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Review Article

Recent Advances in Nanocarriers as Targeted Drug Delivery Systems

Mahira Islam Asfie[1], Junayet Hossain Khan[1], Sultan Alshehri[2], Mohsin Kazi[3], Mohammad Hossain Shariare[1]*

[1] *Department of Pharmaceutical Sciences, North South University, Dhaka, Bangladesh*

[2] *Department of Pharmaceutical Sciences, College of Pharmacy, Al Maarefa University, Ad Diriyah 13713, KSA*

[3] *Department of Pharmaceutics, College of Pharmacy, POBOX-2457, King Saud University, Riyadh, KSA*

***Correspondence *E-mail*:** mohammad.shariare@northsouth.edu

Abstract: Targeted drug delivery and the use of nanocarriers in drug delivery systems have shown significant impacts in mitigating various diseases. The limitation lies in designing nanocarriers for an effective therapeutic outcome. The concept of targeted drug delivery is drawn from the 'magic bullet' concept, which reduces toxicity, enhances effectiveness, and helps control the drug release rate. Targeted drug delivery strategies can be performed in various ways but mainly depend on ligand–receptor binding and the enhanced permeability and retention method (EPR). Different nanocarriers have been developed over the years, including liposomes, solid lipid nanoparticles, lipid-polymer hybrid nanoparticles, niosomes, ethosomes, dendrimers, polymeric micelles, carbon nanotubes, and metallic nanoparticles. Drug loading in nanocarriers occurs by covalent bonding, electrostatic interactions, or encapsulation. Nanocarriers have been developed over the years, and novel nanocarriers have been designed to enhance their effectiveness, reduce side effects, increase circulation time, and accumulate at the target site. This article discusses the different strategies of drug delivery systems, different types of nanocarriers, and their advantages as targeted drug delivery systems. This article also discusses the recent advances of novel designed nanocarriers as targeted drug delivery systems.

Keywords: Nanocarriers 1; targeted drug delivery 2; drug loading 3; receptor binding 4; novel design 5; therapeutic efficacy 6.

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1. Introduction

Nanotechnology has been in use for a long time, but its use has recently emerged in drug delivery. There have been many advances in this field to make effective site-specific medications. Nanotechnology is now widely used to make

drug delivery more effective at the target site, reducing side effects. Targeted drug delivery is required to obtain the maximum efficacy at a lesser amount and enhanced therapeutic effect without side effects resulting from accumulation at the nontarget site. Various nanocarriers have been developed, each with unique properties for targeted drug delivery. Target drug delivery can also reduce multidrug resistance, for which the use of nanocarriers has become a topic of interest for delivering lifesaving drugs. Recent advances in nanocarriers as a means of targeted drug delivery systems have paved the way for mitigating various diseases, such as cancer, acne, Alzheimer's disease, and infections. It is also used for vaccines and the delivery of insulin. Recently, nanocarriers were used to produce the COVID-19 vaccine, which has been an issue worldwide. Nanocarriers that help in the drug delivery system are less than 200 nm in size, and the weight is more than 40 kDa. This specification allows nanocarriers to cross the microcapillaries of the body very easily and reach the desired target site. On the other hand, higher weight does not allow it to be eliminated easily by the kidney. They remain in the circulation system for a long time, which helps them accumulate in the target site, resulting in a maximum therapeutic effect [1, 2].

Nanocarriers are loaded with drugs through three main strategies: covalent bonding, encapsulation, and electrostatic interaction. Moreover, functionalizing nanocarriers with the help of polymers, ligands, surfactants, and biomolecules has made drug delivery more efficient. This has helped in the reduction of toxic effects along with better therapeutic outcomes [3]. Liposomes, solid lipid nanocarriers, carbon nanotubes, polymeric micelles, virosomes, transferosomes, niosomes, dendrimers, carbon nanotubes, and mesoporous silica are some of the most used nanocarriers in drug delivery systems. They are not only used for the delivery of drugs but also have effects in diagnosis, treatment, immunization, biosensing, etc. Functionalization of these nanocarriers by using various ligands, polymers, and biomolecules to make novel-designed nanocarriers that overcome the drawbacks of conventionally used nanocarriers. Some novel-designed nanocarriers are cubosomes, lipid drug conjugates, nanostructured lipid carriers, quantum dots, etc. These novel-designed nanocarriers are more specific and pose little to no threat of toxicity, as they have a specific affinity for the target site [4, 5, 6].

This paper mainly focuses on the advances of nanocarriers in targeted drug delivery, strategies for targeted drug delivery, ways of loading drugs on nanocarriers,

functionalization of nanocarriers, and some of the novel designed nanocarriers that are better than conventionally used nanocarriers.

2. Targeted Drug Delivery

Drug delivery, in general, describes the processes, methods, technologies, and formulations used to carry the drug substance in the body to achieve the required therapeutic effect. The drug delivery system's primary focus is administering the drug appropriately with the proper dosage and target. Targeted drug delivery is the system by which the drug is administered to a specific target in a specific location. Targeted drug delivery systems have made remarkable advances because they are responsible for increased safety due to target specificity, which also increases efficacy [7]. On the other hand, a conventional drug delivery system does not focus on drug delivery at a specific site, minimization of toxicity, or enhancement of effectiveness and, as a whole, has low therapeutic indices [8]. In a targeted drug delivery system, the drug is not released at any other nontarget site.

The concept of targeted drug delivery came from the “magic bullet” vision of Paul Ehrlich to selectively target by drugs and have affinity only for that target without harming other sites [9, 10]. The term magic bullet was postulated, as the drug would pose a lethal effect on the pathogen without harming the human body. This magic bullet acts as a gunman's bullet that exclusively hits the target and nothing else in the surroundings [11].

The concept of a magic bullet mainly included identifying toxic drugs and then modifying those drugs to pose less toxicity by increasing the specificity [12]. The components that help in the effective delivery of the drug to the target site include the selection of the target moiety, selecting a target to effectively bind with the target, and the drug that will provide therapeutic action [13]. Carriers deliver the intact drug to the exclusively selected site of action, and there can be various types of carriers to entrap the drug moiety [14].

2.1 Advantages of Targeted Drug Delivery

Target drug delivery focuses on delivering a specific quantity of drug to a particular site on the organ or tissue. The concept depends on the accumulation of the drug, specifically at the target site. This process helps find solutions to problems faced with conventional medications. Thus, there are various advantages of the target drug delivery system. The drug concentration at the target site due to nanocarrier integrated drug is high, whereas the concentration at the nontarget site is low. At the

same time, side effects and toxic reactions are less as the drug accumulates at high concentrations only at the desired site of action. For this reason, the amount of drug required to obtain a therapeutic effect is lower, reducing the cost of treatment. The toxicity can be reduced which is usually the result of high doses for showing therapeutic effects and drugs with small therapeutic indices. The protocols required for the administration of the drug are also simple. The absorption of the drug from the target site is higher and improved and it helps improve the drug's pharmacodynamic, pharmacokinetic, and other therapeutic effects as desired. After the administration, the drug passes through various pathways, but the biodistribution is controlled before reaching the target site. At the same time, the drug's half-life can also be modified so that the drug is not eliminated before showing therapeutic efficacy. It improves patient compliance as dosing and size of dose can be reduced. Thus, the efficacy of the drug is enhanced [13, 15, 16].

2.2 New Strategies of Targeted Drug Delivery

Target drug delivery strategies are classified into two major methods. They are passive targeting and active targeting. Apart from these three, there are other targeting strategies as well. Although the targeting strategies might differ, the main reason for the release of the drug at the target site is the change in temperature, pH, or both. The target drug delivery strategies for the drugs via nanocarriers are as follows:

2.2.1 *Passive targeting:* Passive targeting is the process that is based on the enhanced permeability and retention (EPR) effect, which is the accumulation of the drug at the target site [17]. In this process, nanocarriers carrying the drug are drained into the leaky vasculature of the target tumor cells. The tumor vasculatures are incomplete and are of size ranging from 100nm to 780nm depending on the type of the tumor whereas, normal vessels have tight endothelial junctions [18]. Accumulation in the blood occurs over time, as they are not small enough to be excreted by the kidney or large enough to be captured by the reticuloendothelial system [19]. The molecular weight of the nanosized drug is more than 40 kDa, which does not allow it to enter through the capillary beds. At the same time, the vasculature of tumors consists of leaky vessels, so it is easier for high molecular weight drugs to specifically enter the target tumor. Apart from leaky vessels, tumor microenvironment lacks a well-defined drainage

system. This results in the enhanced drug entry and retention in the target site, which results in increased efficacy and reduced side effects as the drugs accumulate only at the diseased site [1, 20]. Nanocarriers with hydrophilic surfaces and 200 nm size or less have a greater EPR effect as they circulate in the blood for a longer time [2]. Conversely, if the molecular weight is low, the drug will diffuse away from the target and re-enter the blood circulation [21]. Doxil (doxorubicin in PEGylated liposomes) is a clinically approved drug that follows passive targeting [22].

2.2.2 *Active Targeting:* Active targeting is a type of ligand–receptor binding technique. In this strategy, nanocarriers are bound with a ligand on their surface, and this ligand binds actively to specific receptors [23]. The ligand chosen in this case needs to determine the overexpressed receptors on the diseased cells. Ligands can be peptides, lectins, antibodies, polysaccharides, nucleic acids, etc. [24]. Active targeting proves more specificity than passive targeting, as it binds to the target site with a high affinity. This avoids unexpected bonding of the drug and reduces side effects and multidrug resistance [25]. Receptors that are only expressed in cancer cells are targeted, for example, folate receptors in lung cancer cells and epidermal growth factor receptors in ovarian cancer. [26]. Active targeting can be classified into four orders of targeting. Targeting is different in these four orders. For instance, first-order targeting targets the capillary bed of the desired target site, second-order targeting targets tumor cells, third-order targeting targets intracellular sites, and fourth-order targeting targets macromolecules such as DNA and proteins. The advantage of active targeting is that it does not have to depend on the leaky vasculature of the diseased cell and the EPR effect [27]

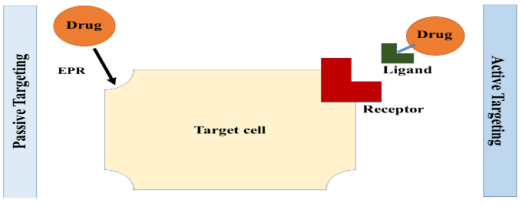

Figure 1: Passive targeting occurs as drug accumulate at the target site due to enhanced permeability and retention effect and active targeting takes place as the nanocarrier is bound with a ligand that can specifically detect the overexpressed receptor on the diseased cell.

2.2.3 *Inverse Targeting:* Inverse drug targeting is the process in which a blank nanocarrier inhibits the activity of the reticuloendothelial system. In the reticuloendothelial system, some cells are responsible for the phagocytosis of foreign materials. The use of inverse targeting results in the accumulation of cells with blank nanocarriers, which will, in turn, suppress the defense mechanism [28].

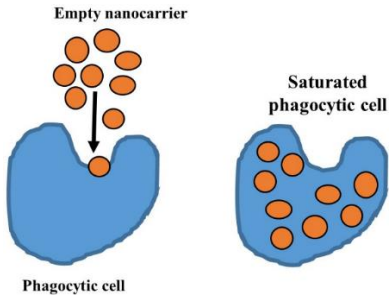

Figure 2: Inverse Targeting.

2.2.4 *Dual Targeting:* Dual targeting is the strategy in which the nanocarrier has the drug's therapeutic activity. It provides synergistic activity, enhancing the effect of the drug. [29].

2.2.5 *Double Targeting:* The double targeting strategy combines the theory of spatial and temporal controls. Spatial control delivers the drug to the specific target site, and temporal control delivers the drug to the target site at a controlled rate [7].

2.2.6 *Combination Targeting:* Various elements with a particular affinity for the target site are used in combination, for which this targeting system is called combination targeting. In combination targeting, the most commonly used molecules are polymers, homing devices, and carriers of molecular specificity. Triple targeting is the most effective and selective form of combination targeting. This helps provide direct interaction with the target site [29].

2.2.7 *Biological Targeting:* Biological targeting involves the delivery of the drug to the target area by using antibodies, peptides, or other biomolecules that have an affinity for the target cell receptor [31].

2.2.8 *Physical Targeting:* Physical targeting is the process that takes specific characteristics such as size, shape, rigidity property, light intensity, electric

field, and composition into account. These characteristics are responsible for the accumulation of the drug in the target site, increased uptake rate, increased drug circulation time in the blood, and tissue retention [32].

2.2.9 *Chemical Targeting:* Chemical targeting occurs when nanocarriers are responsive to pH, temperature, enzymes, and site-specific prodrugs. This responsiveness allows the drug to localize in the target area and leads to controlled drug release [7, 31].

2.2.10 *Local Targeting and Systemic Targeting:* The drug is delivered to the local site in local targeting. It is a noninvasive process. On the other hand, systemic targeting focuses on delivering the drug to the systemic circulation by intravenous administration. It is an invasive process. The major disadvantage of these techniques is that they are not target specific, which affects nontarget cells and may cause adverse effects [33].

2.2.11 *Location-Based Targeting and Disease-Based Targeting:* Location-based targeting is the process by which the drug is delivered to organelles, organs, cells, or intracellular targets in the gastrointestinal tract, brain, etc. On the other hand, disease-based targeting is based on targeted delivery to the disease site. These advanced targeting processes can now be used as an alternative to antibiotic therapy, and nanovaccines can also be produced. This can be done by functionalizing the nanoparticles with antimicrobial agents [7].

3. Nanotechnology and Nanocarriers

Nanotechnology is the science and technology that manipulates matter on a nanoscale, *i.e.*, 1 to 100 nanometers [34]. It helps make new structures and materials on the atomic scale. It has advanced in many areas, including medicine. Nanomaterials have distinct physical and chemical properties [35]. They help enhance the pharmacological properties of medications. The therapeutic effect of drugs made by nanotechnology can be achieved by different routes of administration, such as oral nasal, transdermal, intravenous, intramuscular, intrathecal, and intra-articular routes. [36].

Nanocarriers are nanometer-range colloidal nanosystems. They are loaded with therapeutic agents that help the therapeutic agent reach the desired target site. They selectively accumulate in the target site and show the desired therapeutic effect [37, 38]. Nanocarriers must be biodegradable, nontoxic, nonimmunogenic,

cost-effective, stable, have a high surface area, and release the therapeutic agent at the target site [39, 40].

3.1 Nanocarriers in Drug Delivery

Nanocarriers in drug delivery systems have been rapidly developing since their emergence. It can be used as an effective drug delivery system for almost all routes of administration with some specific modification in shape, size, structure, and surfactant properties. Nanocarriers are used not only in drug delivery systems but also for diagnostic purposes and immunization. It is being used to mitigate various diseases, from COVID-19 vaccines to Alzheimer's. It is also used for acne and infection treatment by loading antibiotics in nanocarriers and as a chemotherapeutic agent delivery system in different cancers [4, 5, 41, 42].

Apart from using nanocarriers for the delivery of drugs in different diseased cells, they have various other advantages. They enable long-term circulation in the blood, resulting in increased accumulation, overcome the reticuloendothelial system, have high stability, have increased biodistribution and are made of biocompatible materials for which they are biodegradable. They also show an increased pharmacokinetic profile, reduced toxicity due to enhanced specificity, controlled release rate, enhanced solubility, and increased accumulation at the target site that decreases secondary effects [43].

3.2 Development and Manufacturing of Nanocarriers

In manufacturing nanocarriers, the vital points that need to be focused on are size, shape, dimension, and structure, as they play a prominent role in the release and stability of the compound. Manufacturing of nanocarriers can be performed by two approaches, *i.e.*, bottom-up or top-down techniques. The top-down method involves the breakdown of the bulk into several nanosized particles. This process produces the desired structure by removing or breaking the bulk material. Breaking down a bulk material might not always be perfect for which the desired shape and size are not achieved. This process creates more waste. This method involves milling, laser ablation, electro-expulsion, etching, etc. The bottom-up method involves the building up of a nanoparticle from the bottom. The atoms, molecules, or clusters are accumulated and made into the desired shape, size, and structure with minimum waste. It is more economical. External stimuli under specific conditions are applied to make the components form a complex structure of the desired type. This process involves spinning, chemical vapor deposition, precipitation, molecular condensation,

etc. Since it poses more accuracy in shape, size, and structure, this is a more widely used method of nanoparticle development by scientists [6, 44, 45].

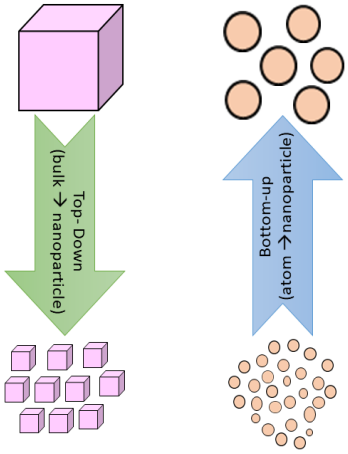

Figure 3: Top-down method involves the breakdown of a bulk material into several nanosized particles and bottom-up method involves the building up of a nanosized particle from atoms and molecules. [6]

3.3 Drug Loading and Release Strategy in Nanocarriers

Drug loading in the nanocarrier is required to deliver the drug to the target site for the desired therapeutic effect. To load nanocarriers with drugs, there are three main strategies, such as, covalent binding, encapsulation and electrostatic interaction.

Covalent bonding: Covalent bonding occurs between the drug and the nanocarrier due to the presence of appropriate functional groups (hydroxyl group, carboxylic group, etc.) on the surface of the nanocarrier and the drug. This forms a nanocarrier-drug conjugate. Sometimes linkers such as succinic acid or succinic anhydride can be used to facilitate the conjugation process [46]. These conjugates diffuse through the cell membrane of the target site, and then enzymes and chemicals break through the covalent bond that releases the drug at the desired site. [47].

Encapsulation: The drug is loaded in the hollow cavity of the nanocarriers where the hydrophobic region encapsulates the hydrophobic drugs, and the hydrophilic region encapsulates the hydrophilic drug. Drug release occurs via hydrolysis, thiolysis, pH change, or temperature change [48].

Electrostatic Interaction: Different high-density functional groups, such as carboxylic or amine groups on the nanocarriers, interact electrostatically with the drug material. This helps the drug to be incorporated into the nanocarriers effectively [49].

3.4 Functionalization of Nanocarriers

The functionalization of nanocarriers is performed by the attachment of functional groups, ligands, polymers, surfactants, or biomolecules by covalent or noncovalent conjugation. It increases selectivity, biocompatibility, and controlled release of the drug in the target site [3, 50].

Polymers such as polyethylene glycol can be used to functionalize nanocarriers, increasing the permeability and retention effect, making it target specific, and helping in the controlled release of the drug [51].

Nanocarriers are also functionalized by ligands that specifically bind to the receptors of the target site. It is also known as an active targeting strategy [52]. It helps reduce the side effects and unwanted binding to other nontarget sites. It also helps increase drug accumulation at the target site, as it does not interact with other sites. It increases treatment accuracy [53].

Surfactants (sodium cholate, polysorbate, span 80, tween 80, etc.) are used in functionalizing nanocarriers, as the nanocarriers may show bursting effects, instability, premature degradation, and poor accumulation in the target site. Using surfactants with nanocarriers can overcome these drawbacks, resulting in better drug delivery and enhanced accumulation at the target site without unwanted drug degradation [54].

Biomolecules can be used to functionalize nanocarriers to reduce cytotoxic effects and enable site-specific drug delivery. Biomolecules have cell-mimicking properties that make them biocompatible and enable them to remain in blood circulation for a long time. This allows them to have time to accumulate at the target site. They also overcome the reticuloendothelial system. This is why they do not pose any immunological disturbance or allergic reaction in the individual. The biomolecules used in functionalizing nanocarriers can be antibodies, oligonucleotides, nucleic acids, peptides, folate, etc. [55, 56, 57].

3.5 Different Types of Nanocarriers

3.5.1 Liposome

Liposomes are spherical lipid bilayer structures. They have a hydrophilic core and a hydrophobic space that encloses the hydrophilic core. The hydrophobic region encapsulates lipophilic drugs, and the hydrophilic core encapsulates hydrophilic drugs. They are made from physiological lipids, cholesterol, or naturally occurring phospholipids. Liposomes can be uni-lamellar or multilamellar. They are

available in cream, gel, suspension, and solid dosage forms and can be administered via the parenteral route. The accumulation of liposomes in the target site is due to their small size and prolonged circulation. Drugs loaded in liposomes are used to deliver drugs such as doxorubicin and daunorubicin for the treatment of mammary gland tumors and AIDS-linked Kaposi's melanoma. [58] Liposomes are metastable, which results in an uncontrolled release of the drug. The phospholipids undergo hydrolysis or oxidation, resulting in a short half-life, leakage, and fusion of the encapsulated drug. Since liposomes are unstable, they need special storage conditions and preparation techniques [59, 60].

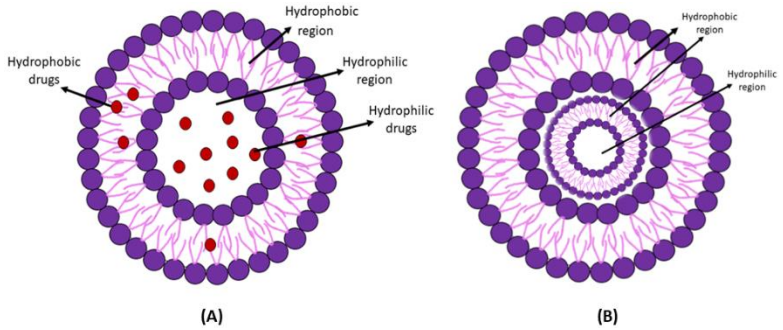

Figure 4: (A) Unilamellar liposome, (B) Multilamellar liposome

3.5.2 Solid lipid Nanocarriers (SLN)

Solid lipid nanocarriers consist of a solid lipid core that is surrounded by surfactants. The lipid core helps to solubilize lipophilic drugs. The surfactant surrounding the solid lipid core works as an emulsifier to keep the lipid nanoparticles stable. The amount and type of emulsifier depends on the route of administration [61]. The solid lipid core is made up of lipids that are solid at room temperature, for example, free fatty acids, steroids, waxes, triglycerides, lecithin, etc. Solid lipid nanocarriers are used to deliver chemotherapeutic agents and ophthalmic drugs and can also be used to deliver genes [62, 63]. Solid lipid nanoparticles for drug delivery have proven safer due to biodegradable lipids that do not pose any toxicity threat. The stability, drug payload, and drug release rate control are better than those of other carriers, such as polymeric carriers [64]. In contrast, burst release can occur if the drug is not homogenously distributed in the drug. This hampers the controlled release effect. It can also have other problems, such as forming a lipid crystal matrix and changing the physical state of the solid lipid. For this reason, novel forms of solid lipid nanocarriers have recently been developed [65].

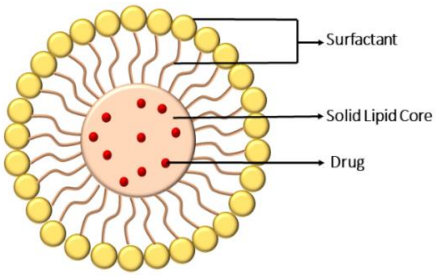

Figure 5: Solid Lipid Nanocarrier.

3.5.3 Polymeric micelles

Polymeric micelles are amphiphilic polymers that contain both hydrophilic and hydrophobic regions. They consist of a hydrophobic core and a hydrophilic shell that can self-assemble and form a unique core-shell structure. There can also be reverse micelle formation with the hydrophilic head toward the core and the hydrophobic tail on the outer surface [66]. In a polymeric micelle, the drugs remain encapsulated at the core, and the outer hydrophilic shell helps keep it stable in the aqueous region. This is also why polymeric micelles are effectively administered through the intravenous route [67]. On the other hand, the opposite occurs in a reverse micelle where the hydrophilic core encapsulates the hydrophilic drug, and the hydrophobic region is integrated within the membrane. This helps transport both hydrophobic and hydrophilic drugs [68]. Drug loading in polymeric micelles increases the therapeutic window of lipophilic drugs, reduces rapid clearance, prolongs circulation, and enhances the accumulation of the drug at the target site. Paclitaxel has been loaded in polymeric micelles to deliver it to the target site. It is known as Genexol-PM [69].

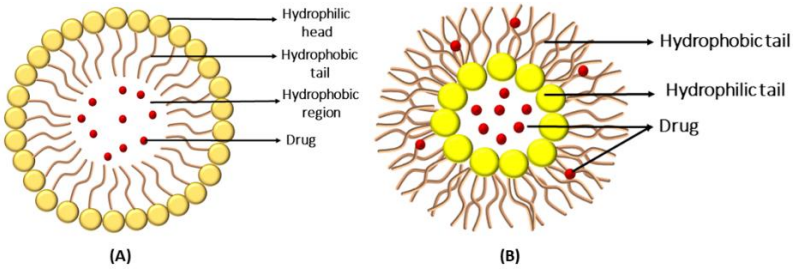

Figure 6: (A) Polymeric micelle, (B) Reverse micelle

3.5.4 Metallic Nanoparticles

Metallic nanocarriers are made of a metallic core. This core can be made of nickel, cobalt, iron, manganese, silver, titanium, platinum, or noble metal gold. These nanocarriers have magnetic and optical properties [70]. They obtain their biocompatibility from the core metal, size, and coating on the nanocarrier. Most metals pose a toxicity profile. Despite this, iron oxide is widely used in biomedicine due to its lower toxicity.

The metallic core has magnetic attraction, resulting in the formation of agglomerates. These agglomerates are identified by the reticuloendothelial system and eliminated [71, 72]. To stop this process, metallic nanoparticles are coated with liposomes, polymers, biological molecules, or surfactants. The nanoparticle can also be functionalized by ligands, nucleotides, antibodies, enzymes, etc. [73]**.** This enhances the stability of the drug, makes it more hydrophilic, enhances biocompatibility, increases drug delivery at the target site, and reduces toxicity [74]. The most commonly used metallic nanoparticles for medicine are gold and iron oxide nanocarriers. An example of iron oxide as a nanocarrier along with conjugation with a ligand is IGF1-IONPDOX (recombinant human insulin-like growth factor 1 as a targeting ligand with iron oxide nanoparticles containing doxorubicin) to inhibit human pancreatic tumors [75, 76, 77].

Recent studies have also shown that metallic nanoparticles have an antimicrobial effect. The shape and charge play the most critical role in antimicrobial activity [78]. This effect arises as the positive charge on the metallic nanoparticle interacts with the negative charge on the bacterial surface. This enhances the binding efficiency targeted to the bacteria and results in a bactericidal effect. This plays a vital role in overcoming antibiotic resistance, which is currently the major reason for death [79, 80].

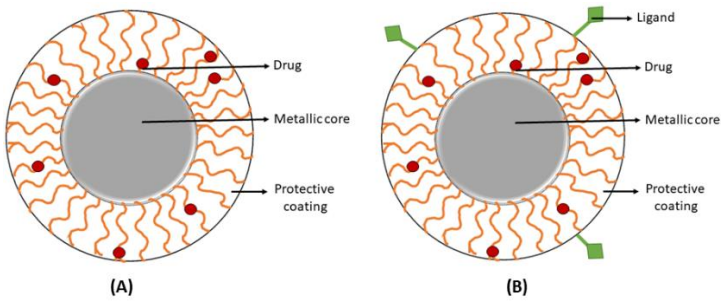

Figure 7: (A) Metallic nanocarrier, (B) Metallic Nanoparticles with ligands

3.5.5 Carbon nanotubes

Carbon nanotubes are hollow tubes with graphene sheets wrapped around them at a specific angle. These are needle-like tubes of carbon. The needle structure makes them better than spherical nanocarriers. This structure helps them to cross the cell membrane very easily by endocytosis. They have a high surface area, enhanced specificity, increased efficacy, fewer side effects, and enhanced cellular uptake [81, 82]. These tubes are formed by carbon atom hexagons in a helical structure. The carbon nanotube diameter is 0.4-100 nm, and the length is a thousand times greater than the diameter [83]. They have been used for diagnosis and drug delivery to the target site [84]. It delivers peptides, APIs, and nucleic acids and can also be attached with fluorescence to help diagnose [85]. These nanocarriers are usually toxic and water insoluble. This can result in the accumulation of nanotubes in different tissues, which can result in toxic effects [86]. To overcome this problem, functionalization of carbon nanotubes can make them water soluble, increase efficacy, and increase circulation time. Functional groups (carboxylic groups or amine groups), polymers (PEG), or ligands enhance biocompatibility [87, 88]. Carbon nanotubes can carry drugs by loading the nanotube with drugs, attaching the drug by surface functionalization, or linking the drug to it by a chemical. They can be made of single- or multilayer graphene, also known as single-walled carbon nanotubes or multiwalled carbon nanotubes [89]. An example of carbon nanotubes for disease mitigation is the use of single-walled carbon nanotubes conjugated with epidermal growth factor (EGF) and cisplatin. It showed higher affinity for entering and killing the targeted cancer cell. [90]

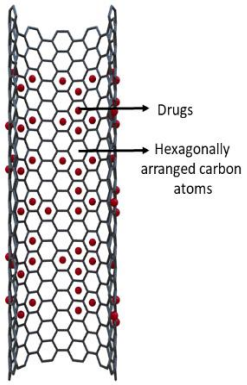

Figure 8: Carbon Nanotube

3.5.6 Dendrimers

Dendrimers are spherical, multivalent, hyperbranched macromolecules [91]. They are radially symmetrical and act as a nonviral vector. They have a central core, branches like a tree, and terminal functional groups. The branches are joined by a junction that makes the dendrimer structure resemble a sphere. These junctions are called generations. As the generation increases, the drug loading capacity and cationic amine group at the periphery also increase. They are made from nucleotides, sugar, or amino acids. The most used dendrimers are PPI (polypropylene imines), PAMAM (polyamidoamines), and PLL (poly-L-lysine). Dendrimers have a unique molecular weight that differentiates them from other types of nanocarriers. There are cavities within the branches where drugs can be encapsulated. This helps in the sustained release of the drug at the target site. The use of dendrimers is immense in gene delivery, antiviral drugs, and vaccine delivery. They can easily cross the blood–brain barrier and are used as an effective treatment for drug delivery in cases of brain tumors. For this reason, a doxorubicin-loaded dendrimer (PLL) functionalized with tumor necrosis factor (TNF) is used to effectively target and treat glioma. [92] In addition, it can also be used in breast cancer, cervical cancer, and colorectal cancer treatment. The release of the drug in the target site occurs due to a change in pH that causes protonation or deprotonation of the tertiary amine group depending on the acidic or basic nature of the microenvironment of the target site [93, 94].

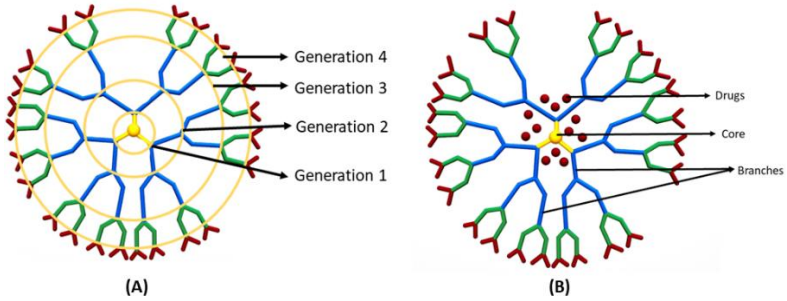

Figure 9: (A) Dendrimer generations, (B) Dendrimer

3.5.7 Mesoporous silicon

Mesoporous silicon is a porous structure that enables drugs to be incorporated more effectively. The pores resemble a honeycomb structure. It can be used to encapsulate both hydrophobic and hydrophilic drugs. For better targeted delivery, it can also be conjugated with ligands. Since they possess a large surface area and are porous, they enable higher drug loading, biocompatibility, and enhanced stability. By using mesoporous silica for the delivery of therapeutic agents, many resistance

mechanisms can be overcome. Methotrexate can be effectively delivered via mesoporous silica nanocarriers [95, 96].

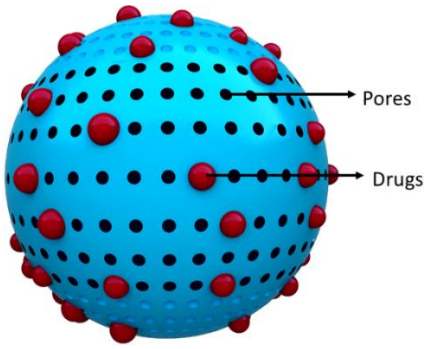

Figure 10: Mesoporous Silica

3.6 Novel Designed Nanocarriers

3.6.1 Hybrid Nanocarriers

A hybrid nanocarrier is a combination of both organic and inorganic nanocarriers. The two types of nanocarriers are combined to eliminate the problems and enhance the benefits as the delivery system's effectiveness and accumulation in the target site become more specific. This combination can also help in biosensing and imaging of the tumor alongside therapeutic effects. One such hybrid nanocarrier is the hybrid of dendrimer and gold nanocarrier. The dendrimer is loaded with the desired drug for therapeutic effect, and the gold nanoparticle helps in computed tomography imaging of the diseased site. The dual nature enhances the properties in many ways [97]. Better encapsulation of drugs, sustained release of drugs, high stability, and high cellular uptake are some of the properties that are observed by this combination. The hybrid of mesoporous silica and lipid polymer showed better intracellular delivery, high retention rate, and controlled release of zoledronic acid in breast cancer therapy. Novel albumin hybrid peptides (for delivery and even distribution of hydrophilic peptides), lipid-polymer hybrid nanocarriers, ceramic-polymer hybrid nanocarriers (ceramic nanocarriers consist of oxides of silica, alumina, etc.) are some examples of hybrid nanocarrier systems. The criteria for the selection of a suitable nanocarrier are its ability to increase bioavailability and decrease side effects compared to the conventional method [98]. Among the hybrid nanocarriers, lipid-polymer hybrid nanocarriers are discussed below:

Lipid-polymer hybrid nanocarriers: Lipid-polymer hybrid nanocarriers comprise a solid polymeric core encapsulated by a lipid shell. The polymeric core acts as a

cytoskeleton, providing a larger surface area, narrow size distribution, and better stability. On the other hand, the lipid shell increases biocompatibility, as it resembles the cell membrane and protects the inner polymer layer. This lipid layer is also responsible for preventing leakage of drugs from the core. The dual nature of the lipid and the polymer helps encapsulate both hydrophilic and hydrophobic drugs, which allows the codelivery of both forms of drugs. In this way, epigenetic (DAC) and chemotherapeutic drugs (Doxorubicin) were able to be code-livered [99].

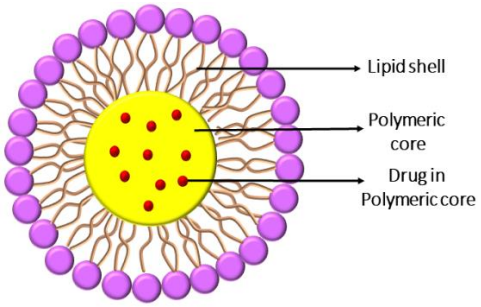

Figure 11: Lipid-polymer hybrid nanocarrier

3.6.2 Novel-Designed Polymeric Micelle

Polymeric micelles have been modified to have better effects, for which some new approaches are taken that make the nanocarrier a novel-designed drug delivery system. Some of the most recently used novel designs of a polymeric micelle include, urosolic acid-loaded polymeric micelle and smart multifunctional polymeric micelle.

Ursolic Acid-Loaded Polymeric Micelle: Ursolic acid is hydrophobic and has been proven to have a therapeutic effect against cancer. Since ursolic acid is hydrophobic, its clinical application is complex. With the help of micelles, ursolic acid can be encapsulated in the hydrophobic core, making it a novel drug delivery system. The hydrophilic shell of the micelle will make it easy to transport in aqueous media [100].

Smart Multifunctional Polymeric Micelle: Target-specific accumulation can be achieved by adding various ligands and specific moieties to a polymeric micelle. The ligands help in binding to specific receptors. Some contrast agents and stimuli-sensitive groups show better drug-release properties when incorporated in the polymeric micelle. All these properties are combined in one type of micelle that gives rise to a smart multifunctional polymeric micelle. This type of polymeric micelle can have target-specific accumulation, circulation, enhanced drug release at the target site, active or passive drug targeting, and improved efficiency. This nanocarrier can

efficiently deliver small interfering RNA (siRNA), hydrophobic drugs, and other therapeutic agents. Small interfering RNA helps in silencing the gene expression of specifically targeted tumor cells. The combination of siRNA and drug in a polymeric micelle helps in targeted delivery. At the same time, it also shows reduced growth of the tumor cell and toxic effects toward the tumor cell by the drug. Therefore, two major functions are being carried out effectively for cancer therapy by smart multifunctional polymeric micelles [101].

3.6.3 Novel Designed Dendrimers

Dendrimers are considered a novel delivery system because of their unique structure. The shape of the dendrimer allows it to have a large surface area. This allows efficient encapsulation of drugs [102]. Dendrimers can be functionalized by adding covalently bonded drugs, encapsulating the dendrimer with micelles, or forming complexes with nucleic acids. These are some novel approaches that makes it more suitable for drug delivery with more precision.

Dendrimers with drugs conjugated to dendrimers: Drugs are conjugated to dendrimers by covalent bonding as shown in **figure: 12 (B).** This conjugation is usually performed at the peripheral region of the dendrimer, where there are multiple sites for the drugs to be conjugated to the dendrimer. This results in one dendrimer being conjugated with multiple drug molecules. Since many drugs are conjugated simultaneously, more drugs will be delivered to the target site, resulting in better therapeutic efficacy and selective accumulation at the target site. This also increased water solubility and slowed drug release to attain the therapeutic index. Drug release occurs through the degradation of chemical bonds. Drugs conjugated with dendrimers showed better properties than free drugs in treating a disease [103].

Encapsulation of the dendrimer: Dendrimers can be encapsulated by liposomes or polymeric micelles so that the drug can be carried effectively to the target site despite being hydrophobic or hydrophilic as shown in **figure: 12 (C).** This enhances the toxicity and solubility of the drug against diseased cells. This encapsulation method also overcomes the stability issues of the drugs and improves drug loading into the dendrimer to many folds at a time [104]. These carriers usually follow a passive targeting strategy, enhancing accumulation and reducing toxicity against nontarget cells [105].

Dendrimers with nucleic acids complexed: Dendrimers can be conjugated to nucleic acids such as plasmid DNA or siRNA as shown in **figure: 12 (C).** The nucleic

acids are negatively charged, and dendrimers contain a cationic amine group at their periphery, for which they can form a bond [106]. The oligonucleotide attached to the dendrimer consists of genetic information for apoptosis, delayed growth of tumor cells, code for TNF-α, etc. These results in obtaining the desired effect on the diseased cell. Dendrimers complexed with siRNA were used in prostate tumors that showed gene silencing in the tumor, which resulted in an anticancer effect against the tumor. The dendrimer branches help bind to the siRNA and effectively deliver it to the target site [107]. Dendrimers can be conjugated with nucleic acids and the drug required for treating the disease to obtain a synergistic effect. They can also be conjugated with PEG or peptides to enhance cellular uptake and accumulation at the target site [108].

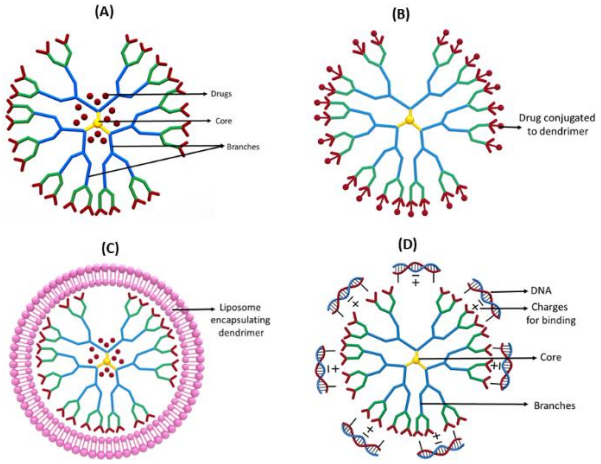

Figure 12: (A) Dendrimer, (B) Dendrimer with drug conjugated, (C) Dendrimer within liposomes, (D) Dendrimer with nucleic acid.

3.6.4 Quantum Dot

Quantum dots are nanosized semiconductor materials used widely for biosensing, diagnosis, drug delivery, therapy, and treatment of diseases. It consists of a core and a shell [109]. It efficiently helps release drugs from the vesicles by transforming the near-infrared light into heat. It is mostly used in the case of cancer diagnosis. The surface of the quantum dots is modified to make it biocompatible and water soluble to reduce toxicity and improve targeting [110]. Quantum dots contain noble metals, semiconductors, and magnetic transition metals in mixed conditions. The noble optical characteristics of the quantum dot are present with quantum dots that contain cadmium. Cadmium poses a toxic threat to humans. To reduce toxicity, ZnS is used to enclose these quantum dots [111].

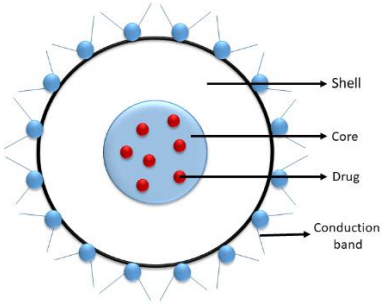

Figure 13: Quantum dot

Carbon can be used in quantum dots with a low toxicity profile and increased biocompatibility. Quantum dots can also be graphene-based, encapsulated in lipid-based micelles, and used as a cap on mesoporous silica, enhancing the encapsulation efficiency of drugs in mesoporous silica. A study showed that the co-loading of quantum dots and drugs in a solid lipid nanocarrier increases the drug loading capacity along with higher therapeutic efficacy [112, 113]. It is a noble-designed drug delivery system, as it can be conjugated with oligonucleotides, peptides, folates, and antibodies for high accuracy. It can help provide multiple attachment sites for drugs that help cross the membrane easily and deliver the drug to the target site [114, 115].

3.6.5 Nanostructured Lipid Carriers (NLCs) and Lipid Drug Conjugates (LDCs)

Solid lipid nanoparticles (SLNs) are stable, have better efficacy, are cost-effective, and can be produced on a large scale. However, it still poses some drawbacks, for which novel-designed carriers are composed of a mixture of lipids. They are nanostructured lipid carriers (NLCs) and lipid drug conjugates (LDCs). These are known to overcome the drawbacks of conventional solid lipid nanocarriers. A nanostructured lipid carrier (NLC) is a mixture of solid and liquid lipids. It has a solid lipid core at room temperature. The lipid mixture and less ordered lipid matrix help in high drug encapsulation, drug loading, controlled drug release, and better storage without a bursting effect, such as in SLN (solid lipid nanoparticle) [116]. Lipid drug conjugates (LDCs) are carriers modified to have better hydrophilic drug loading capacity. These are made to overcome the drawback of conventional solid lipid nanoparticles, which is the low capacity of hydrophilic drug loading. LDC is made by salt formation or covalent linking processed in an aqueous surfactant solution. It can be used as an effective carrier to deliver the drug to the brain in the case of infectious diseases [117, 118].

3.6.6 Cubosomes

Cubosomes are bicontinuous lipids generated by self-assembling amphiphilic molecules in the presence of a stabilizer [119]. Cubosomes have a solid crystalline cubic-like structure similar to a honeycomb structure. This structure helps entrap hydrophobic, hydrophilic, and amphiphilic drugs. They have more bioavailability and at the same time more drug loading capacity. Cubosomes are biodegradable and nontoxic and have high solubility in aqueous and lipid media [120]. They have narrow pore sizes, which allow them to release the drug at a controlled rate. This also helps maintain the stability and efficacy of the drug [121]. The release of the drug occurs depending on the difference in molecular weight and polarity [122].

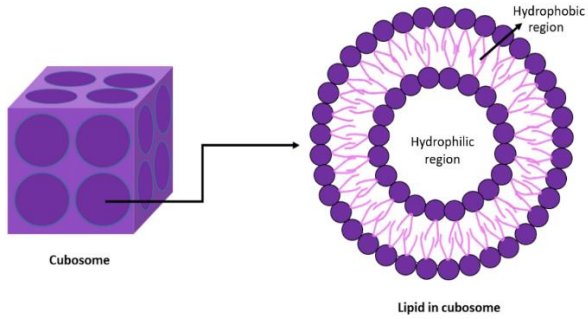

Figure 14: Cubosome

It is considered a novel lipid delivery system because it is nonirritant, has more residence time, has better bioavailability, increased absorption, has fewer side effects, has higher drug loading capacity, etc. It can be used in ocular drug delivery and transdermal administration and has been proven to show a hypoglycemic effect in rats after the oral administration of insulin-loaded cubosomes [123, 124].

3.6.7 Novel-Designed Liposomes

Liposomes used as nanocarriers for drug delivery have various drawbacks, such as uncontrolled release, low drug loading, inability to penetrate the skin and effective delivery of drugs to the blood circulation, and they also show limitations in orally delivered drugs due to the lack of stability of the vesicles. To overcome these drawbacks, liposomes are modified into ethosomes, transferosomes, niosomes, and virosomes for effective delivery of the drug to the target site.

Ethosome and Transferosome: Ethosomes and transferosomes are also vesicular systems that are more flexible and softer. The flexibility comes from the addition of surfactant (sodium cholate, polysorbate, span 80, tween 80, sodium deoxycholate, etc.) and ethanol in it. Transferosomes can transfer high- or low-molecular-weight

drugs through the skin. Ethosomes and transferosomes are both widely used for the transdermal administration of drugs, as ethanol is a known permeability enhancer. They also deliver nonsteroidal anti-inflammatory medications on the skin surface for pain relief. In addition, they can also be used for transdermal delivery of insulin, treatment of fungal infection (e.g., ketoconazole), delivery of vaccines, and treatment of herpes virus. They have a better penetration rate and retention in the circulatory system in comparison with liposome drug delivery, making them a novel designed nanocarrier [125, 126, 127].

Niosomes: Niosomes are nanometric delivery systems in which the drug material is encapsulated in the bilayer of a nonionic surfactant. These contain cholesterol and charge-inducing substances. They can carry both lipophilic and amphiphilic drugs. They are stable and do not require any special storage or preparation technique compared to liposomes. Niosomes are mostly used for drug delivery to the skin (e.g., treatment of herpes virus, transdermal delivery of insulin) [127].

Virosomes: Virosomes are a type of liposome that contains viral protein. It is used for immunization. It can be administered through nasal, vaginal, and intramuscular routes. Virosomes can also be incorporated with other molecules that can uptake dendritic cells. The receptor-mediated pathway performs this process. They can be used for the delivery of vaccines, antitoxins, etc. A study was conducted where plasmid DNA was loaded in liposomes decorated with viral protein. This helps in gene transfer to the targeted cell. Cell targeting is efficient with this process, as some viral proteins target specific types of cells, and as a result, they efficiently deliver the content to the targeted site [128, 129, 130].

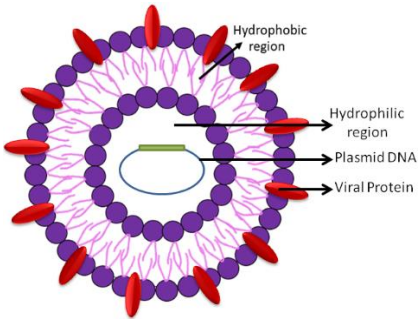

Figure 15: Plasmid DNA-loaded virosome

4. Conclusion

Nanocarriers have shown immense development in targeted drug delivery systems that have helped gain many benefits over the conventional use of free drugs. Target drug delivery has various advantages that are mastered by using nanocarriers. A targeted drug delivery system can exhibit better efficacy by minimizing the toxicity and side effects of the lifesaving drug. Nanocarriers can be used in diagnosis, treatment, and drug delivery. Nanotechnology has shown promising advantages in disease mitigation via targeted drug delivery. Although this technology has advanced considerably and many new carriers have emerged with their novel properties, some challenges remain in developing these nanocarriers. A slight change in the nanocarrier's shape, size, or structure can result in toxicity or altered pharmacokinetic properties of the drug. A desirable size for the nanocarrier is required to pass through the capillaries for therapeutic effect without being eliminated quickly. If these challenges can be overcome in the near future, nanocarriers can be used as targeted drug delivery systems for curing deadly diseases.

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