands specifically bind to receptors or antigens which are overexpressed on cancer cells, enabling intracellular transport and cellular selectivity of polymeric micelles. The effectiveness of polymeric carriers that have been altered with targeting ligands relies on various ligand characteristics, including their affinities and their density of receptors. These attributes have the potential to enhance receptor uptake and the distribution of drugs throughout the body. In the case of drug-conjugates, a drug forms a chemical bond with the polymer via a spacer or linker. The bond between the drug and the spacer/linker is a common point of rupture during drug release at the target site.

Biopolymers, known as natural polymers, encompass various categories of polysaccharides and proteins. They stand out in medical applications, such as gene therapy, tissue engineering, and cell-based transplantation, owing to their biocompatibility and biodegradability. By chemically altering the functional groups of natural polymers, they can be combined with synthetic molecules, resulting in what we refer to

as semi-synthetic polymers. These semi-synthetic polymers are capable of mimicking components found in human tissues. In the context of controlled drug delivery systems, synthetic polymers are receiving more attention than biopolymers. This is primarily owing to the significant capability they offer for modifying their physicochemical properties and designing their structure.

Synthetic polymeric micelles possess a remarkable ability to encapsulate a wide array of bioactive substances. This encompasses photosensitizers, messenger RNAs (mRNAs), interfering ribonucleic acids (iRNAs), small proteins, plasmid DNA, and antisense oligonucleotides. This versatility is achieved by customizing the core-forming segments of the block copolymers. Positively charged block copolymers have been electrostatically bonded to a variety of poly-ion complex (PIC) micelles to incorporate negatively charged biomolecules. Additionally, these micelles can be made more stable by covalently crosslinking their cores with disulfide bonds. Under specific intracellular conditions, these bonds can be selectively cleaved, enabling the complexes to exit endosomal compartments after endocytosis. This ensures the successful delivery of biomolecules to subcellular destinations without degradation. PIC micelles can transport intact biomolecules to therapeutic sites by enhancing stability and prolonging their half-life in the bloodstream through the incorporation of hydrophobic compounds like cholesterol into the core. PIC micelles, which can be formed using block copolymers with a core-forming polycation like polyaspartamides, facilitate both in vivo and in vitro gene transfection as well as improved biomacromolecule transport to cells' cytosols.

Synthetic polymers have enormous potential as drug carriers, which has recently come to light in part due to the possibility of creating DDSs that have a targeted continuous or controlled release of drugs. More effective drug delivery is achieved by encapsulating cancer drugs in polymeric micelles that have been modified for triggered release and cancer targeting. Synthetic polymers employed in DDSs have to be stable in blood circulation, activated at the site of action, have minimal immunogenicity and toxicity, and provide protection against the breakdown of pharmaceuticals prior to the target tissue as well as to being biocompatible and biodegradable. The ability to readily and impure-free produce polymer nanocarriers of DDSs is also important [53]. In figure.4 we are showing some types of polymeric nanocarriers.

2.2.1. Polymeric Nanocarriers for Targeted Drug Delivery to Lung, Colon, and Breast Cancers

Apart from the pain linked to administration and general discomfort, traditional anticancer medications often produce adverse effects. However, because of a lack of an adequate concentration of drug of therapeutic at the site of lung tumor, drug administrations have not proved practical in the treatment of lung cancer. NPs present a novel approach to delivering anticancer drugs due to their distinctive shape, surface charge, and size.

A biodegradable diblock amphiphilic copolymer (mPEG-b-p(LA-CO- CG)) with a carboxylate group for platinum chelation was created. The drug-polymer conjugate's cytotoxicity for breast cancer was comparable to that of oxaliplatin but less than that of cisplatin. Due to its few side effects, this polymer conjugate demonstrated the potential for usage as a targeted carrier vehicle. Paclitaxel-loaded PEG-B-PCL polymer micelles with octreotide and salinomycin modifications were created by Zhang et al [54]. Breast cancer treatment was improved by this combination therapy. The combination was created to remove stem cells of breast cancer as well as cancer cells of the breast that are resistant to standard chemotherapy. Receptor-mediated endocytosis provides the basis for the cancer cells elimination. Salinomycin has a passive targeting mechanism, while paclitaxel with an octreotide modification uses an active targeting mechanism. Curcumin polymeric micelles, created by Liu et al., [55] were biodegradable self-assembled polymeric micelles loaded with curcumin that demonstrated good water solubility and complied with the conditions for intravenous administration. Curcumin polymer micelles' reduced cytotoxicity and sustained release make them potential candidates for use as antimetastatic treatments for breast cancer. For tumor imaging, near-infrared (NIR) fluorophores on polymers offer effective benefits such better targeting, lower toxicity, a larger surface area, stability, and longer plasma half-lives.

The use of NIR fluorophores for in vivo tumor imaging is growing. Along these lines, expensive equipment, an incontinent radionuclide labeling step, or a local cyclotron are not necessary for NIR fluorophores. Hydrophobically modified glycol chitosan NPs (HGC-Cy5.5) with molecular masses ranging from 20 to 250 kDa have been created by Kim et al. [56] using NIR Cy5.5 labeling. According to an in vivo biodistribution investigation, high-molecular-weight HGC-Cy5.5 exhibited a higher ability for tumor targeting than low-molecular-weight HGCCy5.5, but low-molecular-weight HGC-Cy5.5 removed away from the body more quickly. These imaging agents, which are utilized to find solid tumors, are provided by these probes. NIR fluorescent-activatable polymeric NPs (Cy5.5) coupled effector caspase-specific peptide with effective cell permeability and biocompatibility have been produced by Kim et al [57]. These were apoptosis-sensitive NPs, measuring 80–100 nm. This probe may be used to image apoptosis in individual cells [58].

The utilization of polymeric NPs in lung cancer treatment shows encouraging outcomes. Taxanes-loaded in Polyethylene-glycol-modified polylactic acid (PEG-PLA) NPs have substantially enhanced in vivo chemoradiation therapy (A549 lung tumor xenograft model) and in vitro. Kim and colleagues developed NPs for the lung cancer treatment by encapsulating cisplatin and paclitaxel within PEG-PLA block copolymers. These NPs have entered phase II clinical trials under the name Genexol-PM for advanced NSCLC. The same nanocarrier is being used in a phase II clinical trial to deliver gemcitabine for the metastatic lung cancer treatment.

Jiang et al. [59] recently made an attempt to create a nanoformulation that lung cancer patients might take orally. They created a polymeric NP based on polycaprolactone (PCL) that is further modified with chitosan. Chitosan's mucoadhesive characteristics can be used to engage specifically with mucin that is overexpressed in cancer cells. A PCL-based diblock copolymer nanoformulation for the administration by the mouth of a lung cancer treatment was also described by Zhao et al [60]. Docetaxel NPs have recently demonstrated superior lung cancer treatment efficacy over Taxotere, an injectable version of docetaxel. Lomustine NPs based on chitosan were created and demonstrated improved anticancer activity in vitro versus the cell line L132 of lung cancer. Recently, expansile nanoformulations including paclitaxel-loaded polymeric NPs have also been developed for the treatment of early-stage lung cancer, delaying the local recurrence of subcutaneous lesions. Since the drug only affects the lung or target site, pulmonary chemotherapeutic drug delivery or inhalable nanocarriers are becoming more and more common. So, systemic delivery-related toxicity can be avoided. Additionally, prolonged release of therapeutic drugs in the lung is made possible via pulmonary NP delivery. For the most part, aerosols and nebulization forces have been used to deliver NPs to the lungs.

In addition, NPs administered via the pulmonary route have the ability to bypass lung phagocytic mechanisms and mucociliary clearance, resulting in an extended residence time within the respiratory tract. Between various nanocarriers, polymeric NPs play a crucial role in pulmonary drug delivery for the lung cancer treatment. Chemotherapeutic drugs are typically encapsulated within polymeric nanocarriers. A study was conducted in which cisplatin (CIS) was loaded into gelatin-based NPs (GNPs), demonstrating notable antitumor activity against lung adenocarcinoma cells (A549) at an inhibitory concentration of 1.2 mg/mL.

Nevertheless, free CIS solution demonstrated an IC50 1/4, 2.54 mg/

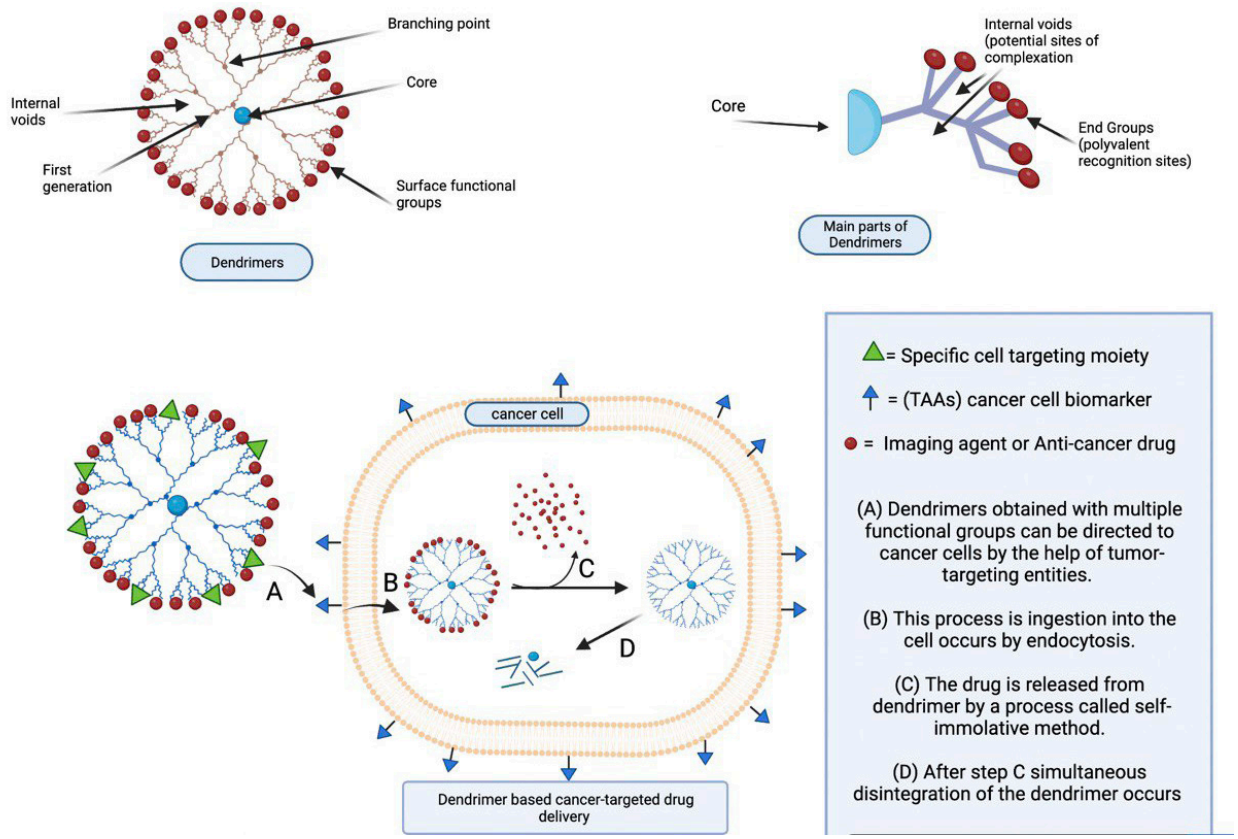

Fig. 5. Dendrimers structure and mechanism of action.

mL. The droplet of a nebulized aerosol containing NPs was confirmed to be suitable for delivering high drug doses deep into the lungs in an in vivo test. This was because the mass median aerodynamic diameter (MMAD) of GNPs ranged from 0.5 to 5 mm. Polyisobutylcyanoacrylate (BIPCA) NPs loaded with Doxorubicin (DOX) were conducted, which exhibited secondary cytotoxicity when taken up by alveolar macrophages. These macrophages, acting like Kupffer cells, can eliminate cancer cells in close proximity after phagocytosis of polymeric NPs.

Octyl aldehyde was used to modify human serum albumin (HAS) so that it acquired hydrophobicity. Amphiphilic HAS readily forms self-assembled NPs with DOX, which has a size of 341.6 nm. HAS-DOX NPs were too small to be transported directly into the lungs, but with the use of an aerosolizer, tiny liquid droplets were produced, and they were successfully carried into the deep lung. Albumin-based NPs, which bind to secreted protein acidic and rich in cysteine (SPARC), overexpressed on the surface of lung tumor tissues, make targeting of tumor tissues easier through pulmonary delivery. Lung instillation was used to carry out the hyaluronan-CIS conjugate, which after 24 hours in vivo demonstrated 5.7-fold more anticancer activity than free CIS (i.v. route) for lung cancer treatment. Also, NPs demonstrated minimal plasma/tissue ratio in both the brain and the kidney, making lung instillation (l.i.) NPs delivery is more advantageous than intravenous. As a result, NPs lessen neuro- and nephro-toxicities brought on by CIS. The improved anticancer effectiveness of polymeric-based NPs for the lung cancer treatment through pulmonary delivery has been demonstrated in all of the aforementioned investigations. The long-term stability and scalability of those NPs haven't been investigated by any of the aforementioned researchers. However, other investigations have reported on the stability of polymer-based hyaluronan NPs, albumin and gelatin [61]

For colon cancer treatment, chemotherapeutic medicines like capecitabine , irinotecan, oxaliplatin, and 5-fluorouracil are frequently utilized. The microenvironment of tumor tissues is typically acidic, and they also have leaky vasculature and poor lymphatic drainage. The extent of cancer spread, the size of the tumor, and the local microenvironment all have a role in colon cancer treatment. Given these physiological characteristics, encapsulating anticolon cancer medications in polymer-based NPs may be an appealing strategy to get beyond biological obstacles. The anticancer medications enclosed in NPs must pass through many biological barriers in order to appropriately target and concentrate on tumor areas while treating a particular malignancy. Additionally, the active ingredients must destroy cancer cells only, boosting therapeutic effectiveness and minimizing adverse effects at the same time. The most important advancements in NP engineering involve controlling the NPs' surface ligands, shape, and size in order to obtain the best therapeutic efficacy. To create the appropriate nanostructure, the synthesis method, the type of the polymer used to prepare the nanocarriers, the options for targeting ligands, and the coupling mechanism chosen should all be carefully considered. For instance, prior research has shown that positively charged surfaces can improve cellular absorption whereas hydrophilic surfaces increase the period that NPs circulates. Polymer systems might provide considerable flexibility in the optimization and customisation for NPs to expedite their advancement and deliver efficient agents to clinical practice, but with numerous parameters possible of optimization, a careful consideration in the design of the system is necessary to achieve the ideal.

Generally, active and passive targeting can be used to deliver NPs to specific areas for the colon cancer treatment. Because vessels of tumor have specific pathophysiologic traits, NP systems can passively target them. The 'leaky' and abnormal microvasculature found in tumor tissues is frequently a result of the endothelial cells' fast proliferation. Additionally, lymphatic drainage is typically ineffective in tumor tissues. Through the extensively described 'enhanced permeation and retention (EPR) effect,' the ensuing tortuosity in the capillaries and the defective lymphatic system can simplify the extravasation of NPs and macromolecules to the tumor interstitium. At present, to develop a DDS that targets tumors, it is essential to investigate the variables that affect the EPR effectAlthough the buildup of NPs within tumors is reduced by the pathophysiological heterogeneity of large tumors and the absence of

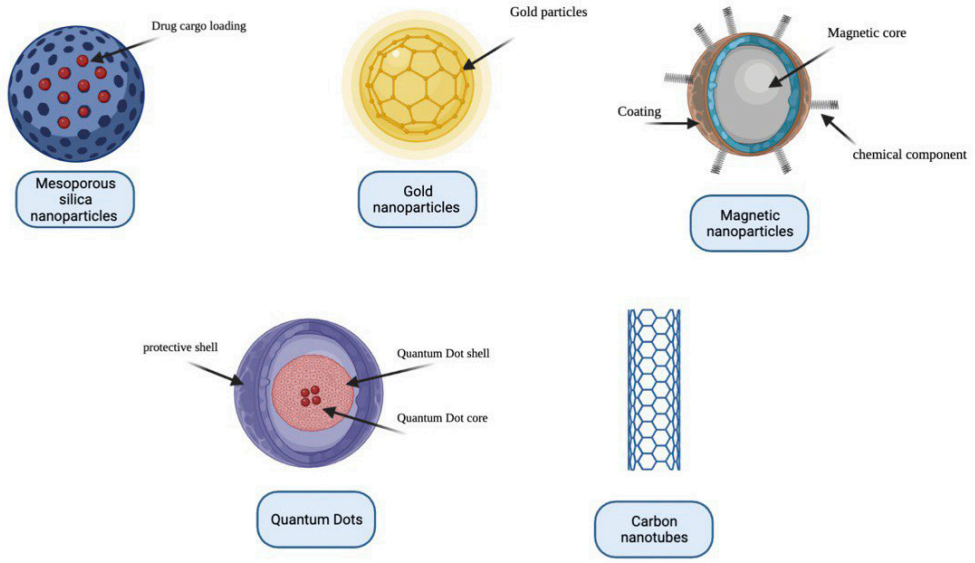

Fig. 6. Inorganic nanocarriers.

Table 2.
Polymer-based nanocarriers

Polymer-Based Nanocarriers					
Cancer	**Material**	**Drug**	**Characteristics**	**Main Results**	**Ref.**
Breast cancer	Star-shaped mannitol-core PLGA-TPGS	Docetaxel	Mannitol, poly- (D,L-lactide-co-glycolide)-D-α-tocopheryl polyethylene glycol 1000 succinate	Therefore, studying novel types of star-shaped block copolymers based on PLGA, TPGS and mannitol can provide a potential pathway for preparing excellent drug carriers in biomedicine applications. Docetaxel, an anti-tumor chemotherapeutic drug, is widely applied in the treatment of solid tumors, especially for breast and ovarian cancer [25].	[75, 76]
Lung Cancer	1- Lipid NPs	1-Cisplatin	1- In 2004, Boulikas developed a liposome-based cisplatin drug called Lipoplatin.	1- To reduce systemic toxicity of cisplatin.	[77]
	2- Metal-Based NPs	2-Methotrexate (MTX)	2-Noble metals such as gold and silver have been extensively investigated for clinical applications, including their use in sensitive diagnostic imaging, detecting, and classifying of lung cancer.	2- Gold nanoparticles have been used to deliver anticancer drugs for enhanced therapeutic effectiveness. For example, methotrexate (MTX) has poor tumor retention ability due to its high water solubility, which likely contributes to its slow or poor therapeutic response in patients. However, gold nanoparticle conjugates of MTX have high tumor retention and enhanced therapeutic efficacy in a Lewis lung carcinoma mouse model.	[78, 79]
Colon Cancer	1-Guar Gum polymers	1- Quercetin	1-It is obtained from seeds of Cyomopsis Tetragonolobus (Fam leguminosae). Guar Gum chemically is a polysaccharide composed of sugars mannose and galactose.	1- Guar gum is used as a targeted drug transporter in the colon due to the drug susceptibility to microbial degradation in the large intestine and release retarding abilities. We can conclude that the formulation based quercetin delivery would help to improve quercetin solubility, stability to exert maximum bioavailability and destined to reach the systemic circulation overcoming the possible barriers.	[80, 81]
	2- β-lactoglobulin (BLG) pectin	2- 5-fluorouracil (5-FU) and Oxali-palladium	2- BLG is an effective drug carrier because of its stability at low pH, resistance to gastric protease, and its binding affinity for hydrophobic molecules.	2- Pectin polysaccharides increase the stability of BLG nanoparticles at pH values below their pI because of increased electrostatic attraction and hydrogen bonding. With the added negative charge, pectin further increases nanoparticle stability. When complexed to platinum, BLG-pectin nanoparticles significantly increase tumor cell death in the HCT116 colon cancer cell line because of the ability of smaller particles to infiltrate the cells easily and exert their cytotoxic activity.	[82, 83]
	3-Chitosan	3- leucovorin	3- Chitosan is obtained from the alkaline deacetylation of chitin and is functional linear polymer. It is biodegradable, bioactive polymer, biocompatible and nontoxic.	3- It is used for colon targeted drug delivery due to its tendency to dissolve in the acidic environment (pH) of the stomach however it gets swollen in the pH present in intestinal region. Modification of chitosan as a new system has an great potential for colonic drug delivery.	[84, 85]

the EPR effect in the central sections of the metastatic tumor. Considerable attention has been directed towards NP delivery systems that incorporate targeting ligands, facilitating 'active' targeting of various cancer types. It has been widely documented that targeting ligands including peptides , antibodies and their fragments, other small molecules, and nucleic acid strands can be used to modify NPs in order to accomplish active targeting. These targeting ligands can improve NP cellular uptake and retention by increasing binding to the receptors that are overexpressed on the surface of tumor cells.

This method further improves therapeutic effectiveness and reduces adverse effects from the buildup of drug-healthy tissue when compared to an untargeted NPs system. The ligand biocompatibility, arrangement, ligand surface density, binding affinity, and cell selectivity must all be carefully taken into account when actively targeted NPs are developed for delivery of medications. However, with improvements in NP optimization and ligand, actively targeted delivery of NPs may be a preferable alternative to passive targeting, enhancing the effectiveness of cancer therapy. Delivering therapeutic NPs to certain tumor areas is essential in the colon cancer treatment, and both active and passive targeting are important. SiRNA is widely employed to suppress the expression of human vascular endothelial growth factor (VEGF) and impede the process of angiogenesis, thereby attaining therapeutic effectiveness in diverse cancer types. Short double-stranded RNA fragments called siRNAs have the ability to selectively inhibit the expression of a specific mRNA sequence.

As previously elucidated, Shin-Yu Lee and colleagues have successfully engineered PDMA-b-PCL micelles as nanoplatforms for the delivery of SN-38, small interfering RNA, and UPSIO NPs, with the explicit objective of targeting the vascular endothelial growth factor (VEGF) for therapeutic intervention in colorectal cancer. The outcomes show that these micelle plexes can synergistically improve chemotherapy and VEGF silencing, passively target tumor sites, and hence dramatically inhibit tumor growth. Because of its high affinity for the CD44 receptor, the linear glycosaminoglycan hyaluronic acid (HA) has been highlighted as a tumor-targeting ligand. Numerous cancer forms, including colon cancer, breast, and ovarian, have been discovered to overexpress the single-chained glycoprotein known as the CD44 receptor. Newly, Bo Xiao and his colleagues have recently developed polymeric NPs that are functionalized with hyaluronic acid, with the aim of enabling targeted chemotherapy for colon cancer. They created a variety of polymeric NPs with various ratios of curcumin (CUR) and camptothecin (CPT). The findings demonstrated that colon cancer can be targeted and cell uptake increased when hyaluronic acid is used as a targeting ligand on the surface of NPs as opposed to non-targeted NPs. Furthermore, some studies indicate that the overexpressed folate receptors in colon cancer cells may act as ligands to target the cell membrane and enhance NP endocytosis. Chitosan NPs that have been loaded with 5-ALA (5-aminolaevulinic acid) have been developed by Shu-Jyuan Yang et al. [62] The nanosystem demonstrated targeted delivery of 5-ALA specifically to the colorectal region, enabling fluorescence endoscopic detection. Additionally, after a brief period of uptake, Caco-2 and HT29 cell lines can absorb it more readily. Table 2 displays a few prospective cancer therapy target areas [63].

Radially symmetric molecules make up dendrimers, nano-sized with homogeneous, monodisperse and clearly defined structures, it consist of tree-like arms or branches [64]. Fritz Vogtle in 1978 was the first to discover these hyperbranched molecules. Dendrimers, also known as starburst polymers [65], arborols, or cascade molecules [66], were developed in 1980s. Dendrimers are macromolecules that are closely monodisperse. They have symmetric branching structures that are built around a linear polymer core or small molecule [67]. A dendrimer is not a compound and is only an architectural motif. Polyionic dendrimers can undergo changes in size, flexibility, and shape as a function of increasing generation and they do not have a persistent shape [68]. Dendrimers are macromolecules which are hyperbranched and possess a thoughtfully crafted architecture. The groups at the outer periphery are referred to as end-groups. The end-groups can be functionalized, this provides a modifying biological or physiochemical property [69]. Dendrimers are characterized by a range of unique features that makes them promising units for a variety of applications, they are distinguished by a large amount functional groups, and combination of a compact molecular structure and they are macromolecules that are highly defined artificially [70]. The emerging and major roles of dendritic macromolecules are the advantages they provides as a macromolecular nano-scale transport device [71]. Dendrimers have emerged as ideal transport vehicles due to their size, shape, and extensive investigation into how the polymer composition affects biologically significant properties. These properties include biodistribution, internalization, lipid bilayer interactions, blood plasma retention time, filtration and cytotoxicity [72]. A group of atoms or the central atom named the core begins the structure of the dendrimer molecule. The branches of the other atom called dendrons develop from the central structure through chemical reactions. The exact structure of dendrimers is a subject of debate and depends on whether the end-groups fully extend with maximum density at the surface or fold back into a densely packed interior.

Dendrimers represent a novel class of polymers, and the exploration of their chemistry stands as one of the most exciting and rapidly advancing fields in modern chemistry [73]. Dendrimers possess a unique structural design that makes them exceptionally well-suited for participation in multivalent interactions, opening up intriguing opportunities for host-guest chemistry. One of the initial suggested applications for dendrimers was in container compounds, where small substrates can be encapsulated within the internal voids of the dendritic structure. Dendrimers have limited structural diversity, or they are highly non-defined. The most significant aspect of dendrimers is their pharmacokinetic properties, it has a variety of potential applications in medicine, such as photodynamic therapy, drug delivery, imaging, Neutron Capture therapy and modifications of dendrimers' peripheral groups enables obtaining the dendritic boxes that encapsulate guest molecules or peptide-dendrimers conjugates, antibody-dendrimer [74]. The structure and mechanism of action of this nanocarrier are visible in figure.2.

2.3. Inorganic Nanocarrier

Tumor imaging and the effectiveness of radiation are improved by a variety of inorganic NPs, including gold NPs, superparamagnetic iron oxides, quantum dots, carbon nanotubes, and other non-metallic and metallic nanoclusters or NPs. The size of certain of these inorganic NPs (10-100 nm) allows them to pass through capillaries and be absorbed by various organs. Some of these entities are of a larger size and require delivery to disease-specific anatomical locations in order to achieve passive targeting. Multipurpose nanodevices are also becoming more common as cancer treatment methods. These devices may also include specialized receptor-targeting substances, such as ligands or antibodies, also contrast materials for magnetic resonance imaging in addition to the drug payload. Magnetic capabilities, unique optical, and electrical that are exhibited by gold NPs and quantum dots make them useful for imaging the intracellular location and trafficking of multifunctional carriers. After being entrapped, absorbed, connected, encapsulated, or dissolved in the nanomaterial matrix, drugs can also be carried at certain places. Many inorganic nanomaterials, for instance silica and gold NPs, have faced difficulties in early clinical studies due to their instability and toxicity. The only iron oxide NP that has been given clinical approval is NanoTherm, which is used to treat glioblastoma. With the utilization of NanoTherm, it is possible to achieve thermal ablation of tumors through the application of magnetic hyperthermia induced by the entrapment of

superparamagnetic iron oxides.

Biocompatibility, the ability to deliver drugs to specific cells, controlled release of therapeutic agents, and the ability to build up in cells without being detected by P-gp all make inorganic NPs well-suited for cellular delivery. This results in an increased intracellular concentration of drugs. A brief presentation featuring utilized inorganic NPs is available. However, one major problem is that these nanocarriers are hazardous. Surface treatment is required as a result. The following references include more details on this subject. The hexagonal arrangement of sp^2 hybridized carbon atoms in fullerenes and carbon nanotubes forms a hollow sphere or tube that can be built as a multilayer structure to simultaneously load numerous medications. The C-C distance is around 1.4 Á. By penetrating cell membranes and forming complexes, carbon nanotubes may deliver medications into the cytoplasm and, in many cases, the nucleus in addition to medications with tiny molecules and genes, DNA, RNA, and proteins. Magnetic NPs, which are often used to target the delivery of therapeutic medicines, are one of the most alluring inorganic nanocarriers. Due to the magnetism of the particles would vanish in the absence of a magnetic field, clogging and obstruction of blood vessels would result, magnetic NP-based construction materials must exhibit super magnetic phenomena at room temperature.

In contrast to drug delivery carriers and agents in magnetic resonance imaging, nowadays iron oxide NPs can now only be utilized in clinical medicine due to their nontoxicity and quick breakdown in the body. The biggest issue with employing these NPs is their rapid clearance from the circulatory system, which hydrophilic coatings can address. The key benefits of Au NPs in the field of nanocarriers include their simplicity in production, well-defined surface chemistry, great biocompatibility, and ease of molecular imaging using fluorescence resonance energy transfer. Au NPs can be employed for gene delivery by surface functionalizing the particles with positively charged molecules, including compounds containing tertiary amines, amino acids, and cationic peptides. In figure.5 we are showing some types of inorganic nanocarriers.

2.3.1. Inorganic Nanocarriers for Targeted Drug Delivery to Lung, Colon, and Breast Cancers

In 2016, Ren et al. [86] conducted a study using hollow gold NPs that respond to NIR to sequentially administer miR-21 inhibitors and release DOX in a burst. They first created hollow gold NPs and then added DOX. Electrostatic interactions allowed miR-21i to be condensed to Poly(amido amine) (PAMAM) bound to HGNPs. Within four hours of entering tumor cells, miR-21i was released into the cytoplasm. NIR laser exposure caused the HGNPs to collapse and release DOX. The study demonstrated the ability to regulate drug release profiles and intervals between the release of two medicines in NP form. Silica can take on various shapes, including nanotubes, hollow silica particles, HMSN, and MSN, with the latter two being more attractive for drug delivery. MSN and HMSN possess characteristics such as great biocompatibility, high chemical stability, variable pore sizes, high pore volumes, large surface areas, and the capacity for modification. Functionalization can be achieved through impression coating processes, grafting, or co-condensation. Surface functionalization allows for loading of hydrophilic and hydrophobic drugs and enables stimuli-responsive release. In 2009, Chen delivered siRNA and DOX simultaneously using mesoporous silica NPs. DOX was added to the NPs first, followed by PAMAM dendrimers and inhibitors on the NP surface. The study showed successful delivery of both drugs to the cytoplasm. These NPs were able to reduce pump resistance and enhance the effectiveness of DOX treatment. Meng et al. [87] functionalized a phosphonate group with MSN to create an electrostatic interaction between the porous interior and DOX. The exterior of the MSN was coated with the cationic polymer polyethyleneimine, allowing for the simultaneous delivery of P-gp siRNA. This approach effectively suppressed the expression of a drug exporter gene and enhanced the drug sensitivity of a specific cancer cell line towards a chemotherapeutic agent. These studies demonstrate the potential of inorganic NPs as carriers for drug delivery, with various strategies and modifications utilized to enhance their efficacy and targeting capabilities [88]. A variety of metal-based NPs have been studied as drug delivery tools in NSCLC therapy, including quantum dots, carbon nanotubes, silver, and gold. Due to the biocompatibility of metal-based NPs and their simplicity of use and surface modification, there has been an exponential growth in the research on these particles. These materials have been used for intracellular tracking according to their ability to extinction visible light. Because of its enhanced drug-loading capacity, attributed to pi-pi stacking between the graphene sheets, graphene, a carbon monolayer organized in a hexagonal honeycomb lattice, is also receiving a lot of attention. Related data of the inorganic NPs and those three cancers can be seen in Table.3. To fully harness the potential of graphene in DDS, there is currently a lack of comprehensive understanding of its physicochemical properties [89]. Gold NPs are the subject of extensive research in relation to diagnosis and lung cancer treatment. Gold NPs have a cytotoxic effect on lung carcinomas when combined with methotrexate.

Table 3.
Inorganic-based nanocarriers

Inorganic-Based Nanocarriers					
Cancer	**Material**	**Drug**	**Characterisation**	**Main Results**	**Ref.**
Breast	Inorganic nanoparticles (NPs)	Cisplatin (cis-diammine-dichloroplatinum (II)) (CDDP)	3–10-fold increase in efficacy on HeLa, MCF-7, A549.	The in vivo activity of CDDP in capped CDDP-multi-walled carbon nanotubes (MWCNTs) towards MCF-7 breast cancer cells was enhanced (IC50 7.7 μM), compared to uncapped CDDP-MWCNTs (IC50 11.7 μM).	[99]
Lung	Nanoparticle albumin-bound (Nab). Nano-Formulation name-(Abraxane)	Paclitaxel	When encapsulating Paclitaxel in non-toxic and biodegradable nano-delivery system, it can protect the body toxic from side effects by reducing its toxicity, also it can protect the drug from degradation in circulation.	It showed in studies that Paclitaxel when kept in a nano-delivery system, it can increase its circulation half-life, demonstrating better patient compliance and exhibit improved pharmacokinetic profile. The nanoparticle-based delivery system showed an advantage of improved retention and permeability effect which is curial in passive tumor targeting, this provides an improve therapeutic index.	[100] [101] [102]
Colon	Gold nanoparticles	Oxaliplatin	The formulation effects on colon cancer cell lines (HCT116, HCT15, HT29, and RKO) in vitro were 5.6-fold more cytotoxic or similar to the free oxaliplatin.	The use of different nanoparticles such as micelles, gold NPs, liposome, polymeric NPs, phytosomes, dendrimers, magnetic NPs, etc., to load platinum drugs resulted in promising anticancer activity for the treatment.	[103, 104]

The surface of gold NPs exhibits a high degree of reactivity. This characteristic makes it simple to couple or modify the surface of these NPs with useful other substances or biomolecules. Gold NPs can be used as the core of dendrimers, covered with various polymer layers, coupled with nucleotides, encapsulated in liposomes, and more. As previously indicated, the targeted delivery of gene molecules uses NPs. It's intriguing that enzymes and less stable siRNA can bind within the microenvironment. After being administered in vivo, NPs may change how siRNA behaves. The benefits of NPs support the delivery of siRNA across biological barriers, which can be accomplished in various ways: siRNA can be surface-conjugated to NPs through a gold-thiol bond, or electrostatic interactions, or it can attach to the NPs through polymer layers.

The non-toxic nature of gold and its capacity to produce tiny NPs, which may be functionalized for effective gene delivery, are its two most significant qualities. SiRNA can be bonded to the metal's surface through covalent or electrostatic bonds. Thiol groups can be used to link siRNA polyvalent molecules to the surface of gold NPs. Higher stability is a characteristic of these particles. The gold NP might be transformed into the ideal siRNA delivery system by the addition of a polyethyleneimine coating. Gold NPs with polyethyleneimine caps and siRNA interact electrostatically. It is important to note that cationic polymer-modified gold NPs make good gene delivery systems. Due to the ability of gold NPs to respond to stimuli, siRNA delivery is accomplished very effectively. Furthermore, scientists have created a system comprised of a gold NP-based sensor that may identify lung cancer by examining the patient's exhaled air. Due to their histology, gold NPs have been evaluated as sensors and are able to identify lung cancer. They could discriminate between the various subtypes of lung cancer as sensors. Gold NPs offer a minimum of three significant advantages for treating lung cancer. First of all, gold NPs can be utilized as a diagnostic tool. These materials offer substantial benefits over conventional organic dyes, such as negligible quenching and low toxicity. Lastly, because of their applications and utilization in Photodynamic Therapies (PDTs), gold NPs have therapeutic effects.

The fullerenes family includes rolled-up, hollow, nanosized, tubular-shaped graphite sheets known as carbon nanotubes. If just one graphene sheet is present, these structures are referred to as single-walled carbon nanotubes; if they are made up of multiple concentric graphene sheets, they are referred to as multi-walled carbon nanotubes. A multi-walled carbon nanotube's dimensions are 1.5-100 nm and 1-50 microns, respectively, while a single-walled nanotube's diameter ranges from 0.5 to 3 nm and its length can be anywhere between 20 and 1000 nm. Due to unique biological properties and physicochemical, multi- and single-walled carbon nanotubes can be used as nanocarriers for the delivery of particular drugs.

The toxicity and poor water solubility of carbon nanotubes as a drug nanocarrier is their principal drawback. Carbon nanotubes are evolving into the perfect nanocarrier for cancer therapy due to their functionalization, which is a critical important parameter in increasing the bioavailability of anticancer medications and lowering thier toxicity. As nanocarriers for the delivery of anticancer drugs, these nanostructures have recently been the subject of extensive research. Carbon nanotubes are particularly helpful in numerous applications, including gene delivery. Studies involving gene silencing or gene therapy frequently make use of carbon nanotubes' ability to carry DNA through cell membranes. In order to selectively affect tumor cells, a highly selective therapy is required for cancer treatment; in this instance, siRNA may be used to carry out gene silencing. Although, due to siRNA's low uptake efficiency and instability, delivering siRNA to certain cells is particularly difficult. On the other hand, a significant benefit of using these nanomaterials in the treatment of lung cancer is their capacity to increase the chemotherapy efficacy just by simply being administered in conjunction with traditional anti-tumor medications. Another significant advantage of these materials is that it has been demonstrated that employing carbon nanotubes may be successful in radioresistant and/or treating multidrug-resistant cancers. The enormous adaptability of these inorganic materials in their role as drug nanocarriers was established in several investigations involving DOX, Paclitaxel, Curcumin, and Gemcitabine carried by carbon nanotubes [90].

Different forms of NPs, including Carbon nanotubes (CNTs) and metallic NPs, which are used in targeted drug delivery to the colon, are described. NPs have transformed the medical business thanks to their differentiated and distinctive properties. For example, Tian et al. [91] reported that doxorubicin loaded by grafting strategy inside polyacrylic acid, a pH-sensitive polymer with mesoporous silica SBA 15, to improve the safety and efficacy of the medicine. The loaded drug achieved a high drug loading of 785.7 mg/g, demonstrated excellent pH sensitivity, and exhibited good bioavailability. We created mesoporous silica NPs of 5-fluorouracil that responded to enzymes and were capped inside a film of guar gum. These NPs had excellent drug release when enzymes were present. It is found that layer-by-layer production of nanospheres with cysteamine-based disulfide cross-linked sodium alginate, which had a cell internalization rate of more than 70%, improved the delivery of paclitaxel to colon malignant cells. According to Theiss et al., [92] NPs supplied in hydrogel were created by electrostatic interactions between the calcium ions or sulfate ions of alginate and chitosan to crosslink, and these crosslinks were then broken down by colonic enzymes to make the medication accessible. In order to treat dextran sodium sulfate-induced mouse colitis, chitosan/alginate hydrogel containing anti-inflammatory peptide Lysine Prolin Valine encapsulated inside NPs was used. By precipitating at the nano level surface-modified paclitaxel-loaded NPs composed of PLGA PEG polymers with carcinoembryonic antigen on the surface to target CRC cells, the formulation to interact with the target diseased cells was eventually created. Aside from their effective use in targeted colon drug delivery, NPs' distinctive surface size and chemistry also enable them to embed and infiltrate inflammatory regions via the gut wall, which will eventually improve drug uptake through tissues. Although particles below the size range of 10 μm tend to collect in the inflamed area and their residence time increases with decreasing size, the size range of NPs limits drug clearance. Additionally, part of the invastigation on polysaccharide-based nanocarriers-/micro- has been shown in Table 2 to have diverse physicochemical features that can be used to reduce systemic side effects and improve medication concentration in the colon.

Most metal NPs are colloidal systems made possible by reductive technology. Some, like NPs of porous silica, are created using seed-based technology. Colloidal suspensions can be used in medicine when they are magnetized in a liquid carrier because of their fluidity and capacity to interact with external magnetic fields. Khan et al. [93] recently created nickel oxide NPs with a size range of 20–25 nm, and an evaluation of their cytotoxicity revealed lowered cytotoxicity; nonetheless, most metallic NPs have been found hazardous as they build up in the body. The magnetic fluctuation (alternating magnetic field [AMF]) in magnetic NPs (MNPs), which has been widely used in biomedicine, especially as a new technique for tumor and cancer therapies, produces heating power. According to a prior study by Mannucci et al., [94] the MSR 1 strain of Magnetospirillum gryphiswaldense is used to naturally manufacture MNPs by magnetotactic bacteria. It was evaluated for its in vivo interactions with cells and its anti-neoplastic effect on human colon cancer HT 29 cell cultures, which demonstrated improved uptake without any signs of being cytotoxic. Thermotherapy has a poor level of specificity while being a potent technique for treating a wide variety of tumor forms. Numerous tactics are recommended and employed in order to improve the technique's efficiency. Magnetic fluid hyperthermia increases the efficacy of the strategy by utilizing AMFs to raise tissue temperature, thereby enhancing the intratumoral distribution of

NPs. According to Creixell et al. [95], encapsulated iron oxide MNPs lead to sustained and monodisperse epidermal growth factor (EGF) production and exhibit a higher level of internalization in cells compared to non-targeted NPs. According to Liu et al [96]., the development of single-walled carbon nanotubes (SWNTs) loaded with paclitaxel, which exhibit substantial tumor-suppressive efficacy despite the drug's poor solubility in water, relies on polyethylated SWNTs. As a result, it makes substances more soluble in water and makes them less harmful to normal cells. According to research by Lee et al. [97], the C225 antibody is produced inside SWNTs for targeted therapy of EGF receptors, which are primarily overexpressed in colon cancer. A topoisomerase I inhibitor called SN38 (7 ethyl 10 hydroxycamptothecin) controls the release of therapy, such as colon in CRC. SWNTs are promising drug delivery systems for chemotherapy. Colon cancer was the objective of gemcitabine multiwall CNTs loaded with hyaluronic acid conjugated with PEG, which were tested for in vivo and in vitro experiments that demonstrated an effective use of CNTs in colon cancer. The findings of this research, published in numerous international scientific journals, have clarified the need for specific drug delivery to the colon. Additionally, it can increase the therapeutic target and decrease cytotoxicity of drug and drug related adverse reactions. Therapeutic effects have improved with newer methods such as NPs and the use of polymers [98].

2.4. Hybrid Nanocarrier

By selectively modifying the surface of inorganic nanocarriers with organic materials or by employing organic colloidal macromolecules as templates for the controlled growth of inorganic materials, inorganic/organic hybrid nanocarriers integrate the benefits of both inorganic and organic materials [105].

These NPs are created by mixing various NPs types to create single nanoplatforms with multifunctional capabilities, such as reducing drug resistance and enhancing the effectiveness of cancer treatments, etc. One of the common methods for creating hybrid NPs is to combine native biomaterial with inorganic or organic NPs. To give one example, inorganic/organic NPs are covered with naturally existing cell membranes to give hybrid NPs biological properties right away, enhancing their safety and potency compared to traditional NPs [106].

For example, the surface coating of mesoporous silica NPs with polyethyleneimine improves cellular uptake and enables the safe delivery of DNA and s constructs. Due to their potential use as biomaterials and in nanomedicine, systems made of lipid bilayers supported on solid material have garnered a lot of attention. Lipid bilayers are utilized to cap the MSN channels in lipid/MSN bilayer hybrid nanocarriers in order to prolong retention of hydrophilic drug cargo, prevent premature release of loaded drugs, avoid multidrug resistance, and provide stimulus-responsive drug release [107]. Lipid-coated mesoporous silica NPs (LC-MSNs) have recently been used to address the serious problems associated with low stability and solubility during the delivery of the antiviral molecule ML336 [108]. The MSN core's vast surface area facilitates hydrophobic drug loading, and the liposome covering holds the medication (ML336) in place while improving biocompatibility and extending circulation time. Mice used in in vivo safety tests showed that LC-MSNs at a dose of 0.11 g/kg/day for four days were not toxic. Mesoporous silica NP (MSN) composites supported by lipid bilayers, celastrol (CST), and PEGylated axitinib (AXT) were developed by Choi et al. [108, 109] to target mitochondria-based apoptosis and angiogenesis in cancer. By preventing mitochondrial activity, this hybrid nano platform reduced cell growth and caused an apoptotic impact against cancer cells, improving antitumor effectiveness.

2.4.1. Hybrid Nanocarriers for Targeted Drug Delivery to Lung, Colon, and Breast Cancers

LPHNPs, or lipid polymer hybrid NPs, have gained prominence recently for their ability to deliver chemotherapy to cancer patients. The mimicked biological properties of the lipid materials and the functional benefits of the polymeric components play a significant role in shaping the recently designed Lipid-polymer hybrid nanoparticles (LPHNPs) system [110]. These NPs are typically constructed with a biodegradable liposome shell and biodegradable polymer core. LPHNPs can be produced by blending synthetic, natural, or semi-synthetic polymers with lipids. These nanoparticles can manifest a range of characteristics, surface charge, geometry, dimensions, configurations, encompassing structural features, reactions to external and internal triggers, and their ability to encapsulate numerous bioactive compounds in both their core and shell locations [111, 112]. The NP's shell promotes cellular uptake and affinity, while the core gives it structural integrity and physical stability. Drugs that are both hydrophobic and hydrophilic can be trapped inside LPHNPs. Hydrophilic medications can be placed in the core, while hydrophobic medications could be placed in the shell. 5-FU was trapped in poly-glutamic acid by Hitzman et al. [113], with diameters ranging from 400 to 600 nm. Tripalmitin/cetyl alcohol was used to create the hydrophobic lipid shell, and a spray-dried nanocore with a 0.9–1.2 mm diameter was used as the core. When comparing these LPHNPs to polymeric NPs and liposomes, it was observed that they demonstrated prolonged 5-FU release. This may be because polyglutamic acid has a higher viscosity. The lipid shell thickness and NPs diameter affect how much medication is released from LPHNPs. Most of the time, the LPHNPs' shell controls the flow of water inside the NPs; as a result, the thickness of the shell affects how quickly the medication dissolves. It has been discovered that after 24 hours, the drug release rate increases from 70% to 85% if the shell thickness is reduced from 300 to 100 nm. LPHNPs can also be created in reverse, with the polymer serving as the shell and the lipid serving as the core. The clearance rate from the lung is slowed down when a polymer forms the shell. In order to deliver paclitaxel (PTX) to deep lung tissues, Gill et al. [114] created hybrid PEG5000e1, 2-distearoylphosphatidylethanolamine (PEG5000-SPE) micelles that were loaded with PTX. Because the PEG5000 protected NPs against macrophage-based phagocytosis, they remained in the lung for a longer time. In rat lungs, NPs demonstrated a 45-fold greater AUC (area under the curve) than intravenous drug delivery. On the other way, a high level of drug concentration was attained by intravenous treatment in the liver, kidney, and spleen, which may be related to the RES macrophages' quick uptake [61].

3. Future Perspectives

Novel drug delivery systems (NDDs) offer a broad array of applications with the potential to enhance the efficacy, safety, and precision of therapeutic regimens. They outperform their predecessors by addressing fundamental issues in traditional treatments, such as low therapeutic efficiency, lack of targeted delivery, drug resistance, and unwanted side effects. Through methods like PEGylation, receptor-ligand linkage, or peptide coupling, NPs can precisely deliver medication to specific target tissues, resulting in optimal local drug concentrations, reduced dosages compared to free drug administration, and lower cytotoxicity [115]. Embedding chemotherapeutics in nanocarriers have reported in multiple investigations to it reduces cytotoxicity in comparison to administering them as free drug solutions. The development of nano-based systems has been recognized as one of the prospective lung cancer therapeutic options.

However, there are still a number of unmet challenges that must be

taken care of before formalization. Drug resistance may result from inadequate drug release from nanocarriers. Strategies such as combination therapy with multiple chemotherapeutics and the development of multifunctionalized nanocarriers for targeted drug delivery can be employed to tackle drug resistance. There is a decline in size as we progress from micro-sized to nano-sized particles, however, there is an inclination in particle number and surface area. Because they have a bigger surface area, NPs are more chemically reactive, making it challenging to forecast how they will respond in certain scenarios. Reactive oxygen species (ROS) are produced due to NPs having enhanced chemical reactivity, this can trigger oxidative stress, DNA deterioration, and inflammatory responses, in time causing cytotoxicity. Although, only a few NP-based compositions and liposomes have obtained FDA authorization until now. When compared to other nanocarriers, lipid-based NPs and liposomes are less stable because they are more susceptible to oxidative breakdown and have a propensity to aggregate. This results in diminished therapeutic efficacy. Additional progress are required to make easier the controlled release of chemotherapeutic drugs, a goal that can be accomplished using stimuli-sensitive carriers.

Cancer theranostics comprises target-specific therapy and diagnosis delivered by multipurpose nanocarriers that such as chemotherapeutic drugs and screening; in the future, this may be crucial to controlling cancer therapy. It is capable of identifying tumor-bearing cells and removing them with little to no side effects, showing the therapeutic advantages, and offering immediate in vivo screening technologies. As a result, research should focus on finding effective NPs in the future that are very stable, have increased infiltrating efficacy, and have improved deagglomeration potential. Varying the physical properties (e.g., mass median diameter and porosity) and chemical properties of NPs (e.g., stable polymers, amphiphilic particles, and target ligands) can prevent agglomeration and assist maintain stability during storage. Nanomedicine allows the incorporation of drugs into various NPs, including as micelles, liposomes, and dendrimers, to increase its systemic and local distribution in a synergistic manner. Researchers must address the current deficiency standards in the assessment of nanomedicines, including manufacturing processes, safety protocols, and functional testing. Additionally, they must consider the challenges associated with synthesizing and engineering nanocarriers.

Nanocarrier therapies face challenges akin to those of newly synthesized drugs, including the development of analytical methods for comprehensive compound characterization, determination of optimal compound compositions and properties, pharmacological evaluation with toxicity testing, reproducible manufacturing methods, and evidence of efficacy and safety through clinical and pre-clinical studies. Unlike conventional medicines that typically contain a single active ingredient, NPs are complex as they encapsulate multiple active substances. Consequently, this complexity necessitates improvements in bioequivalence assessment, traditional pharmacokinetics, and safety evaluations. To facilitate the development of new NPs for drug delivery, regulatory agencies should establish a rigorous set of tests with expedited clearance procedures. This approach is expected to drive significant research in the field, eventually replacing conventional dosing methods with novel drug delivery systems and ushering in new perspectives to enhance healthcare delivery.

4. Conclusions

Nanotechnology, an emerging field of study, offers the potential to enhance and modify essential qualities for applications in diagnosis and drug delivery. Although still in its early stages, nanotechnology has seen some therapies gain approval, with many more under investigation. These innovations hold the promise of delivering safer, more effective, and potentially personalized treatments. Liposomes, due to their high biocompatibility and structural similarity to cellular membranes, are being developed as nanocarriers for drug delivery systems. Their unique properties make them highly advantageous in the field of drug delivery, particularly in cancer research where dendrimers' structural properties can provide precise control. Polymers are great options for administering medications by intravenous, oral, or combined path because of their benefits, which have less toxicity, biocompatibility and biodegradability [116]. Micelles serve as an example of an inventive drug delivery technology because to the high drug accumulation at the stability or target location in physiological circumstances. A form of inorganic material, gold particles have a number of characteristics that enable them to be used to either improve or offer a diagnostic. Nanotubes may be used in the diagnosis of several illnesses, according to studies that have been conducted [117]. With the identification of novel nanosystems implicated in cancer signaling pathways, there is a tremendous chance to develop a tailored treatment that is efficient for each patient.

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