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Review Article

Nanocarriers in Drug Delivery: A Mechanistic Review

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ABSTRACT

Nanotechnology has garnered growing attention recently because of its potential to diagnose and treat numerous tumors, as nanocarriers have been used to overcome the challenges that come with conventional antitumor drug delivery systems, such as not targeting the sites of action, significant side effects, burst release, and damaging surrounding normal cells. Nanocarriers offer preferential accumulation at the target sites and can increase the therapeutic efficacy and bioavailability of antitumor medications. There are numerous nanocarriers, but only a small number of them have received clinical approval for their intended use in delivering antitumor agents to specific locations. The current review is separated into three sections: the first section presents an overview of nanocarriers and the relevance of these in delivering anticancer drugs, the second section includes targeting mechanisms and surface functionalization on nanocarriers and the third section consists of an overview of selected tumors (e.g., breast, lungs, colorectal and pancreatic tumors,) plus the uses of relevant nanocarriers for those Tumors. This shows the potential of nanotechnology in treating tumors in a variety of ways.

INTRODUCTION

Nanocarriers are tiny materials which were used to transport drugs. Nanoparticles are mixed particles that have a sub-atomic particle size of <500 nm1. These types of particles can alter the common properties and the functions of the given drugs. Increasing the absorption and distribution in the body and lowering the toxicity, and improving solubility are key factors of using nanoparticles as a drug delivery system. The properties of nanoparticles can change their composition, sizes, shapes, and surface characteristics. A nano particle-based carrier is effective in drug delivery systems it improves the therapeutic outcomes for cancer-based studies. The overexpressing receptors on cancer cells can be targeted with a nanoparticle-based drug delivery system with

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targeted ligands. The nanoparticles are an effective drug delivery system that can be used to target cancer cells.

2. Organic nanocarriers:

Organic nanocarriers are special small cell materials made to be suitable for the body, like lipids and polymers. Their size can be under 1000nm. They can penetrate the biological barrier and accumulate in tumour cells. The drugs that are less stable or degrade by enzymes in the body can be encapsulated by the nano carriers. These particles can be modified to be in the bloodstream for a longer duration and increase the concentration of the drug gradually. It uses polyethylene glycol, a polymer that protects the drug from degrading and the immune system.

2.1 Solid lipid nanoparticles (SLNs):

Solid lipid nanoparticles (SNPs), which were developed in in early 1990s they were a mixture of drug carriers that ranges from 50-1000 nm. Solid lipid nanoparticles were prepared by spreading melted solid lipid particles in water with the addition of an emulsion reaction to stabilize them. For the drug to dissolve, they provide the highly lipophilic liquid matrix. Lipids are used in solid lipid nanoparticles that can be solidified at normal room temperatures. SLNs are highly advantageous in controlled drug delivery, stability, and less toxicity, protecting water-soluble drugs. SLNs have a clear advantage over the conventional drug delivery system. SLNs give a natural platform to incorporate lipophilic anticancer drugs.

E.g., for SLNs-based anticancer drugs docetaxel, methotrexate, doxorubicin, paclitaxel, etc.

2.2 Liposomes:

Liposomes had under keen observation over a few years in biomedicine, mainly as a drug delivery system for anticancer drugs. Improved drug delivery, drug protection, increased efficacy, stability, and decreased systemic toxicity were the main benefits. Liposomes have a unique absorption property compared to common drug solutions that are common. These can be covered in polyethylene glycol to improve their lifetime in blood bloodstream. Liposomes act as a model agent for vaccines, drugs, cosmetics, and nutraceuticals. They consist of a spherical vesicle that is encapsulated by lipid bilayers. The mixture that makes the liposomes is degradable and compatible, which makes it a therapeutic carrier. Liposomes are soluble in both water and lipids, which increases their uses in biomedicine formulations. The drug-loaded liposomes control the release of drugs and improve the distribution and absorption in the human body. It can be converted into antibodies or ligands to enhance target specificity.

2.3 Dendrimers:

Dendrimers are branched macromolecules that originate from the core. They can be prepared by using organic or inorganic, or synthetic compounds, which can be sugars and amino acids. Their synthesis helps to adapt to molecules and adjust the weight distribution, which makes them an excellent carrier in a drug delivery system. In the synthetic method, it undergoes polymerization because of its linear structure and irregular branch arrangement. Dendrimers are a crucial part of drug delivery systems, characterized by an increased branching system, spherical shape, and a distinctive weight. Their construction origin helps them to control the shape, size, and functional stability. The drugs can be loaded into the core through hydrogen bonds and chemical bonds. The drugs can be attached to the cell wall and active sites to function. Dendrimers are used in various disciplines like anticancer, antiviral, antibacterial,

etc. They were used for various studies to test its potency, efficiency and toxicity studies.

Dendrimer conjugate is formed when the drug is bound to dendrimers at the core and at the branching points. At a certain moment, each drug molecule is cut. A well-designed architectural design in which the generation event was resulted when the release of molecules from the dendrimers. The drug release was followed by a linker to convert the nitro group into an amino group in an acidic environment. The PCI (phytochemical internalization) technology helps to disintegrate the cytoplasmic membrane and helps the trapped molecules in the membrane lead to toxicity in cancer tissues. In intravenous mode, the transformation of dendrimer-platinate results in anticancer activity. Polyethylene glycol-based dendrimers in transformation with doxorubicin enhance the drug circulation in blood bloodstream and reduce the toxic nature and settling of drugs in the body.

2.4 Polymeric nanoparticle (PNPs):

Polymeric nanoparticles (PNPs) are solid nanoparticles made up of biodegradable particles. Based on structural classification, they are categorized as matrix type or reservoir type. Drugs in matrix types are dispersed or trapped within the matrix, whereas in reservoir types, the drug is dissolved or dispersed within the oil's core or water-trapped solid polymeric membrane. In these two types, the adsorption or chemical transformation of the drug to the surface is attainable. The polymeric nanoparticles can be prepared based on their adaptivity and composition.

The compatible and degradable, both organic and inorganic, polymeric materials are utilized in the preparation of polymeric nanoparticles. These degradable polymers are degraded inside the body and removed from the body through metabolic activity that occurs inside the body. Synthetic particles generally used are polylactic acid (PLA), polyglycolic acid (PGA), etc. Organic natural polymers used are albumin, alginate, heparin, etc. Polymeric nanoparticles have higher stability, higher loading of drugs, better size, controlled release of drugs in the body, and are maintained in the bloodstream. The release of drugs through particle counterparts such as polymeric micelles and liposomes.

These types of characters help in cancer treatment. Polymeric nanoparticles can be used in a wide range of applications of polymers as organic (Natural) and inorganic (synthetic). The control of the properties in polymeric nanoparticles, like controlled release of drugs in blood bloodstream, stability, and settling of drugs in the body, helps to control them more accurately. Polymeric nanoparticles can be used to multifunction based on size, shape, structure, and surface alterations. The change in polymer responsive nature to the environment leads to an accurate and modified drug delivery system.

2.5 Polymeric micelle (PMs):

Polymeric micelles (PMs) are nanoparticles formed by self-assembly of synthetic (inorganic) copolymers in an aqueous state. They are amphiphilic, meaning they both love and repel water. These copolymers are blocked when they come in contact with a liquid environment at a higher concentration. The hydrophobic part constitutes the core, while the hydrophilic part forms the protective shell for the micelles. The hydrophobic core helps to trap the drug and contributes to controlled release and regulation of the drug. The hydrophilic protective shell helps to stabilize the core in a liquid environment and controls the absorption in vivo environment. The drugs can be loaded in Polymeric micelles by the

physical trap method or chemical attachment to the surface. The polymeric micelles (PMs) are prepared by the freeze-dry method, solvent evaporation method, etc. It is used to modify and bond to ligands that are targeted to enhance their efficiency.

Polymeric micelles (PMs) have a water-repelling nature that traps the drug in anticancer in their core to increase its water solubility. The protective shell of polymeric micelles (PMs) helps the drugs to circulate in blood bloodstream for a prolonged period and prevents them from being recognized by the immune system. The smaller the size of polymeric micelles, the longer the circulation period in the blood, and it settles in the cancer site and can penetrate and have a retention effect on it. The combined features improve the efficiency of hydrophobic anticancer drugs in therapeutics. The active site of cancer can also be targeted by modifying the surface of polymeric micelles and cancer-targeting ligands. The commonly used copolymers are poloxamers, polyethylene glycolated polylactic acid (PEG-PLA), polyethylene glycolated polyaspartic acid (PEG), etc.

2.6 Virus-based nanoparticles:

Virus-based nanoparticles are nanosized self-assembled tough proteins virus has uniform structures and well-defined geometry. Virus-based nanoparticles are used for wide applications such as gene therapy, vaccines, targeting, and drug delivery. Virus nanoparticles or viruses from different origins, like plant-based tobacco mosaic virus (TMV), bacteriophages (MS2), and animal-based viruses like adenovirus, have been tested in drug delivery applications. Virus nanoparticles have some unique features like similar morphology, compatibility, surface functions, and various shapes and sizes. The chemical and gene alteration on the surface of nanoparticles enables virus-based nanoparticles for drug nanocarriers that include compatibility and water-repelling nature, also to trap the drug inside the carrier. Polyethylene glycolated virus-based nanoparticles can be integrated into blood bloodstream and remain for a prolonged period.

Drugs can be chemically adhered to the surface of virus-based nanocarriers or physically trapped inside virus-based nanoparticles for drug delivery. In the physical method, the drugs are loaded, and the proteins are self-assembled in virus-based nanocarriers. In chemical attachment, drug molecules attach to the surface of the virus-based nanoparticles at some sites where protein is present. Virus-based nanocarriers have a natural affinity that helps to modify the surface of chemicals or genes. Virus-based nanoparticles are used in chemotherapy for cancer targeting.

3. Inorganic nanocarriers:

Inorganic nano carriers are mainly composed of non-carbon-based materials like metals (like gold and silver), metal oxides (like iron oxide and titanium dioxide), silica, and semiconductor nanocrystals (like quantum dots). Inorganic nanocarriers represent an exciting and quickly developing field in nanomedicine. These nanoscale platforms, in contrast to their organic counterparts, provide unmatched robustness, intrinsic optical and magnetic functionalities, and a high degree of physicochemical property tunability. Their large surface area for versatile functionalization and stability in harsh biological environments enables the efficient loading of a variety of therapeutic agents, including genes, proteins, and small-molecule drugs. Additionally, many inorganic nanomaterials have inherent qualities that allow them to function as direct therapeutic agents that can produce heat as well as advanced diagnostic tools (such as fluorescent probes and MRI contrast agents).

3.1 Carbon nanotubes (CNTs):

Carbon nanotubes (CNTs), capable of self-assembling carbon atoms, were discovered by Iijima in 1991. Carbon nanotubes (CNTs) belong to a third allotropic form of carbon and graphene sheets, which look like tube structures. Carbon nanotubes (CNTs) are distinguished in two forms they are single single-walled carbon nanotubes or multi-walled carbon nanotubes, which are arranged by a graphene sheet that looks like a tube. Carbon nanotubes' length can be extended to several thousand times their diameter, and their dimensions are in the nanometre range. The general methods to produce carbon nanotubes are plasma-enhanced chemical vapor deposition, and discharge, etc.

Carbon nanotubes possess a unique set of characteristics and chemical properties that make them highly suitable as drug delivery carriers. Their remarkable mechanical strength, conductivity, and diverse shapes, including a needle-like structure, allow them to efficiently penetrate cell membranes and deliver therapeutic agents directly into cells. Furthermore, their surface can be easily altered, enabling them to be made more compatible, less toxic, stable, and water-soluble, which are all crucial for biomedical applications. These properties have established carbon nanotubes as an ideal carrier for cancer treatment, where they have been used for years as an anticancer drug delivery system. Anticancer drugs like methotrexate, paclitaxel, and mitomycin can be either encapsulated within the nanotubes' core or attached to their surface via various chemical bonds. The ability to fix different targeting agents to the surface of carbon nanotubes facilitates a highly specific and targeted delivery of these drugs to cancer sites, thereby enhancing treatment efficacy while minimizing systemic side effects.

3.2 Mesoporous silica nanoparticles (MSNs):

Silica (SiO2) has an increased use in biomedical applications due to its simple synthesis process and mass production. In silica materials, the mesoporous silicas are important aspects in drug delivery systems as they can host for large quantity of drugs in a honeycomb-like structure with a number of pores. Mesoporous silica nanoparticles have efficient features such as compatibility, huge surface areas, pore size, high loading capacity, thermal conductivity, stability, and water-repelling nature, which make them a nanoscale drug carrier. The surface functions and controlling drug delivery make mesoporous silica nanoparticles an enhanced therapeutic and reduce the toxicity of drugs. Mesoporous silica nanoparticles' special structure and characteristics make them perfect nanocarriers for cancer medication delivery systems. The structure of mesoporous MSNs enables them to store a high amount of drugs, and particle size helps them to store in cancer tissues by passive targeting and functions of MSNs on different sites specific target agents, which enables them to target cancer tissues by active target mechanism. There are several anticancer drugs, including paclitaxel, camptothecin, doxorubicin, and methotrexate.

4. Organic/Inorganic hybrid nanocarriers:

The creation of the organic/inorganic hybrid nanocarrier combines the advantages of both organic and inorganic materials. Special functions of organic materials over the surface of inorganic nanoparticles are used to boost the selectivity and efficiency of anticancer agents. The surface is coated with polyethyleneimine (PEI) enhances the cell uptake of mesoporous nanoparticles and also helps in efficient nucleic acid delivery. When PEI (polyethyleneimine) and MSNs (mesoporous silica nanoparticles) are combined, short

interfering RNA (siRNA) is delivered steadily inside the cell.

These MSNs integrate with PEI, reaching the cancer site, followed by leakage from endosomes to the cytoplasm. MSN/lipids bilayer hybrid nanocarrier is a system in which the lipid layers are utilized as a cap to channel the MSNs in order to prevent the pre-release of drug, multidrug resistance, extended bloodstream circulation, and drug release. The developed hybrid system improves the retention time and delivery of zoledronic acid in breast cancer. These hybrid nanocarriers can release doxorubicin inside the cell and increase the uptake of the drug and storage of the drug inside the cancer cells.

5. Targeting mechanism and surface functionalization on nanocarriers:

Designing efficient nanocarriers for drug delivery requires careful consideration of targeting mechanisms and surface functionalization. To get to particular disease sites, nanocarriers use two main targeting strategies: passive targeting and active targeting.

Surface functionalization is the intentional addition of different molecules to the nanocarrier's surface in order to give it the desired physicochemical and biological characteristics. This is essential for managing drug release, stability, and biodistribution as well as for passive and active targeting. Before being targeted, nanocarriers frequently have to avoid the body's immune system, particularly the Mononuclear Phagocyte System (MPS) or Reticuloendothelial System (RES), which quickly removes foreign particles from the bloodstream. "Stealth" coatings are used to accomplish this. Targeting ligands are attached to the surface of a nanocarrier to facilitate active targeting after it has circulated sufficiently. For theranostic applications, imaging agents like magnetic nanoparticles, radionuclides, or fluorescent dyes can be either encapsulated within the nanocarrier or conjugated to its surface. This dual functionality allows for real-time tracking of the nanocarrier, monitoring of drug delivery to the target site, and subsequent evaluation of the treatment's efficacy.

5.1 Passive mechanism:

cancer-bearing blood vessels are leaking out into the environment, the nanocarriers can enter the space and pass through the endothelium barrier. The solid cancer has poor drainage on the lymphatic system a poor circulatory regression of the molecules leads to the assembly of nanocarriers at the cancer site, which is known as the enhanced permeability and retention (EPR) effect, and it effectively targets cancer. The lower the molecular weight of the drug, the lower the circulation time of the drug inside the bloodstream of the body. The targeting effect of the drug depends on the characteristics of cancer tissues, which are known as “passive targeting.” The use of a nanocarrier improves the targeting of the cancer cells using the EPR (enhanced permeability retention) effect. There are some techniques which used to retain the drugs, like polymeric substances, pH-dependent nanocarriers.

Passive targeting is utilized by a unique and unfavourable microenvironment towards the cancer cells. The fast spreading and hyperactive cancers have an increase in metabolic ratio. Cancer cells get extra energy by performing the glycolysis cycle, causing an acidic environment. Cancer cells release unique enzymes like metalloproteases, which help in the movement and existence of cancer. For targeting these types of cancer, unique nanocarriers were used that consist of polymers, liposomes, micelles, and antibodies.

5.2 Active mechanism:

Active targeting of specific cancer tissues is performed by surface alteration of nanocarriers with specific site-targeting ligands. They target the ligands that have the ability to bind to specific receptors that are overexpressed in cancer cells or the cancer that forms in blood vessel networks. The targeting agents used in specific sites of nanocarriers are small molecules, antibodies, peptides, glycoproteins, vitamins, growth cofactors, and nucleic acids. The larger the surface area to volume ratio, the more likely a nanocarrier is to attach to a specific cancer cell type and multiply. Active cancer targeting is used to avoid the limitation of the passive mechanism and to overcome the multidrug resistance. To effectively use the desired target receptor should be the same and equally expressed towards all the target cells and bind to the overexpressing cancer cells only.

Active targeting is constructed to direct the ligand binded nanocarrier to target the cancer cells or cancer that developed in the blood vessel network. In active targeting, the cell targets have been improved in chemotherapeutic agents to reduce the side effects. Active targeting of cancer cells involves the targeting of overexpressed cells that bind with ligand carriers through ligand receptor interactions. Internalisation improves the uptake of cancer cells through nanocarriers, which increases the drug concentration in the cancer cells. The generally targeted cell surface receptors that are overexpressed on cancer cells include folate receptor, epidermal growth factor receptor (EGFR), and cell surface glycoproteins.

The specific type of cancer may have cancer markers that are overexpressed on its surface. Folate receptors are overexpressed in parts like the breast, lungs, and colorectal cancer cells; these cancer cells can be targeted with folate-altered nano carriers. The surface of endothelial cells of the blood-brain barrier has high expression, and transferrin can be used as a ligand to deliver the anticancer drugs into the brain. Targeting blood vessel cancer entails destroying the cancer vessel's endothelial cells, which prevent the cancer from receiving oxygen and nutrients. This will result in the death of cancer cells. Active cancer targeting the ligand-bound nanocarriers by targeting the vascular wall that includes vascular endothelial growth factors (VEGFs), matrix metalloproteases (MMPs), and alphav beta3 integrins.

Creating docetaxel nanoparticles with transferrin surface modifications to enable active cancer. The folate-based alternative paclitaxel-loaded micelles were most effective in stopping the growth of cancer.

6. Selected tumors and relative nanocarriers:

Cancer is caused by a mutation or any other defect in genes that are present in normal cells responsible for cell growth and division, differentiation, or in the cancer-suppressing genes responsible for stopping cell growth and apoptosis (Programmed cell death). These mutated genes are precursors for the development of cancer cells that have unique features uncontrolled cell growth, unable to turn off excessive cell division, absence of apoptosis, and the ability to invade adjacent and distant tissues. The risk of gene mutations includes radiation, chemical substances, heredity, and viruses. The mortality of cancer has been reduced due to the understanding of cancer biology and enhanced diagnostics and treatments.

The conventional chemotherapy shows more side effects on bone marrow, renal, cardiac, pulmonary, etc. The researchers are trying to restrict the dosage to a minimum to specific cancer cells without exposing normal cells to avoid adverse side effects and toxicity caused by drugs. These type of drug-loaded nanocarriers has the capability to deliver the anticancer chemotherapeutics to

cancer sites by showcasing the characteristics of cancer with specific site ligands. The most deadly cancers in the world are lung, colorectal, pancreatic, and breast cancers.

7. **Breast tumor:**

It is one of the most commonly diagnosed cancers with the highest mortality rate, particularly in females worldwide. Even treating with modernized treatments by using statistical prediction of the outcome of the patient, the no of recurrences is high after a specific time interval. The patients suffer from localized breast cancer advanced to the next stage of cancer. For these types of patients, the first treatment involves shrinking the size of the cancer in the affected area and removing the cancer by surgery when it is deemed safe. The primary goals of cancer shrinkage are to lessen the cancer's size and mass, minimize surgery, and preserve the breast tissue.

The various chemotherapeutic agents used were doxorubicin, paclitaxel, and cisplatin for the shrinkage of cancer, followed by the removal of cancer cells from the body. Doxorubicin is the first drug used to treat breast cancer. To reduce the growth of cancer cells by preventing DNA (Deoxyribose nucleic acid) to reversible insertion of cancer cells and to further prevent the biological processes inside the cancer cells. The biggest adverse effect of doxorubicin is that it promotes hair loss, neutropenia counts and cardiac-related problems, and also can lead to toxicity with an increase in dose. The agents like cisplatin or carboplatin in combination of drugs are used as anticancer drugs in breast cancer.

Cisplatin stimulates to perform apoptosis by binding with DNA and cross-linking to prevent the growth of cancer cells. The unique toxicities related to the drugs include their neurotoxicity, nephrotoxicity, and ototoxicity; they are interconnected to high concentrations in plasma levels. These types of drugs are able to maintain the cancer, but the limitations appear in toxicity, stability, safety, efficacy, and tolerability in combination therapy. Due to the limitations, the different types of anticancer drug-loaded nano-carriers are used for chemotherapeutic action as a unique technique that targets the drug delivery through the lymphatic system with the lowest adverse toxicity while retaining the therapeutic effect.

Degradable nanocarriers loaded with tamoxifen are designed to treat breast cancer by targeting estrogen-positive receptors. A pH-responsive degradable system with ethylene oxide and beta-amino ester nanoparticles was developed for the drug delivery of paclitaxel as an anticancer agent against breast cancer. A controlled nanoprecipitation method was utilized to develop the paclitaxel-loaded nanocarriers. The pH-sensitive soluble nature of drug-loaded nanocarriers helps in drug release at the core of solid cancer, leading to enhancement of therapeutic effects by distributing the drugs within solid cancer.

The most adverse one is MDR (multidrug resistance) characteristics that may lead to the recurrence of cells after a certain period of time. Nanotechnology helps during these types of crucial situations, like recursion and non-responsive characteristics of cancer cells. The Epidermal Growth Factor Receptor (EGFR) developed targeted polymers blended nano-carriers loaded with certain agents like paclitaxel are used to treat breast cancer. The characteristics of polymer-loaded nanocarriers with efficient drug loading result in sustained release of drugs in a controlled manner, thus improving the combination therapy with the EGFR targeting. The combination of paclitaxel with Ionidamine

improves the cell viability and helps to treat Multidrug resistance (MDR).

Nano transformation-based combination drug delivery of doxorubicin and cisplatin is used to treat localized breast cancer with high efficiency and reduce the toxicity to nearby cells. The combination of doxorubicin and cisplatin-loaded nanocarriers was injected at the subcutaneous level, showing the cleavage of hyaluronic acid in the lymph leads to the transport of free drug to the site of targeting through active or passive mechanisms. The nanocarriers are one of the emerging approaches to deal with cancer treatment by using a combination of different drugs loaded in nanocarriers. These types of drug delivery systems are effective and also reduce the toxicity of drugs in cells.

8. **Pancreatic tumor:**

Pancreatic cancer contributes to the highest deaths in both genders, male and female. If early identification is done, the patients can be cured by surgical methods. In some types of surgically removable cancer, it increases the speed of replication and biological processes, which helps to form the cancer in the blood or lymph, advancing it to the 4^{th} stage of cancer can also form after a certain period of time, which promotes resistance to conventional methods like radiation and chemotherapy. The poor management system leads to the advancement of cancer stages. The persons with localized pancreatic cancer can survive up to some months, while those with metastatic cancer they can survive less than 4 months.

Chemotherapy is commonly used to treat cancer (localized cancer) in metastasis, where the cancer forms in the blood vessels and lymph nodes. It can also form a stage where all types of stages of cancer are combined together, and the diagnosis takes a lot of time. Gemcitabine is a type of antimetabolite that is administered intravenously. These antimetabolites, combined with therapeutic mediators like platinum, analogs, or topoisomerase inhibitors, didn't improve the expected results or survival. Folfrinox, a powerful combination of chemotherapy it contains folinic acid, Fluorouracil, IRINotecan, and Oxaliplatin, replacing the antimetabolite gemcitabine-based therapy, and it showed better survival. The combination of Folfrinox and gemcitabine shows a better improvement in pancreatic cancer treatment in in vitro testing.

Nanotechnology is used to produce nanoparticles from organic or inorganic important biomedical sources. Nanotechnology shows better diagnosis of cancer imaging and targeting compared to conventional methods. Nanocarriers are being utilized in dose-dependent therapies or image contrast to improve the bioavailability. They are also utilized to target cancer cells to contrast the image and reduce the toxic effects created by drugs used inside the nanocarrier's core or the drugs attached to the surface of the nanocarrier. These types of nanocarriers are used to treat cancer that forms inside the blood vessels or that forms in the lymph, such as pancreatic and lung cancer. For developing an effective nanocarrier for imaging or therapeutic cofactors, we should understand that the mechanism of the chemical barrier associated with the disease is crucial. The understanding of the mechanism of disease helps to use nanocarriers, especially nanoparticles, spreading of nanocarriers inside the body, to store in specific sites, and to penetrate the cancer cells.

Nanocarriers like liposomes and polymeric nanomers (PMs) are used to trap, target, and deliver the different chemotherapeutic treatments. Doxil, a nanoparticle drug approved by the US Food and Drug Administration (FDA), was a

formulation of a liposome that traps the anticancer drug doxorubicin. This trapping of drugs changes the absorption and adsorption characteristics of the drug, which supports for uptake of cancer cells and increases the efficiency of the anticancer drug. Doxil is utilized for a wide range of solid cancers and platinum-resistant ovarian cancer. The oxaliplatin loaded nanoparticle micelles were developed with slow release of trapped anticancer drug when they come in contact with the cancer environment, increasing the efficiency of the drug. The trapped nanocarriers of antimetabolites (Gemcitabine) were used as primary treatment for localized cancer that spreads and forms in blood vessels or lymph. The pancreatic cancer is also treated with albumin-bound paclitaxel-loaded nanocarriers called nab-paclitaxel. Iron oxide nanoparticles were developed with Urokinase Plasminogen Activator Receptor targeting the surface of cancer. Liposomes, polymers, and dendrimers were created as nanocarriers, which serve as delivery vehicles for small interfering RNA. These nanoparticles have the ability to retain multifunctionality for targeting the small interfering RNA delivery and penetration of the barrier to reach the targeted cell. Similar to nanoparticulate liposomes containing superficially attached Transferrin Receptor antibodies with small interfering RNA against Human Epidermal Growth Factor Receptor 2 HER-2, which is a crucial biomarker in the treatment of pancreatic cancer. In organ transplanted mouse models, the transferrin receptor antibody-nanocarriers improve the distribution of small interfering RNA inside the pancreatic cancer compared to the nanocarriers without transferrin receptor antibodies. The specific site provided of the nanocarriers' small interfering RNA complex can silence the human epidermal growth factor receptor 2 and also the sensitivity of gemcitabine.

9. Colorectal cancer:

Colorectal cancer is a frequently diagnosed cancer type, particularly in males worldwide. The risk factors associated with colorectal cancer are from both the environment and geographic locations. The environmental factors modulate the gene modification, while geography stimulates colorectal cancer in the world. The abnormal cells or clumps of cell that grows on cell lines in the colon can cause colon cancer, which has two types: hyperplastic (This type has a lower rate of forming cancer cells), other adenomatous (This is like a precursor before formation of cancer takes years to form). The hyperplastic polyps contain an enhanced no of glandular cells, but they reduce the healthy tissues (cytoplasmic mucus). These lack nuclear hyperchromatism (a Nucleus that appears darker than normal while staining) and atypia (indicates abnormal cell growth). The adenomatous polyps appear in a cigar structure, inflated, hyperchromatic. An adenoma state may be the outcome of the cancer. Colon cancer is a probable statistic when the patient has an increase in adenoma polyps (the precursor for cancer cells). The situation gets worse if it is familial adenomatous polyps (a genetic mutation that starts in the teenage years caused by germline mutations and the APC genes are responsible for the cancer, which is present in chromosome 5). The colorectal patients may be operated to remove cancer cells of distant metastasis (The cancer cells spread and form at different parts of the body) to avoid the of the intestinal line due to blood leakage or lumen cancer, and systemic chemotherapy is used to treat metastases. Many of the healthcare institutions prefer systemic chemotherapy as the first treatment by following the removal of cancer in parts of the body with noticeable symptoms in the patient. This can be clarified in postoperative clarifications, which may result in stopping of treatment or discontinuation.

There are numerous treatments used to fight against this cancer condition that including surgery, radiation treatment, radiofrequency treatment, targeted therapy, cryosurgery, and chemotherapy. The most used type of treatment in these types is chemotherapy, which improved the patients' behaviour and their quality of life. Even though it is considered a quality treatment, conventional treatment shows less drug concentration of the drug at the specific site of cancer, making it a less effective way for cancer treatment. In this advanced nanotechnology, different types of nanocarriers were tested to result in effective targeted treatment against colorectal cancer. These types of nanocarriers were approved to carry anticancer drugs against colorectal cancer that include irinotecan, oxaliplatin, bevacizumab, and capecitabine, etc. The 5-FU (5-Fluorouracil) is prepared with solid nanoparticles using the emulsion-solvent technique, the nanoparticles have a nano size with a high trapping mechanism, and it is observed that controlled release occurs for hours. The oxaliplatin loaded PGLA microsphere (a combination of lactic acid and glycolic acid) was developed to improve the efficiency of trapping cells. These microspheres showed different release mechanisms, zero-order kinetics (Uniform release of drugs), and sigmoid release (the release pattern looks like “S” stretches plotted against time in a graph).

5-Fu (5-Fluorouracil) loaded with hyaluronic acid (HA) attached with silica nanocarriers was prepared to treat colon cancer. The model view was observed attachment and intracellular storage of 5-FU-loaded nanocarriers on the basis of HA surface modification in colon cancer. The release mechanism of these nanocarriers containing the drug is several hours in a month period. The 5-FU (5-flurouracil) loaded HA attached nanocarriers were observed to show enhanced anticancer efficiency and a decrease in side effects compared to non-targeted nanocarriers. Docetaxel-loaded degradable dendrimers were prepared with multiple binding sites, controlled drug loading mechanism, and release. These type of drug-loaded nanomers shows less toxicity than free docetaxel in colon cancer treatment. The efficiency of treatment of colon cancer in full efficiency is seen in some months.

10. Lung cancer:

Lung cancer is one of the most commonly diagnosed cancers in males and the leading cause of death among males to statistics from 2012 globally. The spreading of lung cancer from one place to another (secondary location), like the breast or any other parts, is a possibility for mortality and acts as a major challenge in cancer therapies. One of the major problems faced in existing treatments for cancer is the inefficiency and specificity. So it is very important to prepare a site-specific and targeted treatment to develop the expected efficiency and reduce the side effects. The developments in nanotechnology have attracted many researchers and are said as the anticancer drug for the next generation due to the contrast in image and therapeutic response.

The problems related to identification methods of lung cancer are that it is an expensive procedure and has inaccuracies. Which makes it a hard choice for cancer screening. For these types of challenges, sensor-based gold nanoparticles were developed and utilized to identify lung cancer. These were developed to differentiate the persons who suffer from lung cancer and the healthy persons in high humidity. These sensor-based nanoparticles were cost-effective and a non-invasive diagnostic device (MRI) for lung cancer. So PLGA (co-polymer of lactic acid and glycolic acid) based anticancer drug was loaded in nano carriers to improve the anticancer efficiency in lung cancer. Doxorubicin with polybutylcyanoacrylate (an

adhesive used in healthcare to treat wounds) nanoparticles is effective against lung cancer. Liposomes were used to treat lung cancer by targeting the specific site of cancer. A multifunctional component liposomes formulation trapping cytotoxic (eptoside and docetaxel) was prepared for p53 cancer suppressing gene (It controls the expression (turning on or off) of other genes by binding to particular DNA sequences) enhanced cytotoxicity in A549 and H1299 lung cancer cell lines (A549 they were used as model in in vitro and in vivo They represent alveolar Type II pulmonary epithelial cells. H-1299 used as models and classified as a non-small cell lung carcinoma cell line).

The liposomal formulation of 9-nitrocampotothecin (extracted from Chinese happy tree, used as a topoisomerase I inhibitor) through steaming (nebulizer) was effective against spreading cancer (metastasis) in vivo and in vitro modes. The interleukin 2 (a cytokine which is a small protein used for signalling and to regulate the immune system, primarily T lymphocytes). It was administered to patients through inhalation, which improved the condition in patients against pulmonary metastasis. Gelatin-based nanoparticles were used to deliver water-loving and water-repelling anticancer drugs such as paclitaxel, cisplatin, curcumin, and methotrexate. Gelatin-based nanoparticles show great anticancer activity, controlled drug release, and less toxicity to cells. Doxorubicin-loaded nanoparticles with a carbon source (effervescent) nanoparticles as an API were developed. These doxorubicin-containing effervescent nanoparticles were dispersed throughout the lung. Mesoporous Silica Nanoparticles as nanocarriers used for inhalation therapy with targeting to cancer in the lungs. The formula consisted of five components: MSN loaded agents, pump, and no pump suppression of drug resistance and targeting for lung cancer. In this mouse model, the chemotherapeutic drug and suppressor proteins were injected, which accumulated in its lungs. The delivery route of drugs preserves the chemotherapeutic agents and small interfering RNA shows apoptotic actions in lung cancer.

Nevertheless, cox2 inhibitor(an anti-inflammatory drug used to treat inflammation and pain) celecoxib(an anti-inflammatory drug) was trapped into nanostructured lipid carrier by using triglycerides like compritol (a matrix forming agent used as a vector in drug delivery system in healthcare) and miglyol (used as carriers for poor soluble drugs like oral capsules etc) through high pressure homogenization method to reduce particle size and enhances the anti cancer efficiency. 5-FU (5-Fluorouracil) loaded lipid coated nanoparticles were developed, and their in vivo absorption was showcased in mice after inhalation. These lipid-coated nanoparticles exhibit sustained 5-FU (5-Fluorouracil) delivery *and efficient local targeting in lung cancer sites.*

CONCLUSION:

Nanotechnology has been developed as one of the latest approaches for cancer drug delivery. Numerous nanocarriers were used as emerging tools for the treatment of various cancer types. These nanocarriers are more efficient in cancer drug delivery by targeting cancer with enriched permeability (passing through cells) and controlled release of the drug. These progressions in cancer therapy have developed numerous novel drug delivery systems against cancer. In upcoming years, management of precise doses of drugs with the highest systemic release from a nanocarrier and toxic effects not only enhances the use of the nanocarrier system for anticancer drug delivery but also improves patient comfort.

Advantages of using nanocarriers as a drug delivery system:

- Improved Solubility and Stability.
- Targeted Delivery.
- Reduced Systemic Toxicity.
- Controlled and Sustained Release.
- Ability to Cross Biological Barriers**.**

Limitations of using nanocarriers as a drug delivery system:

- Toxicity and Biocompatibility Issues.
- Manufacturing and Cost.
- Stability in Biological Environments.
- Limited Drug Loading and Encapsulation Efficiency.

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