Versatility of nanocarriers in drug delivery: a review

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Abstract:

Nanocarriers have emerged as versatile tools across diverse fields, including medicine, cosmetics, and agriculture. In the domain of drug delivery, nanofibers, nanoparticles, and nanotubes have demonstrated efficacy in diagnosing and treating diseases. Central to drug delivery is the optimization of pharmacokinetics and the achievement of therapeutic goals. Nanocarriers with submicron sizes offer advantages such as improved pharmacokinetics, reduced toxicity, enhanced solubility, and controlled release of therapeutic agents. The selection of nanocarriers hinges on factors such as the type of drug, physiological barriers, and site of action. Future research directions should emphasize stimuli-responsive drug release, address toxicity concerns, and broaden the spectrum of nanocarriers for diverse biomedical applications. This review provides a thorough exploration of nanocarriers, categorizing them into organic (liposomes, solid lipid nanocarriers, micelles, dendrimers, and polymeric nanocarriers), inorganic (gold nanoparticles, magnetic nanocarriers, quantum dots, and mesoporous silica), and hybrid nanocarriers.

1. Introduction:

Nanotechnology has exhibited its versatility by finding applications in various fields, including medicine, cosmetics, environmental research, and nutraceutical research (Baskar et al., 2017; Muthukumar et al., 2014; Chamundeeswari et al., 2010). Nanostructures, such as nanofibers, nanocomposites, nanoparticles, and nanotubes, have proven to be highly effective in the diagnosis and treatment of numerous diseases (Verma, 2017; Baskar et al., 2017; Chamundeeswari et al., 2013). Furthermore, these nanostructures have demonstrated their value as carrier molecules or transporting agents for vaccines, drugs, genes, proteins, and enzymes (Baskar et al., 2018). The unique quantum properties possessed by these nanostructures have also facilitated their use in the agricultural and food industries (Baskar et al., 2018).

Drug delivery encompasses the process of effectively transporting therapeutic agents into the body, ensuring optimal pharmacokinetics and achieving the desired therapeutic effect (Allen and Cullis, 2004). Conventionally, drugs are administered either via the gastrointestinal tract or through alternate routes that bypass it. The enteral and parenteral routes are the primary methods of drug administration. The enteral route involves oral, rectal, or sublingual administration, utilizing the gastrointestinal tract as the pathway for drug delivery. On the other hand, the parenteral route involves delivering drugs directly through intravenous, intramuscular, or subcutaneous routes, bypassing the gastrointestinal tract entirely (Bardal et al., 2011). Among these routes, the enteral route is preferred due to its non-invasive nature. However, it is important to note that this route may limit the bioavailability of the drug, as it undergoes first-pass metabolism and incomplete absorption (Sala et al., 2018; Chowdary and Rao, 2004).

Nanocarriers, colloidal drug carrier systems with submicron particle sizes (typically around 500 nm), have gained significant attention and have been extensively studied for drug delivery purposes over recent decades. By virtue of their high surface area to volume ratio, nanocarriers possess the capacity to modify the fundamental properties and bioactivity of drugs. Incorporating features such as improved pharmacokinetics and biodistribution, reduced toxicities, enhanced solubility and stability, controlled release, and site-specific delivery of therapeutic agents, nanocarriers offer substantial advantages in drug delivery systems. Moreover, the physiochemical properties of nanocarriers can be manipulated by altering their compositions (organic, inorganic, or hybrid), sizes (small or large), shapes (sphere, rod, or cube), and surface properties (surface charge, functional groups, PEGylation, or other coatings, attachment of targeting moieties). The ultimate objective of utilizing nanocarriers in drug delivery is to effectively treat diseases with minimal side effects.

Nanoparticles, polymers, and carbon-based materials stand out as promising candidates for both direct drug delivery systems and carriers. An ideal drug carrier should possess key characteristics, including consistency, non-immunogenicity, biodegradability, ease of fabrication, affordability, and the ability to deliver drug payloads specifically to target sites. Organic systems, such as polymers, liposomes, and dendrimers, inorganic systems like magnetic or gold nanoparticles, silica, as well as quantum dots and carbon-based materials, such as carbon nanotubes, are commonly considered for designing drug delivery systems with targeted drug delivery capabilities. The efficacy of these nano-

drug carriers hinges on their dimensions, shapes, and other intrinsic chemical and biophysical features. Therefore, nano-drug delivery systems offer multiple advantages in the treatment of chronic diseases through targeted drug delivery.

Considering the aforementioned information, this review aims to highlight various drug delivery systems based on organic, inorganic, quantum dots, and carbon-based materials. Additionally, we will describe the designs of different nanosystems for the delivery of active drug molecules and discuss evolving methodologies utilizing diverse nanocarriers for therapeutic applications. These methodologies may include functional group modification, PEGylation or other coating techniques, and the attachment of targeting moieties. The overarching goal of utilizing nanocarriers in drug delivery is to effectively treat diseases while minimizing side effects.

2. Types of Nanocarriers

Nanocarriers with high surface-to-volume ratio majorly form three types such as organic nanocarriers, inorganic nanocarriers and hybrid nanocarriers.

2.1 Organic Nanocarriers

Organic nanocarriers encompass a range of nanoparticles, such as solid lipid nanocarriers, liposomes, dendrimers, polymeric nanocarriers, micelles, and viral nanocarriers. These organic nanocarriers exhibit remarkable versatility and lower toxicity levels, making them suitable for conjugating various drugs and ligands in drug delivery applications. Out of these organic nanocarriers, micelles and liposomes are particularly noteworthy for their ability to accumulate at specific target sites due to the enhanced permeability and retention effect (Lopez-Davila and Loizidou, 2012). Among them, polymeric nanocarriers and liposomes represent the first generation of nanocarriers, owing to their simplicity as excipients (Bhatia, 2016).

2.1.1 Solid lipid nanocarriers

Solid lipid nanocarriers have been used since the early 1990s as an effective carrier for delivering lipophilic drugs. These nanocarriers are prepared by dispersing melted solid lipids in water and stabilizing them by adding emulsifiers through micro-emulsification or high-pressure homogenization (Malam et al. 2009; Muller 2000). Commonly used solid lipids for preparing these nanocarriers include free fatty alcohols or acids, steroids or waxes, and mono, di, or triglycerides (Üner and Yener 2007). Depending on the production conditions and composition, drug molecules can be incorporated into the matrix, shell, or core of the solid lipid. As a versatile carrier, solid lipid nanocarriers overcome the limitations of conventional chemotherapy. However, they can be easily eliminated by the Reticuloendothelial System and pose challenges in sustained release of ionic and hydrophilic drugs. In recent years, solid lipid nanocarriers have been used to incorporate both lipophilic and hydrophilic anticancer drugs. For instance, the combination of polymers and lipids in hybrid nanocarriers has been explored as an effective means of oral drug delivery (Hallan et al. 2014). To address the drawbacks of conventional solid lipid nanocarriers, new generation nanocarriers such as nanostructured lipid carriers (a mixture of liquid and solid lipids) and lipid drug conjugates (water-insoluble carrier molecules) have been developed. These nanocarriers have shown promise in topical, parenteral, and oral drug delivery. Furthermore, solid lipid nanocarriers can be tailor-made to deliver specific drugs to desired sites. Extensive research in this field has focused on using solid lipid nanocarriers as vehicles for delivering genes and nucleic acids, treating ophthalmic diseases, achieving controlled release of active agents, and targeting delivery of antitumor agents (Bondi et al. 2007; Muller 2000).

2.1.2 Liposomes

Liposomes, composed of lipid bilayers enclosing an aqueous core, represent spherical vesicles capable of delivering lipophilic and hydrophilic drugs to specific target sites. These vesicles can exist as either unilamellar (with one bilayer) or multilamellar (with more than one bilayer) structures, serving as effective carriers for transporting biologically active molecules. However, the inherent short half-life of these molecules in the systemic circulation necessitates modifications. To address this limitation, liposomes can be coated with polymeric molecules, such as polyethylene glycol, resulting in the formation of PEGylated or stealth liposomes. These stealth liposomes exhibit heightened stability and prolonged half-life in the blood, evading elimination by the Reticuloendothelial System and facilitating sustained drug release (Torchilin, 2005). The incorporation of drug molecules into liposomes not only enhances the pharmacokinetics and biodistribution but also offers targeted drug delivery benefits. For instance, doxorubicin in stealth liposomes demonstrates reduced distribution in plasma and lower concentration in

healthy cells compared to the drug in solution (Wang et al., 2012). Furthermore, innovative nanocarriers like temperature-responsive liposomes, known as controllable switch nanocarriers, have been reported to locally enhance drug release (Rosenblum et al., 2018).

2.1.3 Micelles

McBain coined the term 'micelle' in 1913 to describe colloidal aggregates formed by mixing detergent in water, with amphiphilic molecules arranging such that the hydrophobic tail faces the center and the hydrophilic head contacts the external solvent. Inverse micelles, achieved in nonpolar solvents, have the head facing the center and the tail facing outward. The size and shape of micelle nanoparticles depend on solution conditions (temperature, ionic strength, pH) and the nature of the amphiphilic molecule. Proper micelle formation relies on the critical micellar concentration of the surfactant; below this concentration, micelle formation does not occur. Polymeric micelles, formed by two copolymers in certain solvents, find applications in industry and drug delivery. One copolymer, soluble in the solvent, forms the shell, while the other, insoluble, forms the core (Riess, 2003). These polymeric micelles are employed in drug delivery, as seen in adapalene encapsulation, increasing targeting efficiency 4.5 times, and in aptamer-based oligonucleotide delivery for effective targeting of cancer sites (Shen et al., 2018).

2.1.4 Dendrimers:

Dendrimers, intricate branched macromolecules originating from a central core (initiator core) with multiple arms (terminal active groups), are versatile in drug delivery applications. These macromolecules can be synthesized using nucleotides, sugar molecules, or amino acids, resulting in a highly branched, multivalent structure with diverse peripheral groups. The stepwise synthesis leads to a well-arranged branching pattern, with each added level referred to as a generation. Dendrimers possess a distinct molecular weight, allowing for a unique approach to drug delivery. The synthesis can yield a finely-tuned structure with core cavities for drug encapsulation through hydrophobic bonds, chemical interactions, or hydrogen bonds, enhancing surface functionality. Drug molecules can also be covalently attached to terminal active groups. Despite their advantages, dendrimers with a single generation may cause disassociation of attached molecules. The interaction between drugs and dendrimers involves physical and chemical bond formations. Dendrimers find applications in various fields such as magnetic resonance imaging scanning, gene delivery, drug delivery, antiviral and vaccine delivery, and linking with prodrugs (Stiriba et al., 2002). In anticancer applications, dendrimers are extensively linked with drugs like cisplatin and doxorubicin, enhancing their anticancerous activity (Lai et al., 2007; Bhadra et al., 2003; Lee et al., 2006)

2.1.5 Polymeric nanocarriers

Polymeric nanoparticles are colloidal, solid nanoparticles formed from biodegradable polymers (Bamrungsap et al., 2012). They can exist as either reservoir-type nanocapsules, where the drug molecules are dissolved or dispersed in the polymer core, or matrix-type nanospheres, where the drug molecules are trapped within the polymer matrix. They can also chemically conjugate or adsorb the drug on their surface (Prabhu et al., 2015). When present in the human body, the polymeric nanocarriers undergo biodegradation, resulting in the production of monomers that can be easily degraded by metabolic pathways (Mishra et al., 2010). These polymeric nanocarriers can be derived from both natural polymers (such as chitosan, gelatin, albumin, collagen, alginate) and synthetic polymers (such as poly(lactic-co-glycolic acid), polyethylene glycol, polyglutamic acid, and polycaprolactone) (Wang et al., 2009). Compared to other nanocarriers, these polymeric nanocarriers demonstrate advantages in terms of higher stability, drug payload, half-life time in systemic circulation, and sustained drug release. To target cancerous cells, anticancer drugs like doxorubicin can be entrapped within these polymeric nanocarriers. The release of the drug can be controlled by modifying the physiochemical properties of the polymeric source. Additionally, multifunctional polymeric nanocarriers can be designed to incorporate multiple drugs (Zhu and Liao, 2015). Advancements in polymeric nanoparticle synthesis have led to the development of smart polymers for targeted drug delivery. These smart polymers can release drugs in response to internal stimuli such as low pH, redox reactions, and enzymes, as well as external stimuli such as temperature, light, ultrasound, and magnetic or electric fields. However, the design challenges associated with smart polymers include scalability, toxicity/biocompatibility, and stimuli sensitivity. Moreover, the variation between clinical and preclinical models poses a challenge for intrinsic stimuli, while extrinsic stimuli face issues related to providing compliance, tissue penetration, and localization (Rosenblum et al., 2018). Despite these challenges, polymeric nanocarriers hold promise as effective tools for targeted drug delivery.

2.2 Inorganic Nanocarriers:

Inorganic nanocarriers, such as gold, magnetic nanocarriers, quantum dots, and mesoporous silica, possess advantageous properties that make them suitable for various applications. These applications include biosensing, cell labeling, targeting, imaging, diagnostics, and even therapeutics, as they exhibit synergetic effects. Additionally, manipulating the composition and size of inorganic nanocarriers enhances their magnetic, plasmonic, and optical properties. However, the use of heavy metals as inorganic nanocarriers can lead to long-term health issues.

2.2.1 Carbon nanotubes

Carbon nanotubes, initially discovered by Iijima in 1991, possess distinctive biological and physicochemical properties that make them an ideal and promising option for drug delivery (Bianco, 2004; Iijima, 1991). These tube-like structures consist of graphene sheets rolled together at specific angles, forming either single-walled or multi-walled carbon nanotubes depending on the number of graphene sheets involved. The cross-section diameter ranges from 0.4 to 100 nm, while the length can be thousands of times the diameter. In drug delivery, carbon nanotubes find extensive applications due to their unique characteristics, including a high aspect ratio, ultralight weight with a substantial surface area, nanosized needle structure, and distinctive chemical, thermal, mechanical, and electrical properties (Madani et al., 2011). Their needle-penetration facilitates the endocytosis process, allowing them to easily cross barriers or cell membranes (Pérez-Herrero and Fernández-Medarde, 2015). Functionalized nanotubes are water-soluble, with a long circulation period in the serum, while non-functionalized ones are toxic and water-insoluble. The structural stability, flexibility, and surface modification make them suitable agents for targeting cancer cells. In this context, functionalized carbon nanotubes are widely employed to encapsulate or link with anticancer drugs like Paclitaxel, Mitomycin C, Doxorubicin, Methotrexate, etc., for targeted drug delivery (Lay et al., 2010; Levi-Polyachenko et al., 2009; Das et al., 2013). Beyond biomedical applications, carbon nanotubes are also ideal for various industrial applications due to their inherent properties. Another noteworthy carbon-based nanocarrier for efficient drug delivery is graphene.

2.2.2 Gold nanocarriers

Gold, a noble metal, has influenced nanotechnology in the creation of gold nanoparticles, serving as effective agents for various applications like photoacoustic imaging, chemotherapy, surface-enhanced resonance spectroscopy, gene therapy, and photothermal therapy (Wang et al., 2004; Qian et al., 2008; Garcia, 2011; Lu et al., 2010). The synthesis of gold nanoparticles employs both top-down and bottom-up approaches, resulting in diverse anisotropic shapes such as nanostar, nanorod, nanocage, nanoshell, and nanoprism.

Gold nanocarriers possess distinctive optical properties, making them particularly appealing in the biomedical field. These properties facilitate the attachment of various biomolecules, including enzymes, carbohydrates, fluorophores, peptides, proteins, and genes to the gold nanoparticles. This attachment allows for effective intracellular transport, overcoming associated barriers. A significant application of gold nanocarriers lies in the efficient imaging of tumor cells (Loo et al., 2005). Additionally, nanoshells, when combined with optical coherence tomography agents, enable the acquisition of potential three-dimensional tissue images (Gobin et al., 2007). Gold nanocarriers also find use in positron emission tomography, single-photon emission computed tomography, and computed tomography analysis (von Maltzahn et al., 2009).

2.2.3 Quantum dots

Quantum dots, consisting of atoms from the II-VI (Se, Zn, Te, Cd) or III-V (In, As, P) element groups on the periodic table, are colloidal nanocrystals and energy donors. Their size determines the light emission, with smaller quantum dots (~2 nm) emitting blue fluorescence and larger quantum dots (~5 nm) emitting red fluorescence. Quantum dots, due to their extended light emission and resistance to photobleaching, are preferred over organic dyes for various applications, such as cell imaging. For instance, quantum dot-peptide conjugates have been used for in vivo tumor vasculature targeting in mice (Mkerman et al. 2002). To mitigate the toxicity of cadmium in CdSe quantum dots, they are often encapsulated within a ZnS shell, which enhances their accumulation at specific vascular sites. Moreover, these quantum dots are efficient as delivery and reporting systems. For example, surface-modified quantum dots with homing tumor peptides effectively attach to nucleolin on cancerous cells, enhancing cellular uptake. Likewise, quantum dots bound to small interfering RNAs have been found to enhance gene knockdown (Derfus et al. 2007). Quantum dots also exhibit versatile applications, such as serving as energy transfer quenchers in charge transfer processes

(Medintz et al. 2009), participating in quantum dot-fluorescence resonance energy transfer systems, and acting as chemiluminescence-resonance-energy transfer acceptors (Freeman et al. 2011).

2.2.4 Magnetic nanocarriers

The magnetic nanocarrier typically contains a magnetic core, with metal nanoparticles generally exhibiting greater magnetic properties than metal oxide nanoparticles. This magnetic characteristic, along with modified properties, makes it suitable for biosensing applications (Koo et al., 2011). Superparamagnetic nanoparticles, particularly those with polymer coatings, are highly susceptible to magnetic fields, making them useful in molecular imaging and as contrast agents (Huang et al., 2011). They enhance internalization in cells and particle clearance.Superparamagnetic iron oxide nanoparticles are chosen for molecular imaging due to their magnetic resonance properties, serving as contrast agents (Huang et al., 2011). They are effective in targeting cancer cells through passive targeting (Barry, 2008). Surface functionalization of magnetic nanoparticles allows their use as sensors in implant components, particularly in magnetic resonance imaging (Toma et al., 2005). Examples of magnetic nanoparticles include haematite, maghemite, nanoferrites, and magnetite. The unique properties of magnetic nanoparticles make them suitable for targeted drug and gene therapy, hyperthermia mediators, and contrast agents. Despite attempts to link Epirubicin drug in ferrofluid resulting in drug accumulation at the desired site, the penetration of magnetic fields in animal models poses a limitation, restricting the use of magnetic nanocarriers to targets close to the body (Grief and Richardson, 2005). Magnetofection, employing magnetic nanocarriers in gene and antisense therapy, and size-changeable nanocarriers like the Trojan Horse containing paclitaxel, demonstrating greater penetration into tumor cells with controlled drug release and higher cytotoxicity, showcase the versatility and potential of magnetic nanocarriers in various therapeutic applications (Lai et al., 2018).

2.2.5 Mesoporous silica:

Mesoporous silica, with its extensive honeycomb-like porous structure, allows for the incorporation of a greater number of drug molecules. This simplicity and widespread availability contribute to its significant applications in the biomedical field. Mesoporous silica has the capability to encapsulate both hydrophobic and hydrophilic drugs, making it versatile for targeted drug delivery when attached to a ligand molecule (Li et al., 2017). These characteristics underscore its potential in advancing drug delivery methodologies.

2.3 Hybrid Nanocarriers

Hybrid nanocarriers combine two or more organic and inorganic nanocarriers, such as lipid-polymer hybrids or ceramic-polymer hybrids. This combination enhances their properties significantly by incorporating the dual nature of both nanoparticles (Qian et al., 2012). For instance, organic nanocarriers like liposomes suffer from internal solution leakage and low stability, making them easily removed from circulating blood. To address these challenges, hybrid nanocarrier systems, like lipid-polymer hybrids, offer additional stabilization, making them suitable for drug delivery (Peer et al., 2007). The selection of nanocarriers depends on factors such as the site of action, type of drug, physiological barriers during drug delivery, and the stability and solubility of the nanocarriers. The primary goal is to increase the bioavailability of therapeutic agents with minimal or no side effects. Research on hybrid nanocarriers includes mesoporous silica nanoparticle-lipid bilayer hybrids that demonstrate distinguished intracellular delivery of zoledronic acid in breast cancer with a high retention rate (Han et al., 2015; Desai et al., 2017). This system enables stimuli-responsive drug release, preventing premature release into the body. Novel albumin hybrid nanocapsules efficiently encapsulate hydrophilic peptides or small drug molecules for targeting cancer cells, ensuring even distribution in the tumor microenvironment and reduced toxicity (Zhou et al., 2013). Additionally, ferritin is found to have an impressive advantage in drug delivery, encapsulating therapeutic agents and enabling stimuli-responsive sustained drug release at the target site (Khoshnejad et al., 2018). Various research studies focus on the in vivo delivery of small interfering RNA through core/shell lipid/cholesterol-grafted poly(amidoamine) hybrid nanocarriers, such as polyethylene glycol-liposome/small interfering RNA nanoparticles and peptide HAIYPRH, known as T7-liposome/small interfering RNA nanoparticles.

3. Conclusion:

Therefore, these nanocarriers show significant potential in drug delivery applications compared to conventional treatments. Consequently, there is a substantial need to produce economically viable nanocarriers using good laboratory practices that adhere to the necessary standards for serving as effective agents in drug delivery applications. In the coming decade, nanocarriers are anticipated to play a pivotal role in diagnosing and treating various diseases. The primary challenge lies in expanding novel nanocarriers for biomedical purposes and addressing barriers associated with targeted drug delivery. Tumor localization and imaging capabilities will likely bring unexplored nanocarriers successfully into clinical trials. Future research can focus on stimuli-responsive drug release using non-toxic, biocompatible, and biodegradable nanocarriers, extending drug release strategies while reducing associated side effects and unnecessary cell damage.

For circulating tumor cells, the design of stimuli-responsive surface-modified nanocarriers (bound with antibodies) can target tumor cells with a long half-life circulation, minimizing premature release. Inorganic nanocarriers offer significant advantages over organic counterparts due to their easy preparation and controllable nature. The development of hybrid, composite, or multifunctional inorganic nanocarriers has the potential to enhance the therapeutic and diagnostic efficiency of single nanocarriers.

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