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Review Article

Footprints of Nanocarrier on multi drug resistance therapy

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ABSTRACT: As it is commonly recognized, the phenomenon of multidrug resistance (MDR) is increasingly prevalent on a global scale, posing significant challenges in the realm of treatment. MDR refers to a condition where resistance to various medications, which may differ in their chemical composition and mode of action, arises due to the presence of numerous mechanisms. In response to multidrug resistance (MDR), developing technologies in the field of nanotechnology, particularly Nanocarrier, are being utilized as counteractive measures. Nanocarrier refers to biodegradable materials that are employed in the field of drug delivery. Their primary function is to improve the solubility of medications that have low solubility, boosting their bioavailability. Additionally, nanocarriers enable the timed release of drugs and facilitate the accurate targeting of specific areas inside the body. Nanocarriers exhibit a diverse range of morphologies and dimensions, encompassing nanofibers, nanocomposites, nanoparticles, and nanotubes. These nanocarriers can be administered through injection, subcutaneous delivery, or intramuscular administration. In this review article, we focus on different nanocarriers and their use in MDR.

KEYWORDS: nanocarrier; multi drug resistance; tuberculosis; antimicrobial

1. Introduction

1.1. Multiple drug resistance

Multiple drug resistance (MDR), a state of resistance to medications that are structurally and/or functionally unrelated is known as MDR. It is critical to recognize that clinical MDR is likely to be caused by multiple mechanisms. The resistance may be innate to the cell (primary) or secondary (acquired by mutations)[1].

MDR is a fundamental cellular survival mechanism, and many of the implicated genes are widely distributed[2]. Genetic diversity is a more complicated subject. Where does the opposition come from? Cells subjected to oxidative stress in the form of oxygen-based radicals receive a large number of oxidative hits per day, each of which has the potential to cause a mutation. Humans, whose basal metabolic rate is only about one-seventh that of the rat, are estimated to receive about 10,000 oxidative hits per day. The majority of the damage is repaired, but the process is not perfect, and mutations occur and accumulate with time and exposure[3].

The resistance develops not just to the specific cytotoxic agent being administered, but also as a result of cross-resistance to a wide variety of medicines with various cellular targets[4]. Most drugs are becoming less effective against relatively common strains of infectious agents such as Staphylococcus, Enterococcus, Pseudomonas aeruginosa, Mycobacterium, and Pneumococci. There are three types of resistance mechanisms which includes: Failure of drug penetration into (or ejection from) target cells, enzymatic inactivation of the drug, and alteration of the drug target within the cell. Antifungal, antiprotozoal, antiviral, and antitumor drug resistance are all well known, as is antibacterial drug resistance[5].

MDR has also been reported in cancer chemotherapy through a variety of mechanisms including the ABC transporter family, apoptosis induction, autophagy induction, cancer stem cell regulation, miRNA regulation, hypoxia induction, DNA damage and repair, and epigenetic regulation[6].

Types of nanocarriers

High surface-to-volume ratio nanocarriers primarily consist of three types: hybrid nanocarriers, inorganic nanocarriers, and organic nanocarriers. Organic nanoparticles such as dendrimers, liposomes, and solid lipid nanocarriers are examples of organic nanocarriers. Gold, magnetic nanoparticles, quantum dots, mesoporous silica, and other inorganic materials are examples of nanocarriers[7].

Nanocarriers are objects or materials with a nanoscale (below 1 m) and are composed of a variety of biodegradable substances, including lipids, phospholipids, and even organometallic compounds. Due to their submicron size and extremely high surface-to-volume ratio, nanocarriers dissolve more quickly. RES (Reticulorndothelial system) is typically in charge of absorbing nanoparticles in the body. However, the size and surface characteristics of the nanocarriers are connected to this uptake. Numerous submicron systems, including nanoparticles, nanocapsules, lipid complexes, polymeric micelles, and dendrimers, are examples of nanocarriers[8].

1.2. What is a nanocarrier?

Nanocarriers are materials or devices of nanoscale (below 1 mm) made up of different biodegradable materials like natural or synthetic polymers, lipids or phospholipids, and even organometallic compounds. Nanocarriers aid in efficient drug delivery to improve the aqueous solubility of poorly soluble drugs that enhance bioavailability for timed release of drug molecules, and precise drug targeting.

Over the past ten years, both in pharmaceutical research and in clinical settings, the use of nanoparticulate pharmaceutical carriers to improve the in vivo efficacy of various medications and drug delivery procedures has become well-established[9]. Two main internalisation pathways may occur depending on the physicochemical properties of the nanocarrier and the nature of the target cells: phagocytosis or other endocytic pathways.

The Greek term for "dwarf" is nanos. Matter with at least one dimension between 1 nm and 100 nm is referred to as nanotechnology. A sheet of paper is roughly 100,000 nanometers thick, and one nanometre is equal to 10 m to 9 m. Because of their small size, materials in such a universe have unusual physical, chemical, and biological properties. NPs are solid particles that come in a wide range of shapes, sizes, and properties.

Lipids, metal or silicate crystals, proteins, or polymers are typically used in their construction[2]. Colloidal particle systems between 10 nm and 1000 nm in size are known as nanocarriers. Liposomes,

which are synthetic phospholipid vesicles with sizes ranging from 50 nm to 1000 nm and greater that can be loaded with a range of medications, are the most prevalent and well-studied nanocarriers[10].

Nanostructures come in a variety of shapes and sizes, including nanofibers, nanocomposites, nanoparticles, and nanotubes, and they can be used to treat and diagnose a wide range of illnesses[11]. The field of medicine delivery has been substantially impacted by advances in nanotechnology. The use of nanotechnology in medicine, or "nanomedicine," has the potential to significantly advance medical treatment, particularly for cancer.

The miniaturization of devices for use as diagnostics, biosensors, and imaging agents over the past few decades has sparked a revolution in materials science. On the other side, ever-evolving synthetic chemistry is developing nanocarriers for drug delivery[12].

Nanocarrier can be injected [i.e., intravenous (i.v.), subcutaneous, intramuscular administration] or can enter the body through the upper airways and gastrointestinal tract (GIT), respectively. To access diseased tissues through the bloodstream, they must pass through various specialized epithelia, such as the lung or GIT epithelia, tumoral vascular endothelium, or the blood-brain barrier (BBB). Even for nanometric particles (1–1000 nm), this is not a trivial task, and the only viable channels are transcytosis or epithelial porosity routes[13].

1.3. MDR in cancer

Compared to previous decades, cancer therapy has significantly improved because of more efficient medications and safer formulations. Despite these advancements, the mystery of undesired side effects caused by a lack of selectivity in traditional chemotherapy must be solved. Systems created to support chemotherapy and photothermal therapy together have implications for metastasis and cancer recurrence.

Strong photothermal converters, and carbon nanotubes (CNTs) may be used in chemo-thermal combination therapy. They aid in the delivery of drugs into cells and produce heat when exposed to NIR (near infrared) light, which can facilitate the penetration of biological tissues Antiangiogenic therapy has limitations due to tumor invasion brought on by metastasis, which can be solved via therapy involving nanotechnology. CNTs' surface functionalization improves their cellular absorption, non-cytotoxicity, water dispersion, and accumulation within tumors.

The creation of a smart nanocarrier is made possible by the modification of CNTs with stimuli-responsive polymers. With pH-thermo dual responsive drug release, synergistic cocktail chemotherapy, and photothermal therapy-mediated cell death, the nanocarrier demonstrated cell death. By using a CAM assay on a chick embryo, the anti-angiogenic potential of the dual drug-loaded carriers has also been successfully proven. Upon treatment with the curcumin and DOX medication pair loaded CD-CNT, a down-regulation of important growth factors (FGF2 and VEGF) was seen[14].

1.4. MDR in tuberculosis

Drug-susceptible tuberculosis is treated for six months with a standard four-drug regimen of isoniazid, rifampicin, ethambutol, and pyrazinamide, which has several limitations including low efficacy, relatively higher toxicity (hepatotoxicity), prolonged duration, patient noncompliance, and the emergence of multidrug-resistant (MDR) and extensively-drug resistant (XDR) tuberculosis.

Multidrug-resistant tuberculosis is defined as a disease caused by Mycobacterium tuberculosis strains that are at least resistant to isoniazid and rifampicin treatment; extensively drug-resistant

tuberculosis is defined as a disease caused by multidrug-resistant strains that are also resistant to any fluoroquinolone and any of the injectable drugs used in treatment with second-line anti-tuberculosis drugs (amikacin, capreomycin, and kanamycin.

In such cases, various advanced novel controlled-release drug delivery platforms can be used in the treatment and prevention of Mtb, potentially opening up new avenues in tuberculosis treatment by ensuring maximum patient compliance while minimizing side and adverse effects[15].

1.5. Types of nanocarriers used in MDR

The reported types of nanocarriers are shown in **Figure 1** which include Nanocrystals and nanosuspensions, Nanotubes and nanowires, Ceramic nanoparticles, Liposomes, Solid lipid nanoparticles, Polymeric nanoparticles, Hydrogel nanoparticles, Dendrimers, Polymeric micelles, and Functionalized nanoparticles.

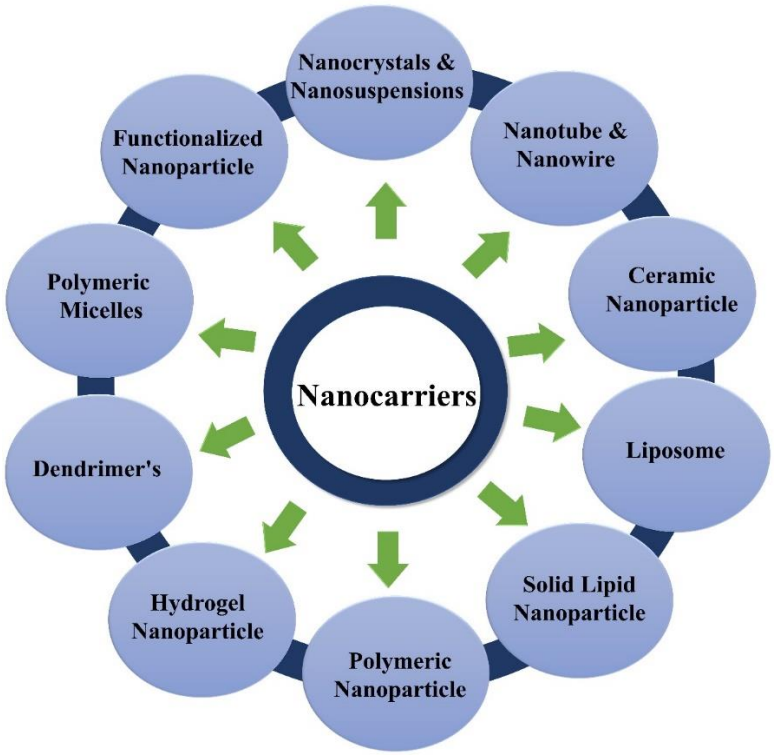

Figure 1. Types of nanocarriers.

1.5.1. Nanocrystals and nanosuspensions

To get around the problems that poorly soluble medications have with bioavailability, numerous strategies have been developed over time. The formulation of pharmaceuticals as nanocrystals, which are composed of "pure medications and a minimum of surface-active agents required for stabilization," is one way that science and industry have been addressing this issue in light of recent advancements in nanotechnology.

According to their definition, they are "carrier-free submicron colloidal drug delivery systems having a mean particle size in the nanometer range, often between 10–800 nm[16]". A thin coating of a surfactant or combination of surfactants forms the core of nanocrystals, which are aggregates of hundreds or thousands of molecules that assemble into a crystalline form. The process of making nanocrystals is called "nanonisation[8]".

Disulfiram (DSF), an MDR modulator, was incorporated into pure paclitaxel (PTX) nanoparticles to create smart paclitaxel disulfiram nano cocrystals (PTX-DSF Ns) to reverse MDR and thus increase cytotoxicity towards Taxol resistant A549 cells (A549/TAX). A precise mass ratio of PTX-DSF Ns provided efficient cytotoxicity against Taxol-resistant cells[17].

On the other hand, D-α-Tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS inhibits permeation glycoprotein (P-gp) and is used to overcome the MDR effect of anticancer drugs by improving cellular uptake[18].

1.5.2. Nanotube and nanowire

Nanotubes and nanowires are sheets of atoms that self-assemble into tubes and thread-like structures at the nanoscale[8] Carbon nanotubes (CNTs) are cylindrical carbon allotropes from the fullerene family. A significant increase in publications has been observed in this fascinating sector as a result of the special physicochemical characteristics of CNTs and their simple surface modification. In addition to their use in cellular imaging, nanomedicine uses them for diagnostic purposes[19].

The zinc oxide nanotubes synthesized have strong antimicrobial activity against some Gram-positive and Gram-negative bacteria and can be used as nano-control materials against medicinal bacteria. When compared to Gram-negative bacteria, Gram-positive bacteria appeared to be more resistant to zinc oxide nanotubes[20].

1.5.3. Ceramic nanoparticle

These are the inorganic (ceramic) substances like silica, titania, and alumina nanoparticles. Ceramic nanoparticles are smaller than 50 nm, which aids them in avoiding the body's reticuloendothelial system (RES). Because they don't experience swelling or changes in porosity with pH variations, these particles completely shield molecules such as proteins, enzymes, and medicines from the denaturalizing effects of ambient temperature and pH[8].

Among the most prevalent natural and man-made nanomaterials, ceramics include. Technology-wise, ceramic nanostructures are crucial for catalysis and medicine. Because of the long-term interest in elucidating the function of early earth minerals in the prebiotic creation of peptides, proteins, and other biomolecules, the adsorption of amino acids on various ceramic surfaces is well investigated[21].

Because of their large pore volume and surface area, mesoporous silica nanoparticles (MSNs) can hold large amounts of drugs. Doxorubicin-loaded MSNs (DMNs) induced more doxorubicin accumulation in drug-resistant tumors than free doxorubicin. Drugs encapsulated in nanomaterials can enter target cells via various mechanisms, avoiding the drug transporters P-gp, MRP, and BCRP and increasing intracellular drug accumulation, thereby reversing MDR[22].

1.5.4. Liposome

Liposomes are spherical vesicles made of lipid bilayers surrounding an aqueous core that can be employed to transport both lipophilic and hydrophilic medicines to the target region (**Figure 2**). One or more bilayers can be separated into unilamellar and multilamellar vesicles (more than one bilayer). This vesicle acts as a vehicle for the delivery of chemicals that are physiologically active to the desired location. However, in the systemic circulation, these compounds have a shorter half-life[11]. The most common method for giving drug carriers in vivo longevity is to add synthetic polymers to their surfaces, like poly (ethylene glycol) or PEG, as was first proposed for liposomes[9].

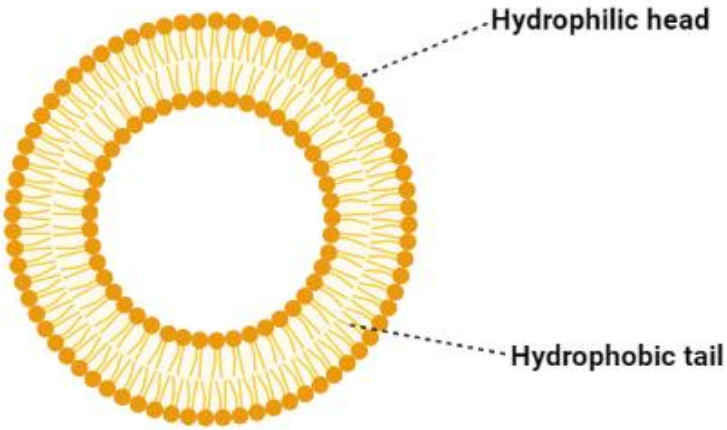

Figure 2. Liposome.

Antineoplastic agents such as daunorubicin, carboplatin, and etoposide are found in liposomes. Depocyt®, for example. Liposomal cytarabine (ScyePharma Inc.) is actually serving in the Malignant lymphomatous meningitis clinical treatment, these Liposomes are delivered in the form of non-concentric vesicles, each with an internal aqueous chamber containing cytarabine encapsulated a solution surrounded by a bilayer lipid membrane dipalmitoyl phosphatidylglycerol, dioleoyl phosphatidylcholine Triolein and cholesterol[23].

MDR tuberculosis is caused by Mycobacterium tuberculosis (M. tuberculosis) which is resistant to first-line drugs (rifampin-isoniazid). Liposomes containing dipalmitoyl phosphatidylcholine and cholesterol were tested as ZnPc carriers in two strains of M. tuberculosis, it was found that ZnPc-liposomes inactivated susceptible and MDR-M. tuberculosis strains. As a result, photodynamic antimicrobial chemotherapy with ZnPc-liposomes could be an option for treating MDR-M[24].

1.5.5. Solid lipid nanoparticles

Solid lipid nanoparticles are a different lipid-based formulation that uses solid lipids. Aqueous surfactant solutions or water are used to disperse the submicron colloidal carriers (50–1000 nm) that makeup SLN particles formed from solid lipids. These are made up of a monolayer of phospholipid covering a solid hydrophobic core. The medication is disseminated or dissolved in the solid, high-melting fat matrix of the solid core. The fat matrix contains the hydrophobic chains of phospholipids. When compared to polymeric nanoparticles, SLN is non-toxic[8].

Doxorubicin-loaded solid lipid nanoparticles (SLN-Dox) made from biocompatible compounds were tested in vitro and in vivo on drug retention and apoptosis intensity in P-glycoprotein-overexpressing MCF-7/ADR cells, a representative Dox-resistant breast cancer cell line. In comparison to Dox, SLN-Dox efficiently increased apoptotic cell death by increasing Dox accumulation in MCF-7/ADR cells.

As a result, SLN-Dox may be a useful therapeutic approach for overcoming chemoresistance in adriamycin-resistant breast cancer[25].

VOR-SLNs [a histone deacetylase inhibitor, vorinostat (VOR), in combination with solid lipid nanoparticles (SLNs)] successfully increased VOR's oral bioavailability, circulation half-life, and chemotherapeutic potential on multidrug-resistant cancer cells. Furthermore, in both sensitive (MCF-7

and A549) and resistant (MDA-MB231) cancer cells, VOR-SLNs were found to be more cytotoxic than the free drug[26].

1.5.6. Polymeric nanoparticles

For well-established pharmacological compounds, polymeric nanoparticles, such as nanospheres or nanocapsules, may result in better bioavailability profiles. Nanocapsules are vesicular systems in which the drug is contained in an aqueous or oily cavity and covered by a polymeric covering, as opposed to nanospheres, which are matrix systems in which the medication is disseminated. In the creation of nanoparticles, polymer materials of both natural and synthetic origins were employed, giving them excellent drug-delivery capabilities. Due to their capacity to maintain the stability of the loaded medication and transport it over time, boosting bioavailability, nanoparticles are utilized as drug delivery systems in a variety of administration methods. Additionally, nanoparticles can make medications more permeable to biological barriers like the intestine and respiratory epithelium[27].

Natural polymers such as albumin, dextran, hyaluronate, and chitosan are used in this application, as are synthetic polymers such as PLGA, PLA, PCL, PEG, PVA, poly(cyanoacrylate) (PCA), poly(N-(2-hydroxypropyl) methacrylamide) (PHPMA), and PEI. PNPs can be made using a variety of methods, including precipitation, emulsification, coacervation, and layer-by-layer methods[28].

The effect of MDR-1 gene silencing using siRNA and paclitaxel (PTX) co-therapy in overcoming tumor multidrug resistance was investigated. To efficiently encapsulate MDR-1 siRNA and PTX, poly(ethylene oxide)-modiWed poly(beta-amino ester) (PEO-PbAE) and PEO-modiWed poly(epsilon-caprolactone) (PEO-PCL) nanoparticles were created. The combination of MDR-1 gene silencing and nanoparticle-mediated delivery significantly influenced the cytotoxic activity of PTX in SKOV3TR cells, as it did in drug-sensitive SKOV3. These preliminary findings are extremely promising for the development of combination nano-therapeutic strategies that combine gene silencing and drug delivery to provide a more potent therapeutic effect, particularly in refractory tumors[29].

1.5.7. Hydrogel nanoparticles

Another polymeric system that self-assembles and self-aggregates are hydrophobized polysaccharides like cholesteroyl pullulan, cholesteroyl dextran, and agarose, where cholesterol groups act as non-covalent cross-linking sites. These polymers are known as hydrogel nanoparticles. The size and density of hydrogel nanoparticles can be altered by modulating the degree of replacement of cholesterol groups. The complicated viscosity of the thermoresponsive hydrogel was enhanced by adding nanoparticles, while the initial hydrogel's gelation temperature was lowered. Functionally, the incorporation of inorganic nanoparticles altered bone differentiation biomarkers and improved bone mineralization.

Negatively charged 700 nm alginate and chitosan NCs encapsulating insulin were created. In diabetic rats, the results show a 40% reduction in glycemia. Encapsulation into mucoadhesive NCs was crucial in improving oral absorption and activity[30].

To alleviate tumor MDR, a highly engineerable hydrogel nanoparticle (NP) was used as a carrier for the optimal codelivery to tumor cells of the chemo drug doxorubicin (Dox) and the chemosensitizer verapamil (Vera). Dox-NPs and Vera-NPs increased the intracellular accumulation of Dox and significantly improved Dox's cell-killing ability in vitro against NCI/ADR-RES cells.

This study demonstrated that such codelivery nanoplatforms could offer a promising path to overcoming tumor[31].

1.5.8. Dendrimers

Dendrimers, which are highly branched, symmetrical macromolecules, are novel and intriguing drug encapsulation systems. These compounds have characteristics that distinguish them from linear polymers, such as monodispersity, globular shape, high surface functionality, the presence of internal cavities, and so on. Because of the open nature of dendritic architecture, several groups have investigated the possibility of encapsulating drug molecules within dendrimer branches (dendrons). In particular, very encouraging data on methotrexate (MTX) delivery in an in vitro model of the BBB for the treatment of gliomas using polyester-polyether (PEPE) dendrimers with the same butanetetracarboxylic core, PEG spacers, and different branching agents were reported: 3,5-dihydroxybenzoic acid, gallic acid, and 2,2-bis(hydroxymethyl)butyric acid are all examples of organic acids[32–34].

Dendrimers are made from polymers such as poly(amidoamine) (PAMAMs), polyamine, polypeptide, polyesters, PEI, PEG, or carbohydrates. Because of the high density of function groups (amine groups) on the surface, PAMAM is frequently used to make dendrimer carriers. Furthermore, its cationic charges allow for the delivery of nucleic acids[35,36].

Dendrimer was formed by combining 4 polyamidoamine (G4 PAMAM) with a polyethylene glycol (PEG)-phospholipid copolymer. This system was tested for cytotoxicity against MDR cancer cells, including human ovarian carcinoma (A2780 ADR) and breast cancer, after being co-loaded with doxorubicin (DOX) and therapeutic siRNA (siMDR-1) (MCF7 ADR). The combination nanopreparation effectively reduced P-gp expression in MDR cancer cells and reversed DOX resistance[37].

1.5.9. Polymeric micelles

Polymeric micelles (PMs) are created through the self-assembly of amphiphilic block copolymers that form a core-shell structure. PMs are used as drug carriers because of their ease of preparation, narrow size distribution (diameters up to 100 nm), and ability to solubilize hydrophobic drugs[38].

In an aqueous solvent, PMs are typically composed of hydrophobic segments forming an inner core and loading hydrophobic drugs, and hydrophilic segments forming an outer shell. In contrast, reverse polymeric micelles (RPMs) formed in organic solvents have a hydrophobic shell and a hydrophilic core and are suitable for the encapsulation of hydrophilic drugs[39].

Hydrophilic segments of PMs include poly(ethylene glycol) (PEG), PVP, and poly (N-isopropyl acrylamide) (PNIPAAm), whereas hydrophobic segments include biodegradable polymers such as PLGA, PCL, poly(L-aspartic acid), and their derivatives. Genexol-PM is a paclitaxel (PTX) encapsulated in a PEG-poly(l-lactic acid)) PM system that has been approved in South Korea[40].

Micelles composed of poly(histidine (His)-co-phenylalanine (Phe))-b-poly(ethylene glycol) (PEG) and poly(L-lactic acid) (PLLA)-b-PEG-folate were used with PLLA(3K)-b-PEG(2K)-folate in the presence of a basic anticancer drug, doxorubicin (DOX). Both wild-type and DOX-resistant ovarian carcinoma cell lines were tested in vitro. DOX-loaded micelles effectively killed both wild-type sensitive and DOX-resistant ovarian MDR cancer cell lines[41].

1.5.10. Functionalized nanoparticle

Functionalized nanoparticles are the combination of functionalities of biomolecules and non-biologically derived molecular species used for special functions such as markers for research in cell,

molecular biology, biosensing, bioimaging, and marking of immunogenic moieties to targeted drug delivery.

In the treatment of human MDR breast cancer, the NPs were loaded with doxorubicin (DOX) and indocyanine green (ICG) for dual modality cancer treatment and coated with cholesterol-PEG (C-PEG) for MDR abrogation. The effective inhibition of P-gp activity by C-PEG and -PGA receptor-mediated endocytosis increased the in vitro cellular uptake of DOX/ICG loaded nanoparticles (DI-NPs) by MDR cancer cells. As a result, after photo-irradiation, the C-PEG coated DI-NPs demonstrated a synergistic effect of combination (chemo/thermal) therapy in suppressing the proliferation of MDR cancer calls. The findings show that the CP2k-DI-NPs dual modality therapy system developed in this study is promising for effective combination therapy of human MDR breast cancer[42].

2. Future prospects and conclusion

Nanocarriers are biodegradable substances used in pharmaceuticals to help deliver drugs, which makes them more soluble in water and increases their overall bioavailability. In the field of pharmaceutical research and clinical practice, these substances find application in order to enhance the in vivo effectiveness of drugs. Nanocarriers exhibit a diverse range of morphologies, dimensions, and characteristics, encompassing lipids, metals, proteins, and polymers. Liposomes, which are synthetic vesicles composed of phospholipids, are widely recognized and extensively investigated as nanocarriers. The field of nanotechnology has made notable strides in its influence on the administration of medicine, with a specific emphasis on its application in the treatment of cancer. Nanocarriers possess the capability to be introduced into the body by injection, subcutaneous administration, intramuscular administration, or by traversing the upper airways and gastrointestinal tract. In order to reach sick tissues via circulation, it is necessary to traverse specialized epithelial barriers, wherein the only feasible pathways are transcytosis or paths characterized by epithelial porosity. The field of nanotechnology holds promise for advancing medical therapy, specifically in the context of cancer.

Abbreviations

CNTs	Carbon nanotubes
DOX	Doxorubicin
ICG	Indocyanine green
MDR	Multi drug resistant
PAMAM	Polyamidoamine
PMs	Polymeric micelles
SLNs	Solid lipid nanoparticles

Conflict of interest

The authors declare no conflict of interest.

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