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Review Article

Nanocarriers in Drug Delivery Systems: An Overview

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ABSTRACT

Nanocarriers have emerged as a transformative technology in drug delivery systems (DDS), offering significant advancements over traditional methods. This review delves into the various types of nanocarriers, including liposomes, polymeric nanoparticles, micelles, dendrimers, and solid lipid nanoparticles, highlighting their unique properties and advantages in targeted drug delivery. Liposomes have demonstrated extraordinary effectiveness in clinical applications due to their biocompatibility. Conversely, polymeric nanoparticles offer improved stability and regulated drug release, which makes them appropriate for a variety of therapeutic treatments. Because of their structural adaptability, micelles and dendrimers provide accurate medication targeting. Solid lipid nanoparticles offer a steady and regulated release mechanism. Drug loading in nanocarriers involves encapsulation, covalent bonding and electrostatic interactions. These nanocarriers offer significant benefits over conventional drug delivery systems, including improved solubility, stability, and controlled release of drugs. The review also explores the mechanisms by which nanocarriers enhance drug delivery. These attributes enable nanocarriers to deliver drugs more efficiently to specific tissues or cells, reducing systemic toxicity and enhancing therapeutic efficacy.

Keywords: Drug delivery systems, Nanocarriers, Liposomes, Polymeric nanoparticles, Drug release.

INTRODUCTION

Nanocarriers are a broad class of materials designed to transport active pharmaceutical ingredients (APIs) and other therapeutic agents to targeted sites within the body, enhancing the efficacy and safety of treatments. Drugs with low immunogenicity and adverse effects can be better administered and biodistributed using nanocarriers.[1] It is difficult to achieve the desired therapeutic efficiency of many drugs using conventional drug delivery methods due to a number of related problems, such as inadequate bioavailability, sensitive toxicity, poor specificity, etc. Therefore, to guarantee site-specific therapeutic administration, an appropriate carrier is needed.

Target-specific therapeutic delivery has shown great promise in nanomedicine, which works with nanosized biomaterials for applications in disease detection and treatment. Numerous materials and techniques based on nanotechnology have been developed throughout the years for use in the detection and treatment of diseases.[2] The diameter of nanocarriers spans from 1 to 1000 nm^2. There are several types of nanocarriers, each with unique properties and applications. Nanocarriers deliver drugs to the ailment site either actively or passively. In the former scenario, direct chemical conjugation anchors peptides and antibodies attached to the DDS to the receptor, lipids, or antigens at the targeted location.[3]

Types of Nanocarriers

The three main types of nanocarriers with a high surface-to-volume ratio are hybrid, inorganic, and organic nanocarriers.

Organic nanocarriers

Solid lipid nanocarriers, liposomes, dendrimers, polymeric nanocarriers, micelles, and viral nanocarriers are examples of organic nanocarriers.[4]

- *Liposomes*

Liposomes are phospholipid-based composites that may also include trace amounts of other substances. Liposomes, derived from the Greek words “lipo” (fat) and “soma” (body), are phospholipid-based composites that can encapsulate both hydrophilic and hydrophobic drugs.[5] Their versatility makes them valuable in drug delivery. However, liposomes have some drawbacks, such as a short half-life in the body after parenteral injection and the potential for chemical degradation, fusion, and aggregation during storage. To enhance stability both in vivo and in vitro, liposomes can be coated with polymers like chitosan and alginate using the electrostatic deposition approach (Figure 1).[6]

- *Dendrimers*

Dendrimers, also known as hyperbranched polymers, are used in a variety of biological applications, including drug delivery systems as multifunctional nanocarriers.[8] The ability to physically sequester or covalently attach drug molecules and ligands, as well as their precise surface end group count, customizable structure, controlled size and shape, various attachment sites, and efficient cellular absorption, are some of the benefits of dendrimers. For drug delivery, poly amido

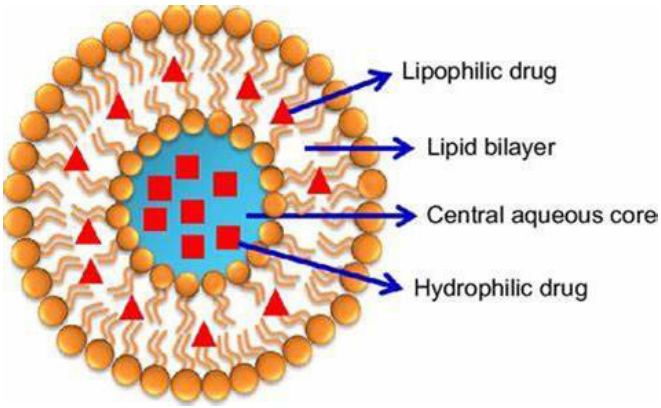

Figure 1: Liposomes [7]

amine (PAMAM), polypropylene imine (PPI), and poly L-lysine (PLL) are among the most commonly utilized dendrimers (Figure 2).[9]

- *Solid lipid nanocarriers*

Solid lipid nanocarriers are created by dispersing melted solid lipids in water and stabilizing them with emulsifiers through high-pressure homogenization or micro-emulsification.[10] They are often made from lipids that are solid at room temperature, such as free alcohols, acids, steroids, waxes, and mono-, di, or triglycerides. Depending on the production conditions and composition, drug molecules can be integrated into the matrix, shell, or core of the solid lipid. This versatility allows solid lipid nanocarriers to overcome the limitations of traditional chemotherapy (Figure 3).[11]

- *Polymeric micelles*

The composition and conditions of manufacture will determine whether the drug molecules are integrated into the core, shell, or matrix of the solid lipid. The constraints of conventional chemotherapy can be solved by this solid lipid nanocarrier due to its adaptability. When the block copolymer concentration rises above a specific threshold known as the critical aggregation concentration (CAC)or critical micelle concentration (CMC), micelles are formed in aqueous solution. Block copolymer hydrophobic segments begin to bind together at the CAC or CMC to reduce contact with water molecules, resulting in the development of a vesicular or core-shell micellar structure (Figure 4).[12]

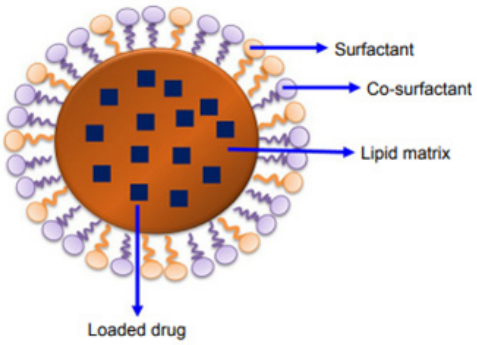

Figure 3: Solid lipid nanocarriers [7]

Inorganic nanocarriers

Inorganic nanocarriers such as gold, magnetic nanocarriers, quantum dots, and mesoporous silica, can be used in biosensing, cell labeling, imaging, targeting, and diagnostics efficiently. These inorganic nanocarriers have a synergistic therapeutic impact as well.

- *Carbon nanotubes*

Carbon nanotubes are a perfect and prospective source for medication delivery because of their unique biological and physicochemical characteristics. These are hollow, tube structures with graphene sheets wrapped together at precise angles. The amount of graphene sheets folded together determines whether the carbon nanotubes are single-walled or multi-walled. These tubes length elongates thousands of times their width, but their cross section can range from 0.4 to 100 nm (Figure 5).

- *Gold nanoparticle*

Gold nanoparticles are small particles of gold typically ranging from 1 to 100 nm in size. They are usually spherical. A variety of gold nanoparticle anisotropies exist, including nanostars, nanorods, nanocages, nanoshells, nanoprism, and others.[14] The ability to bind to gold nanoparticles allows for the attachment of various biomolecules, including enzymes, carbohydrates, fluorophores, peptides, proteins, and genes. This makes it possible for molecules to pass through the cell's barriers and be transported efficiently (Figure 6).[4]

- *Magnetic nanocarriers*

A magnetic core usually makes up the magnetic nanocarrier compared

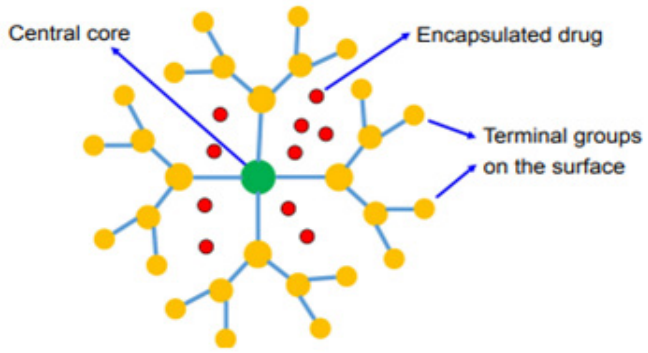

Figure 2: Dendrimers [7]

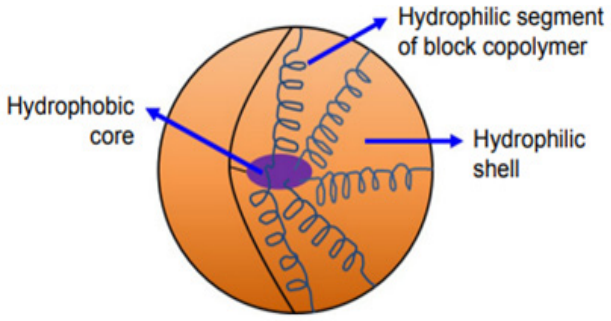

Figure 4: Polymeric micelles [7]

Figure 5: Carbon nanotubes [13]

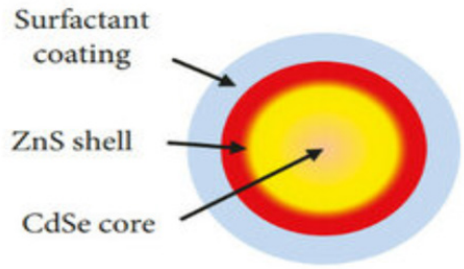

Figure 7: Quantum dots [13]

to metal oxide nanoparticles, metal nanoparticles are often more magnetic. It can be used for biosensing applications because of its magnetic properties and altered properties. It has been discovered that superparamagnetic nanoparticles are more susceptible to magnetic fields than paramagnetic ones. Due to its magnetic resonance, the polymer-coated super-paramagnetic iron oxide nanoparticle has been widely used for molecular imaging and therefore used as a contrast agent in the imaging process.[14]

- *Quantum dots*

Quantum dots are colloidal nanocrystals made from II-VI (e.g., Se, Zn, Te, Cd) or III–V (e.g., In, As, P) elements. Their light emission between UV and near IR varies with size; larger dots (~5 nm) emit red fluorescence, while smaller dots (~2 nm) emit blue fluorescence. Compared to organic dyes, quantum dots have superior optical properties, longer emission, and reduced photobleaching, making them ideal for cell imaging. For instance, quantum dot–peptide conjugates can target tumor vasculature in mice (Figure 7).

- *Mesoporous silica*

Mesoporous silica, with its large porous honeycomb structure, can incorporate numerous drug molecules, making it widely used in the biomedical industry for its accessibility and ease of use. It can encapsulate both hydrophobic and hydrophilic medications and link them to a ligand molecule for targeted drug delivery. This feature allows mesoporous silica to be used effectively for both active and passive targeting in cancer treatment, such as with camptothecin and methotrexate anticancer drugs (Figure 8).[15]

Hybrid nanocarriers

Nanocarriers that combine two or more organic and inorganic nanocarriers either individually or in combination are known as hybrid nanocarriers. It consists of many components, inorganic–inorganic, and organic–inorganic. Examples of hybrid nanocarriers include ceramic-polymer hybrids and lipid-polymer hybrids, among others.

DRUG LOADING

Drug loading is a method to create stable amorphous medications with enhanced solubility, bioavailability, and dissolution rate. The optimal loading procedure requires large drug loads, minimal external drug deposition, maximum pore filling, and the desired drug release pattern to targeted sites. Drug loading capacity depends on the carrier's properties, such as surface area, pore size, pore volume, and surface functional groups.[16] Additionally, the solution's physicochemical characteristics, including pH, solubility, and the affinity of the solvent, medication, and carrier, affect loading capacity. The loading method impacts drug distribution within the carrier, degree of crystallinity, and quantity of drug released. The following equations represent the content and effectiveness of drug loading:

$$loading\ efficiency\ \% = \frac{mass\ of\ drug\ in\ nanocarriers}{initial\ mass\ of\ drug} \times 100\%$$

$$Drug\ loading\ content\ \% = \frac{mass\ of\ drug\ in\ nanocarriers}{mass\ of\ nanocarriers} \times 100\%$$

The presence of functional groups on its surface allows for efficient drug loading and release. The effective loading of the therapeutic substance into the nanocarrier system is rendered possible in three main ways. They are:

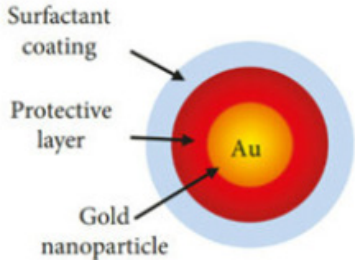

Figure 6: Gold nanoparticle [13]

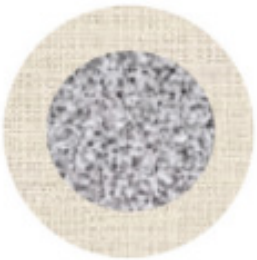

Figure 8: Mesoporous silica[13]

Encapsulation

Encapsulation is the primary method for loading therapeutic drugs into nanocarrier systems. The hollow area within nanocarriers like dendrimers, polymeric nanocarriers, and nanocapsules allows for effective drug encapsulation, particularly for hydrophobic drugs, which can be incorporated through hydrogen bonding or hydrophobic interactions. Liposomes use both active and passive drug-loading methods.[4] Drug release occurs via mechanisms such as tocolysis, hydrolysis, pH-neutralization, and thermolysis. Encapsulation in carrier systems protects drugs from harsh environments and allows for controlled release, significantly influencing drug administration and therapeutic effects.[17]

For hydrophobic drugs encapsulation lipid-coated nanocarriers and polymeric nanocarriers are preferred. For encapsulation of hydrophilic drugs, liposomes and polymeric nanoparticles are mostly used.[18]

Covalent bonding

The presence of functional groups on a nanocarrier's surface allows it to incorporate high concentrations of therapeutic drugs by forming covalent bonds. This covalent coupling ensures stable drug binding and controlled release. Following conjugation, the drug can be released chemically or by enzymatic cleavage. The delayed diffusion of the nanocarrier-drug conjugate to the cell membrane allows for specific, targeted drug release.[4,19] Covalent bonding in nanocarriers offers several advantages, including improved drug stability, targeted delivery, and controlled release, making it particularly useful for drugs sensitive to degradation or requiring precise delivery to specific tissues.

The type of bond, the environment, and the carrier's degradation are some of the variables that can affect the release of medications from covalently bound nanocarriers.[20] Typical release methods include enzymatic degradation, pH sensitivity, and thermal sensitivity.

Electrostatic interaction

The loading and release of both hydrophilic and hydrophobic medications depend heavily on electrostatic interactions in nanocarriers. The drug molecules and the nanocarrier system engage electrostatically as a result of these high-density functional groups. These interactions, which can be used to improve drug loading efficiency and regulate release profiles, are based on the attraction between molecules with opposing charges. For hydrophobic drugs, these interactions enhance drug loading and drug release.[4] Modification of certain nanocarriers facilitates the encapsulation of hydrophilic drugs. The release of drugs from nanocarriers through electrostatic interactions can be controlled by several factors, including changes in pH, ionic strength, and enzymatic activity [21].

TARGETING MECHANISMS

To deliver medications precisely to target locations within the body, nanocarriers use a variety of targeting methods. Systems for targeted drug delivery include two different types,

Active targeting

Active targeting of nanocarriers entails adding specialized chemicals known as ligands to their surface that may identify and attach to specific target cell receptors. By accurately delivering the drug-loaded nanocarriers to the diseased cells, this focused strategy maximizes therapeutic efficacy and reduces side effects.[22] By adding ligands or by modifying their structure physically or chemically, drug-loaded nanoparticles can be used to recognize particular receptors or antigens target cells, limiting the non-specific distribution of drugs throughout the body's cells and reducing cytotoxicity and adverse drug effects (Figure 9).[23]

Ligands

The selection of ligands is based on their capacity to bind selectively to target cell receptors that are overexpressed. Common types of ligands include antibodies, peptides and proteins. The ligands on the surface of the nanocarriers attach to the target cells' particular receptors once they are injected into the body. The drug payload can be delivered straight into diseased cells according to this binding, which can cause the nanocarriers to internalize into the cells.[24] Following internalization of the nanocarriers, the drug payload is

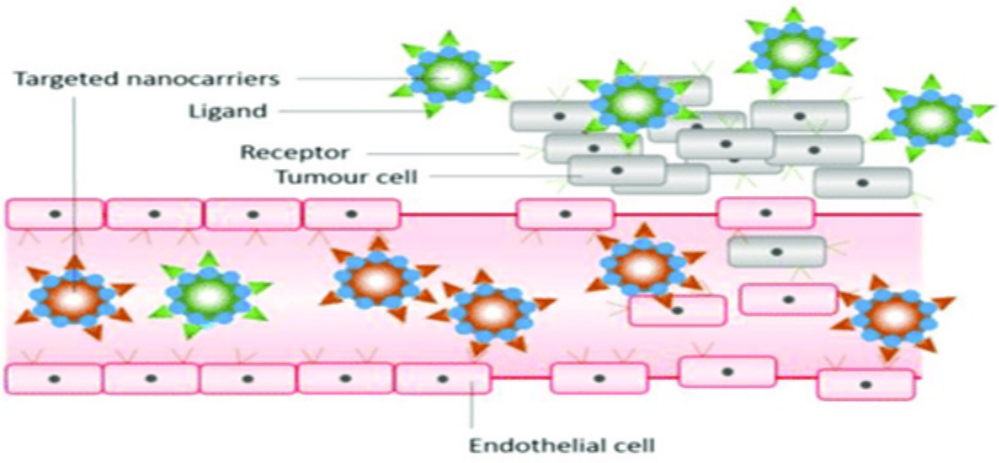

Figure 9: Active targeting mechanism[25]

released either passively or in response to particular triggers such as modifications in the target cells' pH, temperature, or enzymatic activity.[22,24]

Examples of active targeting in clinical use[26]

Herceptin (Trastuzumab)

This monoclonal antibody targets the HER2/neu receptor, which is overexpressed in certain breast cancers.

Abraxane (albumin-bound paclitaxel)

Utilizes albumin nanoparticles for improved drug delivery to tumors by interacting with the albumin receptor (gp60) on endothelial cells.

Passive targeting

Drug delivery systems based on nanocarriers use passive targeting as one of their main tactics. The enhanced permeability and retention (EPR) effect, which arises from the unique biological characteristics of some tissues, most notably cancers, is the main force behind passive targeting.[27] Passive targeting is based on the idea that nanoparticles, due to their size and other properties, can accumulate at disease sites where conventional therapies may not reach effectively (Figure 10).[28]

Passive targeting performs effectively with nanocarriers that are between 10 and 200 nm in size. Larger particles (>200 nm) may have trouble entering the tumor vasculature, while particles less than 10 nm may be quickly removed from circulation by the kidneys.[29] Spherical nanocarriers are commonly used due to their favorable circulatory distribution. They are often modified with polyethylene glycol (PEG) or other "stealth" compounds to avoid immune system detection. Encapsulated chemotherapeutic drugs can concentrate more effectively in tumor tissues, enhancing the therapeutic index and reducing systemic toxicity.[30] To improve penetration and drug release, passive targeting is combined with external stimuli like hyperthermia or ultrasound to enhance the EPR effect and promote deeper diffusion of nanoparticles.

Examples of passive targeting in clinical use:

Vyxeos

Used to treat acute myeloid leukemia (AML). It has demonstrated improved efficacy and reduced toxicity compared to the free drug combination.

Nanoparticle-based formulations of sirolimus (an immunosuppressive drug) are being tested in clinical trials for various applications, including cancer therapy and inflammation.

Applications

Nanocarriers have garnered significant attention in various fields due to their ability to encapsulate and deliver active substances (such as drugs, genes, or other therapeutic agents) in a controlled manner.

Drug delivery

Nanocarriers are widely used in drug delivery due to their ability to improve the pharmacokinetics and pharmacodynamics of therapeutic agents. These systems can enhance the solubility of poorly soluble medications, shield delicate molecules from deterioration, and allow for regulated or prolonged release by encapsulating them in nanocarriers.[31]

- *Cancer Therapy*

Nanocarriers are extremely beneficial in cancer treatment because they may deliver drugs to tumor sites precisely while minimizing negative effects. Drugs can be precisely delivered to malignant cells by engineering nanoparticles to recognize tumor-specific markers. Examples: liposome, gold nanoparticles.

- *Gene delivery*

The aim of gene therapy is to treat diseases by introducing genes into cells. Nucleic acids including DNA, RNA, and siRNA have been delivered to cells using nanocarriers such as lipid nanoparticles, polymers, and viral vectors.

Delivery of Biopharmaceuticals

The use of nanocarriers for efficient delivery of biopharmaceuticals [enzymes, vaccines, monoclonal antibodies, cytokines, hormones] is essential due to their practical benefits such as protecting from degradation in a hostile physiological environment, enhancing plasma half-life and retention time, facilitating absorption through the epithelium, providing site-specific delivery, and improving access to intracellular targets.[32]

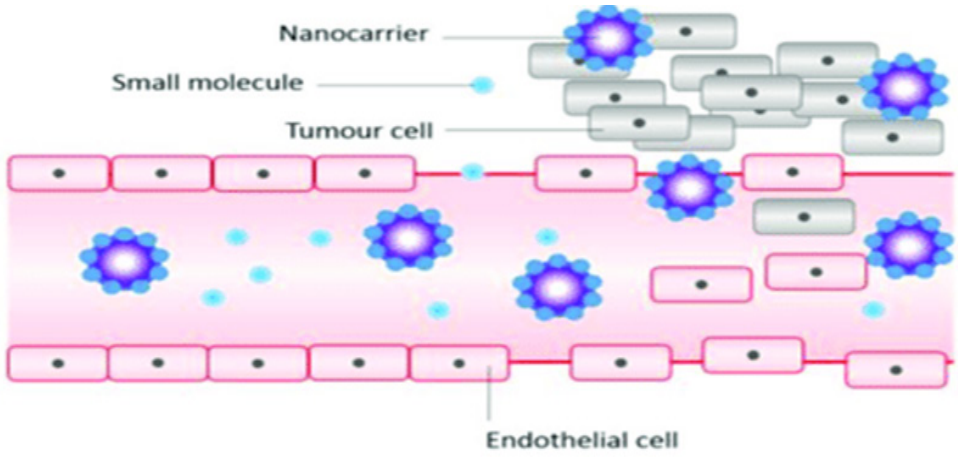

Figure 10: Passive targeting mechanism[25]

Targeted drug delivery

Through the recognition of unique markers on their surfaces, nanocarriers can be designed to target particular cells or tissues, including cancer cells. This minimizes harm to healthy cells and guarantees that the medication is delivered exactly where it is required.[33]

Enhanced Drug Solubility and Stability

The effectiveness of several medications may be limited by their poor water solubility. Surfactants and polymers are frequently used in nanocarriers to improve the solubility of hydrophobic medications. They shield the medication from being broken down by the body's enzymes and other biological processes. This makes the medication more stable.[4]

Overcoming Biological Barriers

Nanocarriers can help drugs cross biological barriers with the help of the EPR effect and surface modification.

CONCLUSION

Nanocarriers are mainly designed for targeted drug delivery systems to enhance the safety and therapeutic efficacy of various drugs. The primary objective of nanocarriers is to overcome the drawbacks associated with conventional drug delivery techniques, including their low specificity, toxicity, and low bioavailability. Nanocarriers offer a precise targeted delivery of drugs by using nanosized biomaterials. Drug loading in nanocarriers involves encapsulation, covalent bonding and electrostatic interactions which enhances their solubility and dissolition rate. Nanocarriers follow either an active targeting mechanism or a passive targeting mechanism to deliver drugs to the target site. In the active targeting mechanism, ligands are attached to the drug delivery system which bind to the receptor site. The passive targeting mechanism depends on the enhanced permeability retention effect to accumulate in the receptor site.

CONFLICT OF INTEREST

None

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