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Shekhar Kamble
Department of Pharmaceutical Chemistry, Dattakala Collage of Pharmacy, Swami-Chincholi, Maharashtra, India

Dr. Vishal Babar
Dattakala Collage of Pharmacy, Swami-Chincholi, Maharashtra, India

Dr. Sudarshan Nagarale
Department of Pharmaceutical Chemistry, Dattakala College of Pharmacy, Swami-Chincholi, Maharashtra, India

Amit Pondkule
Department of Pharmaceutics, Dattakala College of Pharmacy, Swami-Chincholi, Maharashtra, India

Pragalbh Misale
Dattakala College of Pharmacy, Swami-Chincholi, Maharashtra, India

Snehal Khartude
Dattakala College of Pharmacy, Swami-Chincholi, Maharashtra, India

Correspondence
Shekhar Kamble
Department of Pharmaceutical Chemistry, Dattakala College of Pharmacy, Swami-Chincholi, Maharashtra, India

Incorporation of nano-particles in cancer treatment

Shekhar Kamble, Dr. Vishal Babar, Dr. Sudarshan Nagarale, Amit Pondkule, Pragalbh Misale and Snehal Khartude

Abstract
Cancer has a complicated pathological process. Lack of specificity, cytotoxicity, the development of multi-drug resistance, and the proliferation of stem-like cells are issues with current chemotherapy. Nanomaterials are substances with unique optical, magnetic, and electrical properties. They are substances with a size between 1 and 100 nm. There are numerous major categories into which nanomaterials employed in cancer therapy can be divided. These nanomaterials have been modified for a variety of cancer therapies to overcome toxicity and lack of selectivity, boost drug capacity as well as bioavailability, and target cancer cells, tumour microenvironment, and immune system. The number of authorised nano-drugs has not significantly risen over time, despite an increase in investigations. Further investigation is required for targeted drug delivery via nano-carriers to reduce side effects and enhance clinical translation. Since nanoparticles can be an effective drug delivery technique, nanotechnology has been intensively researched and used to treat cancer. Nanoparticle-based drug administration has distinct benefits over conventional drug delivery methods, including greater stability and biocompatibility, increased permeability and retention effect, and precision targeting. This kind of drug-carrier system has advanced thanks to the use and development of hybrid nanoparticles, which incorporate the combined properties of many nanoparticles. Additionally, it has been demonstrated that nanoparticle-based drug delivery systems contribute to the reduction of cancer-related treatment resistance. Overexpression of drug efflux transporters, compromised apoptotic pathways, and hypoxic environments are some of the processes underlying cancer treatment resistance. Improved multidrug resistance reversal may result from nanoparticles that target these pathways. Nanoparticles are also being created to target these pathways as more tumour drug resistance mechanisms are discovered. Additionally, researchers have lately begun to look into how immunotherapy, which is increasingly crucial in the treatment of cancer, uses nanoparticles. In this study, we examine how nanoparticles and hybrid nanoparticles are used to deliver medications in the contexts of chemotherapy, targeted therapy, and immunotherapy. We also detail the targeting mechanism of nanoparticle-based drug delivery and how it works to overcome drug resistance. The rapid growth of nanotechnology towards the development of nanomedicine agents has great potential to improve therapeutic approaches to cancer. Nanomedical products offer opportunities for sophisticated targeting strategies and multi-functionality. Today, nanoparticles (NPs) have diverse applications in various fields of science. In recent years, it has been repeatedly reported that NPs play an important role in modern medicine. A wide range of nanomaterials based on organic, inorganic, lipid, glycan compounds, and synthetic polymers have been used to develop and improve new cancer therapies. This study describes the role of NPs in treating cancer among different methods of drug delivery for cancer therapy

Keywords: Nanoparticles, cancer therapy, hydrogel, nanocarriers, polymer

Introduction
Its primary role is to indiscriminately kill rapidly dividing cells, including tumour and healthy cells. This has potentially substantial adverse effects, such as the suppression of the bone marrow, hair loss, and gastrointestinal problems. Therefore, a significant chunk of cancer-related research over the past few decades has focused on creating medications that more precisely target tumour cells rather than normal cells. Precision therapy has greatly advanced with the creation of tailored therapy, but there are still numerous inevitable side effects, and drug resistance has always been an issue. Cancer is still the second greatest cause of death today, and many malignancies are not well treated by available treatments. Therefore, more research is being done to find effective cancer treatments and ways to combat medication resistance. Nanotechnology has been used in medicine more and more over the past few decades, including applications for safer and more efficient tumour targeting, detection, and therapy. In the treatment of cancer, nanoparticle (NP)-based drug delivery systems have demonstrated numerous benefits, including good pharmacokinetics, accurate targeting of tumour cells, a decrease in adverse effects, and reduced drug resistance [1].

Nanoparticles are now a promising candidate for regulated medicine delivery systems thanks to advancements in nanotechnology. Particles with a diameter of roughly 10-1000 nm are frequently referred to as nanoparticles. When employed as a DDS, nanoparticles can enhance the drug's efficacy by lengthening the drug half-life, making some hydrophobic drugs more soluble, and releasing the medication gradually or steadily. Nanoparticles that respond to stimuli can also aid in reducing drug toxicity and managing biodistribution. In the 1960s, liposomes—the first nanoparticles to be identified by DDS—were utilised as protein and medicine carriers. Since then time, an increasing number of materials are created into nanoparticles and employed as DDSs Large parts of all the materials that have been approved for use as nanoparticles are polymeric and liposomal compounds. However, scientists think that more sophisticated materials, such as micelles, metallic materials, and protein-based materials, can also be employed as nanoparticles [4]. Types and properties of nanoparticles, how nanoparticles can be used as drug delivery systems to kill cancer cells more effectively and reduce or overcome drug resistance, nanoparticles designed to be therapeutically effective and functional in future cancer treatments focus on how to increase [5]. With all these details in mind, the demand for advancing new strategies to search for precise cancer treatments has gained momentum in recent years. Recently, efforts have been made to address the limitations of existing therapeutic approaches using nanoparticles. Nanoparticle-based drug delivery systems reflect advantages in cancer treatment and management by demonstrating superior pharmacokinetics, precise targeting, reduced side effects, and drug resistance [2]. The use of nanocarriers leads to an increased therapeutic index and increased tumor tissue concentration of drugs, providing superior pharmacokinetic properties, increased blood circulation time, cellular uptake, volume of distribution, and half-life compared to current use. It can improve the effectiveness of treatments that are being used. A factor in the improved therapeutic window and subsequent clinical success Advances in nanotechnology are also expected to provide the basis for the development of new therapeutics and the broader application of cancer diagnostic methods Nanotechnology in cancer therapy [6] The ultimate goal of these strategies is to eliminate the tumor with limited effect on normal tissue [7].

Discussion

Nanotechnology applied in cancer therapy

Properties of nanomaterials

Medical nanotechnology typically uses nanoscale materials from 1 to 100 nm. These materials are used in the development and manufacture of therapeutic drugs and devices. As sizes shrink to the nanoscale, many unique optical, magnetic, and electrical properties emerge that distinguish nanomaterials from conventional macromolecules. Typical nanomaterials share some common properties: high surface-to-volume ratio of, enhanced electrical conductivity, superparamagnetic behavior, optical absorption spectral shift, and unique fluorescence properties. In the medical field, nanomaterials can be used for drug delivery and controlled release. Enhanced permeability, penetration of biological barriers, and enhanced biocompatibility are also prominent features. These special properties of nanomaterials suggest that they can be used for cancer therapy. The high surface-to-volume ratio of some nanomaterials may be associated with biomolecules or residues, improving the specificity of chemical drug conjugates in targeted therapy, thereby reducing toxicity to normal cells. PDT and PTT reduction are two therapeutic methods related to optical interference, which can enhance the efficacy of nanomaterials-based treatments while others. In PDT, a photosensitizer accumulates at the cancer site. When irradiated with light of specific wavelengths, cytotoxic reactive oxygen species such as singlet oxygen are generated, and apoptosis and necrosis are induced. PDT and PTT are new cancer treatments with great potential, and the materials used in these two treatments are being intensively studied. Some nanomaterials can be used in PDT and PTT due to their unique fluorescence properties. The superparamagnetic behavior of nanomaterials offers multiple applications in cancer diagnosis and therapy. Superparamagnetic iron oxide nanoparticles (SPIONs), a common nanomaterial, have potential for cancer hyperthermia due to their small size, high target specificity, controllable release rate, and immune evasion ability [2].

Progress of nanotechnology in targeted delivery

One of the main advantages of nano material-based cancer therapy over free medicines is targeted delivery. Targeted delivery based on nanoparticles has recently advanced. Using either passive or active targeting, the concept of targeted delivery seeks to precisely target particular cancer cells. Passive targeting uses the enhanced permeability and retention (EPR) effect, whereas active targeting uses conjugation with antibodies, peptides, aptamers, and small compounds. Targeted drug administration, as opposed to free medication, reduces toxicity in normal cells, guards against drug deterioration, lengthens half-life, increases loading capacity, and increases solubility. Through careful design and adjustment, nano-drugs can preserve advantages over conventional chemical therapy, such as greater specificity, bioavailability, less cytotoxicity to healthy tissue, larger loading capacity, longer half-life duration, and distinctive drug release patterns. Numerous nanomaterials for cancer treatment and diagnosis have been produced over the course of the last 20 years thanks to rapid advancements in cancer pathology and nanoscience, technology, and industry (NSTI) [2].

Nanotechnology applied in cancer therapy

Properties of nanomaterials

Materials having a nanorange size, which is typically 1–100 nm, are used in medical nanotechnology. These materials are used in the design and production of medicinal medications and devices. The unique optical, magnetic, and electrical features that emerge when size decreases to the nanoscale set nanomaterials apart from conventional macromolecules. High surface-to-volume ratio, improved electrical conductivity, superparamagnetic behaviour, spectral shift of optical absorption, and distinctive fluorescence properties are only a few of the traits that characterise typical nanomaterials. Nanomaterials can be used in the medical industry for drug delivery and controlled release. Additionally apparent characteristics are enhanced biocompatibility and increased permeability for overcoming biological obstacles. These specific characteristics of nanomaterial imply that it can be applied in the treatment of cancer. Some nanomaterials' high surface-to-volume ratios enable them to join with biomolecules or residues, improving the specificity of chemical drug complexes in

targeted therapy and minimising the toxicity of nanomaterial-based treatments for normal cells. Two approaches to treating optical interference are PDT and PTT. In PDT, malignant areas accumulate a photosensitizer that, when exposed to specific wavelengths of light, produces singlet oxygen and other deadly reactive oxygen elements, leading to apoptosis and/or necrosis. PTT raises the temperature of the targeted malignant areas, which results in the killing of the cancer cells. It utilises materials with high photothermal conversion efficiency. The materials employed in PDT and PTT, two cutting-edge cancer treatment modalities with considerable potential, are being thoroughly researched. Some nanomaterials can be used in PDT and PTT because of their unique fluorescence properties the superparamagnetic behavior of nanomaterials provides several usages for cancer diagnosis and treatment. A common nano material, superparamagnetic iron oxide nanoparticles (SPION), has potential in cancer hyperthermia treatment due to its smaller size, higher targeting specificity, controllable releasing speed, and immune evasion capability(2)

Progress of nanotechnology in targeted delivery

Targeted delivery is one of the main advantages of nanomaterial-based cancer therapies over free drugs. Recently, advances have been made in targeted delivery based on nanomaterials. The concept of targeted delivery aims to precisely target specific cancer cells and is achieved by either passive or active targeting. Enhanced permeability and retention (EPR) effects are used in passive targeting, while active targeting is achieved through conjugation with antibodies, peptides, aptamers, and small molecules. Compared to free drug, targeted delivery can help reduce normal cell toxicity, protect drugs from degradation, and improve half-life, loading capacity, and solubility. Overcoming the drawbacks of conventional chemotherapy, it has a large loading capacity, a long half-life and a unique drug release pattern. Over the past two decades, tremendous advances in cancer pathology and nanoscience, technology and industry (NSTI) have created numerous nanomaterials for cancer therapy and diagnosis. However, only a relatively small number of nanodrugs have been fully developed and incorporated into clinical use. These nanomaterials can be broadly classified into several categories [2].

Classification of nanocarriers of drugs

In general, excipients can be divided into two main groups. Organic and inorganic carriers each have several subcategories. Drug carriers containing organic particles as the main structure fall into the first group, while drug carriers containing inorganic particles as the central core fall into the second group. Liposomes, dendrimers, carbon nanotubes, emulsions, aptamers, solid lipid NPs, nanobodies, and other polymers are considered organic particles [3].

Organic nanocarriers

Liposomes

Liposomes were first discovered by Alec D. Bangham in 1961. These bilayer vesicles consist of an isolated liquid portion of a bilayer lipid membrane containing natural or synthetic phospholipids. These structures are suitable for drug delivery as they are amphipathic and feasible in nature with simple surface modifications. He was in 1995 when liposomal formulations were first introduced. This was his PEGylated liposomes containing Doxil doxorubicin. The presence of polyethylene glycol prolongs the half-life of doxorubicin flux [3].

Solid lipid NPs

Another form of lipid NPs is solid lipid NPs, which are matrices of solid lipid NPs containing triglycerides, lipids, fatty acids, steroids, and waxes. Their size is less than 1 μm. Surfactant compounds should be used in the formulation to increase the sustainability of these particles. These NPs act as drug carriers with very low solubility in aqueous environments. They are released at specific times and delivered to the target location via food, injection, etc [3].

Polymer NPs

The most common NP drug carriers are polymers. Polymers used for controlled drug release must be biocompatible, contaminant-tight and non-toxic. They must have physically relevant structures with suitable half-lives. The polymers used in the construction of the polymeric NPs can be either natural or synthetic. Polymer NP is mainly selected as a biodegradable type. The advantages of polymeric NPs are high stability and mass production. Polymer NPs contain vesicles (nanocapsules) and matrix systems (nanospheres). In nanocapsules, the drug is stored in a polymer reservoir. However, in nanospheres, the drug is dispersed on a polymer matrix. Abraxane is the first polymer he nanomedicine introduced to the pharmaceutical market in 2005. Contains the albumin-linked drug paclitaxel NP. This formulation does not contain chromophoric electroluminescent (EL) compounds. Chromophore-EL increases the solubility of paclitaxel. It causes severe allergies and fatal symptoms in some patients. Nanotechnology has been shown to overcome the limitations of formulation science [3].

Polymer micelles

Polymeric micelles are self-assembled macromolecules built from block copolymers via non-covalent bonds. Block copolymer micelles have a core-shell structure. Special properties of micelles are the critical micelle concentration (CMC), cumulative number, size and shape of the final structure. These properties depend on the polymer chains within the copolymer block. Polymeric micelles with lower CMC have higher charged drug solubility and higher micelle stability. Micelles are highly efficient in DDS due to their high performance, variable drug loading, high stability under physiological conditions, low dissolution rate and higher accumulation of drug at target sites. and surface modification. Two polymeric micelles, called NK911 and NK105, have been introduced into the pharmaceutical market, containing doxorubicin and paclitaxel, respectively [3].

Dendrimers

Synthesized branched macromolecules having a shape and size that are unique to themselves are called dendrimers. These are monodispersed formations. Through physical and chemical manipulations, their surface can be changed. The existing dendrimers, which are used in DDS, are made of the following polymers; in the 1970s, Fritz Vögtle and Donald Tomalia were the first to attempt dendrimers synthesis and invented tree-like structures by conjugating

the monomers to one another. Vivagel® is the first dendrimer NP system that was released onto the pharmaceutical market. Local antiviral medications called Vivagel® products are used to stop the spread of the herpes and h. i. d. viruses. The dendrimer structure of this substance indicates that it stops the virus from attaching to the host body [3].

Polymersomes

Amphiphilic copolymers with a bilayer structure in water make up polymersomes. They will also have a three-layer structure if they are a particular kind of three-block copolymer. Compared to liposomes, these structures are less capable of entering cells. In the copolymer's longer hydrophobic regions, this feature will increase. It is also a helpful trait for managing drug release. Due to the decreased interference from visceral and macrophage structures in copolymers, these structures are more mechanically and biologically stable than liposomes. As a result, the medication will be very protected [3].

Hydrogel NPs

Drug delivery and encapsulation are accomplished using three-dimensional polymer constructs called hydrogel NPs. In situations with water or living things, these structures swell. They consequently take in more liquids. In reaction to changes in pH and temperature, responsive polymers release the medications. These systems are utilised for biosensors, tissue engineering, DNA and protein delivery, and wound healing [3].

Nanomaterials used for cancer treatment.

Nanoparticles

Polymeric nanoparticles

Particles of a nanoscale size are known as nano-particles. Extracellular vesicles (EVs), polymeric nanoparticles (PNPs), metal nanoparticles, and mAb nanoparticles are all commonly explored nanoparticles (NPs) Colloidal macromolecules with a submicron size of 10–1000 nm are referred to as PNPs. PNPs act as drug transporters for chemical medications, enabling sustained release to specific malignant areas. A nanocapsule or nanosphere is created when drugs are enclosed within or affixed to the surface of nanoparticles. Over time, nanoparticle components have undergone changes. Initially, non-biodegradable polymers such as polymethyl methacrylate (PMMA), polyacrylamide, polystyrene, and polyacrylate were used to fabricate nanoparticles. To avoid toxicity and chronic inflammation, polymeric nanoparticles from these materials should be elucidated in time. These types of polymer-based nanoparticles are difficult to degrade, excrete, or physically remove, thus solving the problem of accumulating to toxic levels in tissues. Biodegradable polymers are designed to reduce toxicity, improve drug release kinetic patterns, and increase biocompatibility. Natural polymers consist of chitosan, alginate, gelatin and albumin. These improved polymeric nanoparticles have certain advantages due to their properties and structure [8]. For volatile pharmaceuticals, PNPs can help improve stability. For chemicals, PNPs offer optional delivery methods such as oral and intravenous and offer higher loading capacities compared to free drugs. The ability to protect drugs from degradation helps minimize unwanted toxicity to normal tissues. For example, cisplatin-loaded PNPs such as dexamethasone and α-tocopheryl succinate have been used in chemotherapy to prevent cisplatin-induced ototoxicity. There are two main methods of drug delivery: Passive and Active Targeting Dense extracellular matrix makes drug penetration more difficult, while over-activated angiogenesis offers a particular advantage, objectively known as his EPR As the tumor grows, it requires large amounts of food and oxygen. Tumor-induced angiogenesis, on the other hand, creates many immature vasculatures that inhibit lymphatic outflow. These leaky blood vessels allow chemicals to enter the cancer site. However, the size of the drug is important because normal particles are not small enough to penetrate cancer cells. In contrast, nanoparticles and related chemical carriers readily enter target sites and can accumulate due to impaired lymphatic drainage [8].

mAb nanoparticles

Recent progress has been made in mAb nanoparticles. Monoclonal antibodies (mAbs) are widely used in targeted therapy due to their specific targeting ability and anti-tumor activity. Moreover, in recent years, mAbs have been used to develop novel anti-tumor nanoplatforms, putting them at the forefront of this field. To further enhance the therapeutic efficacy of cancer drugs, mAbs are conjugated with cytotoxic drugs called antibody-drug conjugates (ADCs). Specific antigens that are differentially expressed in cancer and normal cells regulate drug conjugates, resulting in greater specificity and lower toxicity. Trastuzumab (Herceptin) is his mAb for the treatment of breast cancer with positive expression of human epidermal growth factor receptor 2 (HER2). Studies have been conducted with trastuzumab (Tmab) in ADC systems, which show improved therapeutic efficacy compared to Tmab alone. Abedin *et al*. prepared antibody-drug nanoparticles consisting of a paclitaxel (PTX)-loaded core and a trastuzumab-modified surface. Two HER2-positive and one HER2-negative cell lines were treated separately with this new NP, PTX and trastuzumab with stimulating results.NP conjugates exhibited superior anti-tumor efficacy over PTX or trastuzumab alone, and relatively low cytotoxicity was observed in the NP conjugate group in controls on human mammary epithelial cells [8].

Lipid-based Nanomaterials.

Research on lipid-based nanomaterials is intensive, with three main categories receiving significant attention in current research and clinical trials. Liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC). Approved in 1965, liposomes are believed to be the first closed microscopic phospholipid bilayer nanosystems. Liposomes are spherical vesicles composed primarily of unilamellar or multilamellar phospholipids, and liposome sizes typically range from 20 nm to over 1 μm. Liposomes generally have a hydrophilic core and a hydrophobic phospholipid bilayer This type of structure can entrap both hydrophilic and hydrophobic drugs, depending on the pharmacokinetic properties of the drug. Liposomes with their typical structure encapsulate hydrophilic drugs in their aqueous core and hydrophobic drugs in the lipid bilayer. Drugs encapsulated in the central cavity of liposomes are protected from environmental degradation during circulation through the human bloodstream[8] The size and number of bilayers are two important parameters that affect drug loading and half-life. Liposomes can therefore be classified

into two types according to the following two terms: Unilamellar vesicles and multilamellar vesicles (MLVs). Unilamellar vesicles are further subdivided into small unilamellar vesicles (SUV) and large unilamellar vesicles (LUV). In multilamellar liposomes, an onion-like structure is formed, but multiple unilamellar vesicles are formed inside other vesicles, forming multilamellar concentric spheres of phospholipids separated by water molecules. Therefore, new applications based on liposomal materials have emerged. During the development of liposomes, three key problems were discovered and resolved. Breaking through biological barriers and avoiding rapid elimination is a problem researchers have encountered. As mentioned above, biological barriers have always been the major technical obstacles that nanocarriers have to overcome. For liposomes, cells of the mononuclear phagocytic system 'MPS', mainly in the liver and spleen, function as sentinels and phagocytic nanoliposomes in humans. Membrane modification is one of the most important techniques for extending the half-life of liposomes. Coating the membrane with proteins, peptides, polymers, or other molecules greatly enhances the ability to escape the MPS system and prolongs the half-life of liposomes [8]. This type of liposome is called a "stealth" liposome. Polyethylene glycol-conjugated liposomes were subsequently found to have a longer half-life compared to other modified liposomes. Based on this observation, his PEG liposomes loaded with doxorubicin (DOX) have been used to treat Kaposi's sarcoma in HIV patients. Drug loading and controlled release of liposomes are also important issues to consider when designing liposomal nanocarriers. In cancer chemotherapy, bioavailability affects drug efficacy. Compared to free DOX, DOX-liposomes have lower bioavailability, indicating that improved bioavailability should be considered when designing liposomes. Co-delivery and controlled release are her two main applications of liposomes. Combinations have been formed with chemicals, metals, genetic drugs and other chemotherapeutic agents. Overactivation of specific signaling pathways is a pattern of cancer development, and agents that target these signaling pathways are used. To achieve higher potency, the researchers investigated a novel, small-molecule inhibitor of the phosphoinositide-3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway and mitogen-activated protein kinase kinase/extracellular signal regulation. PEGylated liposomes were loaded with ncl240 and cobimetinib. Protein kinase (MEK/ERK) pathway. The results showed that the synergistic effect enhanced the cytotoxic effect. A novel liposome-encapsulated nanocarrier loaded with both irinotecan and foxridine showed superior efficacy in advanced solid tumors. The delicate structure of the novel multilamellar liposomes enabled effective loading of up to 3500 siRNA molecules in a single bilayer and simultaneous delivery of DOX, demonstrating the effectiveness of DOX in breast cancer treatment and tumor burden. Decrease improved [8]. Triggered release and targeting methods have been extensively studied Because the average extracellular pH of cancerous areas is 6.8–7.0, which is slightly more acidic than healthy tissue, liposomes can be designed to release drugs when they reach acidic cancerous areas. Cationic liposomes (CL) preloaded with sorafenib (Sf) and siRNA (Si) acquired pH-sensitive properties by coating the surface with carboxymethylchitosan (CMCS), a pH-sensitive material. The results showed that the release and intracellular uptake of sorafenib increased at pH 6.5.NLC carriers have been developed over the past two decades as an improved generation of both liposomes and SLNs. To enhance stability and loading capacity while maintaining intrinsic protective functions, biocompatibility, and non-immunogenicity, NLCs are designed as systems consisting of both solid and liquid lipid-loaded core matrices. It has been. NLC can be managed in several ways. Oral, parenteral, inhalation and ocular. NLCs have been attracting attention in recent years because many of the drugs used for cancer treatment are lipophilic [8].

Cancer treatment and Nanomaterials design

Approaches in cancer treatment

Numerous common techniques to treating cancer have been widely used up to this point. Additionally, despite variations in working environments, active components, and methods, the majority of researchers focus on two primary targets: tumour cells and TME, which includes the immune system associated with the tumour [8].

Strategies targeting cancer cells

A natural way to get rid of cancer is by concentrating on cancer cells. Modified nanocarriers like NPs, Dendrimers, or CNMs can deliver chemical medicines or biomaterials into cancer cells with the help of EPR and active targeting. These platforms frequently employ antibodies that target particular antigens that are overexpressed on the surfaces of cancer cells. Depending on the encapsulated cargo, chemical medications that are endocytosed by cancer cells either exert cytotoxicity or nucleic acid materials promote cell apoptosis. Progress has been achieved in the delivery of nucleic acids, and nano-DDS based on exosome PNPs and liposome dendrimer are heavily investigated in the treatment of cancer [8].

Strategies targeting TME

Another approach focuses on the TME that has tumour cells in it. As was already established, angiogenesis is quite active in almost all tumours due to unchecked cell multiplication, which requires a lot of energy. Findings from research on this particular trait were encouraging. Sengupta created an NP system that uses combretastatin to specifically target aberrant tumour angiogenesis. DOX was also co-encapsulated into the PLGA core. As a result, the combretastatin-induced fast shutdown of the malignant arteries allowed the DOX to be effectively taken up by the tumour, improving both the total therapeutic index and toxicity. Extracellular matrix (ECM), in addition to aberrant vasculature, has been studied in the treatment of cancer. Cancer proliferation, migration, invasion, and angiogenesis are guided by the ECM. Collagen, HA, and different enzymes are a few of the key substances causing these malignant characteristics. Collagen, the primary structural protein of the ECM, helps tumour cells migrate along these tracks, whereas HA raises the interstitial fluid pressure (IFP), which inhibits medication diffusion and penetration. Matrix metalloproteinases (MMPs), a type of enzyme, can control TME by modifying the function of non-ECM molecules such growth factors, receptors, and cytokines. ECM is one of the aspects to be taken into account in the design of nanocarriers. When combined with traditional pharmacological medications, Patients with metastatic

pancreatic cancer, particularly those with high hyaluronidase expression, benefited from the therapeutic benefits of recombinant human hyaluronidase (PEGPH20) in PEGylated form, which aims the ECM hyaluronic acid. By coating carriers with hyaluronidase, efforts have been undertaken to improve the penetration ability of chemical medicines loaded onto nanocarriers in solid tumours (HAase) This straightforward method has superior anti-tumor activity [8].

Nanomaterial and drug metabolism.

Drug metabolism is a complex process. The MPS, also called the reticuloendothelial system or macrophage system, consists of blood monocytes, tissue macrophages, and other immune cells. When dealing with exogenous molecules (chemicals in this case), some of the MPS, such as immune cells in the liver, spleen, or lungs, react and activate macrophages or leukocytes to rapidly eliminate the drug, thus reducing drug exposure. Has a shorter half-life. Nanocarriers with surface modifications such as PEG or certain peptides exhibit lower MPS clearance, resulting in longer drug half-lives. Renal filtration is an important function of the renal system. Renal clearance rate is related to several properties such as particle size, shape and surface charge. For conventional chemicals, renal clearance is one of the most important requirements for drug delivery. Adequate renal clearance helps to minimize nanocarrier toxicity. These barriers are obstacles to many conventional drug delivery, reducing drug efficacy at cancer sites and indirectly increasing dosage and toxicity to normal tissues [8].

Applications of nanotechnology in cancer therapeutics

Conventional cancer therapies

Chemotherapy remains the first-line treatment for most cancers, and drug discovery continues to evolve and shift to cancer-specific targets. Conventional chemotherapeutic agents include alkylating agents and antibiotics that induce DNA damage, antimetabolites, antimitotic agents, and topoisomerase inhibitors that interfere with cell replication. Despite the high efficacy of conventional chemotherapy, patients suffer from nonspecificity. Although conventional chemotherapy is highly toxic to cancer cells, it has systemic effects on healthy cells and causes severe side effects in patients. There are specific signaling networks that are known to drive and perpetuate cancer, and various inhibitors that target enzymes within these signaling pathways currently exist and are under development. Various inhibitors of tyrosine kinases, cyclin-dependent kinases, poly-ADP-ribose polymerase, and proteasomes make up most of the small-molecule drugs currently used in clinical targeted therapy. Tumor growth and proliferation are driven by components found in the TME, including immune and inflammatory cells, blood and lymphatic endothelial cells, cancer-associated fibroblasts (CAFs), and bone marrow-derived mesenchymal stem cells. Protein synthesis, glucose metabolism, and other key components of cell survival are often hyperactivated in the PI3K/Akt/mTOR signaling pathway, often redirecting the signal in response to initial treatment increase. Because the RAS/RAF/MEK/ERK signaling pathway initiates cell proliferation, differentiation and development, multiple mutations are common in many cancers [9]. Mutations in the RAS protein are among the most common mutations found in human cancers, and sotrasib is the first FDA-approved KRAS-targeted drug. EGFR mutations also contribute to oncogenesis, and approximately 14 EGFR tyrosine kinase inhibitors (TKIs) are on the market and/or in clinical trials. Targeting these pathways and factors involved in cancer progression has been a focus in the development of new drug therapies, but new drug development costs billions of dollars and has a long delay from development to FDA approval. It will take 10 years or more. Cytotoxic and targeted therapies can select for drug resistance, making complete eradication nearly impossible. Drug resistance can arise through alterations in drug metabolism, Efux/Infux alterations, overactivated repair pathways, signaling rerouting, and mutated drug targets. Methods of overcoming drug resistance include multiple therapies, combination chemoradiotherapy, and personalized medicine. Co-administration of drugs with different molecular targets can help modulate cancer cell mutations and halt adaptive processes in cancer. Effective combinations are being discovered in which drugs can sensitize or reintroduce cancer cells to existing therapies, and new combination therapies are constantly being investigated in clinical trials. However, combination therapies have limitations, mainly due to different PK/PD profiles and disjoint uptake of complementary drugs, reducing their efficacy and synergy. Co-delivery of cancer therapeutics within a single nanocarrier can alleviate these problems and enhance the therapeutic index.1 molar ratio for the treatment of adults with newly diagnosed acute myeloid leukemia (AML) with myelodysplastic-related changes and treatment-attributable AML. A synergistic molar ratio of daunorubicin and cytarabine has been shown to promote leukemic cell killing *in vitro* and in mouse models. In preclinical studies, VYXEOS liposomes were preferentially taken up by leukemic cells over normal bone marrow cells in mouse models. Furthermore, liposomes were strategically designed to interact with receptors overexpressed in leukemia cells compared to their expression in normal myeloid cells. Although this is a promising therapeutic option, more innovative techniques are needed to address drug resistance and treatment-associated toxicities [9].

Current clinical testing of nanoformulated therapeutics

Nanotechnology represents a unique set of tools to overcome both inherent and acquired drug resistance through a variety of mechanisms, including the use of novel immunotherapies such as mRNA vaccines and the identification of resistance and long-term disease. allows targeting of Various nanoformulations for cancer therapy, including liposomes, polymer microspheres, protein conjugates and polymer conjugates, are in clinical use, and new nanomaterials are being investigated for improved efficacy and targeting. As mentioned above, targeted delivery is the pinnacle of cancer therapy as it can greatly reduce toxicity associated with non-specific effects. There are several new developments involving targeted entities currently being tested in clinical trials [9].

Formulations for enhanced PK and specific targeting

Liposomes are a particularly advantageous class of nanomaterials for drug delivery applications due to their ease of fabrication, drug loading, ability to surface modify, and biocompatible components. Liposomes are vesicles composed of a lipid bilayer composed primarily of

amphiphilic phospholipids containing an aqueous interior. Liposome properties can be tailored depending on the polar phospholipid headgroup, the length and hydrophobicity of the fatty acid tail, additional components on the membrane or surface, and the nature of the synthetic or natural lipids. Due to their versatility and relative ease of fabrication, liposomes are one of the most studied nanomedicine used to treat many diseases. Doxil, a liposomal formulation of the highly toxic chemotherapy drug DOX, was the first product approved by the FDA in 1995. A year later, DaunoXome®, another liposomal formulation of daunorubicin, was approved for the treatment of advanced HIV-associated Kaposi's sarcoma [9]. Marqibo, a liposomal sphingomyelin/cholesterol formulation of vincristine sulfate, FDA-approved in 2012, showed improved PK/PD profiles and increased concentrations in solid tumors compared to vincristine. Depocyt® (Cytarabine/Ara-C), Myocet® (DOX), Mepact® (Mifamurtide), and Onivyde® (irinotecan) are also clinically approved liposomal therapeutics for the treatment of cancer and are currently on the market. There are only 7 in total, but it should be noted that the depot site is microscale and has been discontinued. Cisplatin is one of the most commonly used chemotherapeutic regimens due to its efficacy against multiple cancers, but has serious side effects, indicating a critical need for specificity and reconstitution. LiPlaCis is the first liposomal formulation with a triggered-release mechanism being developed in clinical oncology development, where selective hydrolysis occurs by the tumor-expressed phospholipase A2-IIA isoenzyme. Colon cancer, stomach cancer, breast cancer. LiPlaCis has an extended therapeutic window compared to cisplatin with superior PK profile, superior efficacy, and increased maximum tolerated dose (ClinicalTrials.gov identifier: NCT01861496). Drug Response Prediction (DRP®) is used to significantly increase the chances of clinical trial success. Patients undergo genetic screening for their tumors and are selected for study based on those most likely to respond to treatment. This provides a well-defined patient population and reduces subsequent costs and risks. DRP® was statistically significantly predictive of clinical outcome of drug therapy in cancer patients in 29 out of 37 clinical studies in glioblastoma multiforme, and in anaplastic astrocytoma For patients he predicted 24 to 36 months. Currently available therapies for malignant glioma are limited by decreased activity, drug resistance, therapy-induced brain damage, and limited access to privileged intracranial sites. A Phase 1 clinical trial evaluating convection-enhanced delivery (IBD) administration of liposomal irinotecan and Gd is ongoing (ClinicalTrials.gov Identifier: NCT02022644). Liposomal formulations enable delivery across the blood-brain barrier and Gd offers real-time delivery imaging capabilities. IBD improves intraparenchymal delivery of chemotherapeutic drugs to brain tumors by exploiting fluid convection. By maintaining a pressure gradient from the tip of the delivery needle to the surrounding tissue, IBD can deliver small and large molecules, including liposomes, to clinically relevant target volumes [9].

The future of cancer diagnostics and imaging

As was previously mentioned, the key to practically applicable diagnostics will be non-invasive, sensitive cancer screening techniques. Due to their buildup at tumour sites and effective urine clearance, ultrasmall gold nanoclusters (AuNCs) have been shown to provide ideal probes for *in vivo* imaging. A colorimetric signal generated by multifunctional protease nanosensors in the cancer cell microenvironment might be detected in urine. The amount of signal in urine samples taken from mice with colon cancer tumours was found to be 13 times higher than in unaffected mice [9]. Additionally, new imaging agents with increased sensitivity and specificity can aid in the visualisation of the tumour margin during surgical resection and enhance early identification during routine screening. Multiple colours and pigments used in FDA-approved tattoo inks, foods, pharmaceuticals, and cosmetics have recently had their optical properties examined. Several demonstrate a variety of beneficial optical features, outperforming some of the commercially available imaging dyes that have received clinical approval, according to an evaluation of their absorption, fuorescence, and Raman scattering characteristics. To evaluate the tumor-targeting and optical imaging potential of the best performing optical inks (Green 8 and Orange 16) in mice xenograft models of colorectal, cervical, and lymphoma cancers, these inks were combined into liposomal NPs. Fuorescence imaging after intravenous injection showed that the new "optical ink" liposomal NPs were significantly localised in all three tumour models as opposed to the surrounding healthy tissues (p 0.05). Highly sensitive imaging contrast agents with nanoformulations have the potential to significantly advance cancer imaging, diagnosis, and surgical excision of tumour tissue. Through various nanopore-based systems, nanotechnology has had a significant impact on genetic sequencing, which has therefore had an impact on disease screening. The single DNA polymerase within 60-100 nm cavities created by electron beam lithography on a thin aluminium 100 nm sheet coated on a silica substrate is the basis of the single molecule real time sequencing (SMRT) device. This method uses fluorescent nucleotides added to the complement strand to optically monitor the DNA sequence. Oxford Nanopore works by allowing a single DNA molecule to pass through a protein pore that is only a few nanometers wide that is enclosed in a polymer membrane that is electrically resistive. Each DNA nucleotide base creates a different disruption in the current flowing across the membrane. Although both methods are extremely useful for gathering omics data, circulating tumour DNA (ctDNA) analysis is still difficult. A recent technique has showed promise in locating the specific location of genetic alterations by statistically analysing how long it takes for genetic code to unzip and blocking current. On oligonucleotides, this proof-of-concept study was demonstrated, and it is currently being improved for liquid biopsies. Alternatively, as miRNA, mRNA, and proteins in/on EVs constitute potential cancer biomarkers, targeted extracellular vesicle (EV) collection holds promise for the development of liquid biopsy. Recently, total internal reflective fluorescence microscopy was used to construct a high-throughput nano-biochip (HNCIB) for very effective, targeted EV capture. When compared to EVs from healthy donors, HNCIB found that lung adenocarcinoma patients' EVs had higher levels of miR-21, programmed death-ligand 1 mRNA, and protein. In addition to its high throughput capability, it has the advantages of low sample requirements and short assay times. EV monitoring has also helped monitor the effects of drug treatments that were previously limited to invasive

tissue biopsies and complex drug-target interaction analysis processes. EV monitoring of small molecule chemical occupancy and proteins [deleted] ExoSCOPE) measures changes in drug occupancy and protein composition present in small volumes of blood to assess disease status and the success of targeted therapies. measure. ExoSCOPE has monitored a variety of targeted therapies and demonstrated EV signatures that accurately reflect the efficacy of cell therapy. Using a small amount of blood, ExoSCOPE accurately categorized disease states and rapidly differentiated between treatment outcomes of interest within 24 hours of treatment initiation [9]. Theranostics aims to provide point-of-care diagnostics and therapeutics in the same nanoformulation. Theranostic agents can monitor the accumulation of nanomedicine compounds at target sites, visualize biodistribution, quantify evoked drug release, and assess therapeutic efficacy. One of the most important aspects of theranostics is its ability to predict individual patient responses, paving the way for personalized medicine.It can also indicate the presence and precise location of targets within the body, providing a means of addressing tumor heterogeneity. Although the innovative concepts and strategies of theranostics have not yet been fully evaluated in clinical trials, there is a wealth of preclinical research on the fringe of clinical translation. Theranostic NPs were prepared by encapsulating the NIR-II nanofluorophore boron dipyrromethene into amphiphilic poly(styrene-co-chloromethylstyrene) grafted poly(ethylene glycol) nanocarriers Functionalized with a death ligand 1 (PD-L1) monoclonal antibody. Upon 808 nm laser excitation, the target NPs produce emission wavelengths greater than 1200 nm, imaging tumors with a signal-to-signal ratio (T/NT) approximating normal tissue of 14.1. These NPs exhibit high singlet oxygen quantum yields ($\Phi\Delta$=73%) and primary tumor elimination efficacy. NP also allows profiling of PD-L1 expression and accumulation in MC38 tumors, enabling molecular imaging *in vivo*. Her MC38 tumors in mice were eliminated within 30 days by a combination of photodynamic therapy and immunotherapy, and no tumor recurrence occurred within 40 days. Furthermore, tumors in rechallenged mice did not grow within 7 days after inoculation. These NPs exhibited a sustained immunomemory effect against tumor reclamation without toxic side effects on major organs. A proof-of-principle report showed that aggregated single-walled carbon nanotubes (SWCNTs) are potentially promising theranostic tools, enabling photo-activated destruction of cancer cells while preserving the local environment. Absorption of picosecond light pulses by SWCNTs induces photoacoustic cell destruction without disturbing the surrounding environment, enabling continuous monitoring [9].

Future perspective of research

To enhance their properties, most scientists are currently working on hybrid organic-inorganic NPs. Superparamagnetic nanoparticles (NPs) have special features that make them useful for drug delivery, and surface modifications and hybridization with one of the aforementioned polymer systems can stop NPs from oxidising. Furthermore, the method of medication delivery will be enhanced by the alteration of polymer structures. One of the important goals of rapidly expanding research is the fabrication of multifunctional structures, in addition to the creation of hybrid particles. One illustration of these multifunctional structures is a superparamagnetic NP that has undergone polymer-polymer hybridization and has been given an antibody or unique receiver. This receiver significantly improves the system's sensitivity and specifications while reducing the drug's negative effects. Additionally, MRI can be used to track the dispersion of these particles throughout the body [3].

Conclusion

Different types of NPs with diverse architectures have been introduced as a result of the advancement of nanotechnology and its integration with other sciences. They both have some benefits and drawbacks. However, they are regarded as a successful step in enhancing particle functionality. In DDS, NPs serve as their most effective function. They serve as polymer, lipid, metal, ceramic, and other types of carriers for the delivery of drugs to treat many diseases, particularly resistant disorders like cancer. Drug delivery, biomedical imaging, and the diagnosis and treatment of diseases are all possible uses for NPs. As nanotechnology develops, there will be more options to target several tumour samples' molecules at once and to use the best therapeutic approaches. The use of NPs for *in vivo* cancers is quickly advancing. Targeting malignant antigens may be viable as a result of these advancements. Nanotechnology science will soon bring about a significant transformation in oncology as well as all other medical specialties. Nanomedicine developments present fresh chances to enhance the arsenal against cancer. The preclinical and clinical stages of targeted and nontargeted nanoparticles show the influence of delivery mechanisms on the field. Additional research in nanomedicine will increase the therapeutic window for medications with far fewer side effects, improving patient outcomes.

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