**ROLE OF NANOCARRIERS AND NANOSENSORS IN DRUG DELIVERY SYSTEM: A REVIEW**

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**Abstract-** Nanotechnology has gained popularity in several industries, as it offers better-built and smarter products. The application of nanotechnology in medicine and healthcare is referred to as nanomedicine, and it has been used to combat some of the most common diseases, including cardiovascular diseases and cancer. The present review provides an overview of the recent advances in nano-technology in imaging and drug delivery.

Nanotechnology is the exploitation of the unique properties of materials at the nanoscale. Nanotechnologies have had a significant impact in almost all industries and areas of society as it offers i) better built, ii) safer and cleaner, iii) longer‑ lasting and iv) smarter products for medicine, communications, everyday life, agriculture and other industries. Nanomaterials allow the mass‑ creation of products with enhanced functionality, significantly lower costs, and greener and cleaner manufacturing processes, to improve healthcare and reduce the impact of manufacturing on the environment. In this present review, an overview of the role of nanocarriers and nanosensors in drug delivery is discussed.

**Keywords:** Nanocarriers, nanosensors, nanomedicine, diseases, drug delivery

**Introduction:**

Nanotechnology is the frontier research area of the twenty first century. Long thought to be commercially uninhabitable, the once-barren nanotechnology landscape suddenly looks fertile. With the support of some of the brightest minds in science and engineering, this emerging field of the super small is now firmly on the shortlist of technologies poised to produce big things in medicine.

Nanoscience is the study of the unique properties of materials between 1‑100 nm, and nanotechnology is the application of such research to create or modify novel objects. The ability to manipulate structures at the atomic scale allows for the creation of nanomaterials (Drexler, 1989 and 1986, Belkin et.al., 2015).

Nanotechnology stands to produce significant scientific and technological advances in diverse fields including medicine and physiology. Nanotechnology has been actively integrated as drug carriers over the last few years to treat various cancers. The science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale. A nanometer is one billionth of a meter or three orders of magnitude smaller than a micron (Palit and Datta, 2010). Nanoparticles get their name from their nanometer (nm) size (a billionth of a meter). Nanoparticles range from 1 to 100 nm, allowing them to be easily taken up by cells. Thus, their use as carriers of drugs (nanocarriers) has increased significantly in the past decade.

In order for nanoparticles to function as a drug delivery system, the drug has to be attached to the nanoparticles first. This step is crucial, and there are several ways of achieving this: the drug can be adsorbed or covalently attached to the nanoparticle's surface or the drugs can be encapsulated in the nanoparticles.

There are specific advantages to each method. During covalent attachment, the molecules are attached to the nanoparticles using recognition ligands. The use of covalent linkage gives the ability to control the number of the therapeutic compound attached to the nanoparticles.

Nanotechnologies exhibit significant potential in the field of medicine, including in imaging techniques and diagnostic tools, drug delivery systems, tissue-engineered constructs, implants and pharmaceutical therapeutics (Filipponi,2006), and have advanced treatments for several diseases, including cardiovascular diseases, cancer, musculoskeletal conditions, psychiatric and neurodegenerative diseases, bacterial and viral infections, and diabetes (Lombardo et.al.,2019).

**What are Nanocarriers?**

Nanocarriers involved in drug delivery offer several advantages when compared to conventional treatments, allowing an increase in water solubility of slightly soluble/insoluble drugs and protection against degradation and inactivation (Din et. al., 2017). These characteristics may provide enhanced stability in comparison with traditional formulations. Further, the design of the nanocarriers involved in drug delivery facilitates the drug lingering in the bloodstream for a prolonged period, which supports more efficient accumulation at the site of action (Chenthamara et. al., 2019, Halwani, 2022).

It also highlights the recent advances in nanocarrier-based delivery systems, including polymeric nanocarriers, micelles, nanotubes, dendrimers, magnetic nanoparticles, solid lipid nanoparticles, and quantum dots (QDs). The nanocarrier-based composites are discussed in terms of their structure, characteristics, and therapeutic applications in various kinds of ailments.

Nanocarriers are colloidal drug carrier systems having submicron particle sizes typically, 500 nm. (Neubert, 2011)Nanocarriers have been extensively investigated in the past few decades as they showed great promise in the area of drug delivery. Nanocarriers, owing to their high surface area-to-volume ratio, have the ability to alter the basic properties and bioactivity of drugs. Improved pharmacokinetics and bio-distribution, decreased toxicities, improved solubility and stability, controlled release and site-specific delivery of therapeutic agents are some of the features that nanocarriers can incorporate in drug delivery systems (Mishra, et. al.2010 and How et. al., 2013).

Nanocarrier-based approaches play a dynamic role in biomedical applications, particularly in drug delivery of chemotherapeutics. Versatile modifications are brought together to overcome conventional chemotherapy’s limitations and reduce the toxicity in different nanocarriers. This review summarized the polymeric-based nanoparticles, magnetic nanoparticles, lipid-based carriers, dendrimers and quantum dots mediated drug delivery systems for anticancer agents that hold promising therapeutic outcomes. We also discussed the applications of these few important groups of nanocarriers in cancer drug delivery, drug targeting and cancer diagnosis. So based on the current review, it might be suggested that the nanocarriers developed from the healthy cells-friendly biomaterials conjugated with tumour cell markers for the targeted and increased drug delivery at the site of action are better than the conventional nanocarrier systems ( Edis et. al. 2021).

Advances in surface technology of nanoparticles have allowed nanocarriers to engage applicants for future work involving targeted drug delivery. The utilization of nanotechnology in medicine has a great influence on human health in terms of diagnosis, prevention and treatment of illness. Numerous nanocarriers have been authorized for clinical use, and they are currently used to diagnose and/or treat several types of cancer. Additionally, there are different formulations, which are now in different stages of clinical trials. Nanocarriers are intended to deliver drugs by different mechanisms: passive targeting, active targeting, solubilization and activated release. Nanocarriers increase therapeutic effectiveness, decrease the effective dose and decrease the danger of systemic, adverse effects. Key problems associated with the clinical development of nanocarriers were discussed, comprising biological difficulties, large-scale fabrication, biocompatibility and protection, intellectual activity, authority rules and whole-cost efficiency compared to current therapies (Alshawwa et. al. 2022).

Nanocarrier-based platforms have enabled the effective delivery of anticancer drugs into tumours by exploiting the pathophysiology of the tumour microenvironment, thereby significantly improving the therapeutic outcomes.

**Types of nanocarriers**

**Liposomes-** Liposomes were the first type of nanocarriers, and are around 80−300 nm in size. They are spherical and consist of phospholipids and steroids. They can be prepared spontaneously by dispersing lipids in aqueous media. A drug can be encapsulated inside the liposome, and it can be subsequently released from the drug by changing parameters such as pH, osmotic gradient, and surrounding environment. Different surface modifications also improve the half-life of the liposomes. For example, the addition of polyethylene glycol (PEG) increases the half-life of liposomes by preventing recognition by phagosomes. Similarly, polyethylene glycol-phosphatidylethanolamine (PEG-PE) conjugates have also been added. PEG-PE conjugates are non-toxic and can be used to specifically target the nanocarriers to the mitochondria.

**Nanoparticles based on solid lipids**-Lipid based nanoparticles include solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and lipid drug conjugates (LDC). The SLNs are based on solid lipids and provide good physical stability and tolerability. NLC and LDC are combinations of solid and liquid lipids with increased load capacity and reduced drug expulsion properties.

**Polymeric micelle**- They are derived from synthetic polymers and range from 10−100 nm. They can be further subdivided into biodegradable and non-biodegradable. Drugs can be conjugated on the surface of these nanocarriers by polymerization and they can be released by desorption or diffusion in the target tissue. Biodegradable nanocarriers can undergo hydrolysis inside the body to give lactic and glycolic acid. They are also stable in blood, non-toxic, and non-thrombogenic.

**Dendrimers nanocarriers-** Dendrimers nanocarriers consist of the following features: core, dendrons (dendrimers), and surface active groups. The dendrons are attached to the core and the properties of the nanocarriers are determined by the type of surface functional groups. Several ligands can attach to the surface of dendrimers, such as folic acid, antibodies, peptides, PEG, or antimicrobial agents. These additions modify the physical and chemical properties of dendrimers.

**Silica materials-** Silica materials used as nanocarriers include xerogels and mesoporous silica nanoparticles. MCM-41 is a well-known silica nanomaterial. The drug loading in these materials occurs via adsorption and the drug release is governed by diffusion. However, recent studies have also shown certain hazardous effects where silica nanoparticles trigger oxidative stress and the production of reactive oxygen species in cells. Thus, there is a need for further investigation into the effects of these silica nanocarriers.

**Carbon nanotubes (CNTs)-** Carbon nanomaterials include nanotubes and nanohorns. They can be formed of single nanotubes rolled into a sheet or multiple nanotubes arranged concentrically. Surface modifications can be added to these to improve their biocompatibility. They have high mechanical strength and thus have also been used as a support for other nanocarriers. Drugs can be added to carbon nanotubes by encapsulation, adsorption, or attaching active agents to the nanotubes. The drug can be released by physical or chemical modifications.

**Quantum dots-** Quantum dots are fluorescent semiconductor nanocrystals (1-100nm) and have potential use for several biomedical applications. Quantum dots possess a shell-core structure, in which the core structure is typically composed of II-V or III-V group elements of the periodic table. Due to their distinctive optical properties and size, with high brightness and stability, quantum dots have been employed in the field of medical imaging ( Probst et. al., 2013; Sim and Wong, 2021).

**Delivery of nanocarriers to the target site**

The delivery of drugs to the target site can be achieved via active or passive methods. Active methods involve modifying the physical conditions, such as temperature, pH and magnetism to get the nanoparticles to specific regions.

Passive methods involve modifying the vascular permeability and retention (EPR) parameters. For example, smaller particles preferentially localize in tumours due to the EPR of tumours.

The nanocarriers should not accumulate in the cell for too long, as they could affect innate biological processes. However, smaller particles may be more reactive due to their increased surface area, and thus potentially more toxic.

 It is believed that in future, the management of precise doses of drugs with the highest systemic release from the nanocarriers and minimum toxic effects will not only enhance the use of nanocarriers systems for antitumor drug delivery but also improve patient compliance (Din et.al.2017).

**What are Nanosensors?**

Nanosensors are tiny sensors that measure very small changes in physical or chemical properties. They are used in drug delivery systems to monitor the concentration of drugs in a patient's bloodstream and to adjust the amount of drugs being delivered. Nanosensors are also used in other applications, such as environmental monitoring, and biomedical sensing.

Nanosensors possess great potential for diagnostic medicine, enabling early identification of disease without reliance on observable symptoms. Ideal nanosensor implementations look to emulate the response of immune cells in the body, incorporating both diagnostic and immune response functionalities while transmitting data to allow for monitoring of the sensor input and response. However, this model remains a long-term goal, and research is currently focused on the immediate diagnostic capabilities of nanosensors. The intracellular implementation of nanosensors synthesized with biodegradable polymers induces signals that enable real-time monitoring and thus pave the way for advancement in drug delivery and treatment (Yeo et.al.2015).

**Types of Nanosensors**

Classification based on structure includes

i) Electromagnetic nanosensors

ii) Mechanical nanosensors,

iii) Optical nanosensors.

Use-based classification includes

1. Deployable nanosensors,
2. Biosensors,
3. Electrometers,
4. Chemical sensors.

Classification based on energy sources includes

1. Active nanosensors, for which energy is required (thermistors, for example),
2. Passive nanosensors, for which no energy is required (piezoelectric and thermocouple sensors, for example).

One example of these nanosensors involves using the fluorescence properties of cadmium quantum dots as sensors to uncover tumours within the body. A downside to the cadmium-selenide dots, however, is that they are highly toxic to the body. As a result, researchers are working on developing alternate dots made out of a different, less toxic material while still retaining some of the fluorescence properties. In particular, they have been investigating the particular benefits of zinc sulfide quantum dots which, though they are not quite as fluorescent as cadmium selenide, can be augmented with other metals including manganese and various lanthanide elements. In addition, these newer quantum dots become more fluorescent when they bond to their target cells (Ratner et.al.2003).

Another application of nanosensors involves using silicon nanowires in IV lines to monitor organ health. The nanowires are sensitive to detect trace biomarkers that diffuse into the IV line through the blood which can watch kidney or organ failure. These nanowires would allow for continuous biomarker measurement, which provides some benefits in terms of temporal sensitivity over traditional biomarker quantification assays such as ELISA (Bourzac, 2016).

Nanosensors can also be used to detect contamination in organ implants. The nanosensors are embedded into the implant and detect contamination in the cells surrounding the implant through an electric signal sent to a clinician or healthcare provider. The nanosensor can detect whether the cells are healthy, inflammatory, or contaminated with bacteria (Mclntosh, 2017). However, a main drawback is found within the long-term use of the implant, where tissue grows on top of the sensors, limiting their ability to compress. This impedes the production of electrical charges, thus shortening the lifetime of these nanosensors, as they use the piezoelectric effect to self-power.

Similarly to those used to measure atmospheric pollutants, gold-particle based nanosensors are used to give an early diagnosis of several types of cancer by detecting volatile organic compounds (VOCs) in breath, as tumour growth is associated with peroxidation of the cell membrane. Another cancer-related application, though still in the mice probing stage is the use of peptide-coated nanoparticles as activity-based sensors to detect lung cancer. The two main advantages of the use of nanoparticles to detect diseases are that it allows early stage detection, as it can detect tumours the size in the order of millimeters. It also provides a cost-effective, easy-to-use, portable, and non-invasive diagnostic tool ( Peng et.al., 2010).

A recent effort towards advancement in nanosensor technology has employed molecular imprinting, which is a technique used to synthesize polymer matrices that act as a receptor in molecular recognition. Analogous to the enzyme-substrate lock and key model, molecular imprinting uses template molecules with functional monomers to form polymer matrices with specific shapes corresponding to their target template molecules, thus increasing the selectivity and affinity of the matrices. This technique has enabled nanosensors to detect chemical species. In the field of biotechnology, molecularly imprinted polymers (MIP) are synthesized receptors that have shown promising, cost-effective alternatives to natural antibodies in that they are engineered to have high selectivity and affinity. For example, an experiment with an MI sensor containing nanotips with non-conductive polyphenol nano-coating (PPn coating) showed selective detection of E7 protein and thus demonstrated the potential use of these nanosensors in the detection and diagnosis of human papillomavirus, other human pathogens, and toxins ( Mustansar,2018). As shown above, nanosensors with molecular imprinting techniques are capable of selectively detecting ultrasensitive chemical species in that by artificially modifying the polymer matrices, molecular imprinting increases affinity and selectivity.Although molecularly imprinted polymers provide advantages in selective molecular recognition of nanosensors, the technique itself is relatively recent and there still remain challenges such as attenuation signals, detection systems lacking effective transducers, and surfaces lacking efficient detection. Further investigation and research in the field of molecularly imprinted polymers is crucial for the development of highly effective nanosensors (Cai, 2010).

In order to develop intelligent health care with nanosensors, a network of nanosensors, often called Nanonetworks, needs to be established to overcome the size and power limitations of individual nanosensors. Nanonetworks not only mitigate the existing challenges but also provide numerous improvements. Cell-level resolution of nanosensors will enable treatments to eliminate side effects, and enable continuous monitoring and reporting of patients’ conditions.

Recently, there have been enormous developments in the field of delivery systems to provide therapeutic agents or natural-based active compounds to their target location for the treatment of various ailments (Obeid et.al, 2017). There are a number of drug delivery systems successfully employed in recent times, however, there are still certain challenges that need to be addressed and an advanced technology needs to be developed for successful delivery of drugs to its target sites. Hence the nano-based drug delivery systems have currently been studied that will facilitate the advanced system of drug delivery.

Nanoparticles can be modified in several ways to prolong circulation, enhance drug localisation, increase drug efficacy and potentially decrease the development of multidrug resistance through the use of nanotechnologies (Sim and Wong, 2021). There is no doubt that nanotechnologies have helped to improve the quality of life of patients by providing a platform for advances in biotechnological, medicinal and pharmaceutical industries. They have also facilitated healthcare procedures, from diagnosis to therapeutic interventions and follow-up monitoring.

Advances in nanotechnology are providing nanofabricated devices that are small, sensitive and inexpensive enough to facilitate direct observation, manipulation and analysis of a single biological molecule from a single cell. It seems quite likely that there will be numerous applications of inorganic nanostructures as biomarkers. Given the inherent nanoscale of receptors, pores, and other functional components of living cells, the detailed monitoring and analysis of these components will be made possible by the development of a new class of nanoscale probes. Biological tests measuring the presence or activity of selected substances become quicker, more sensitive and more flexible when certain nanoscale particles are put to work as tags or labels (Agrawal and Prajapati, 2012).

**The potential risk of nanotechnology in the healthcare system**

Nanoparticles can infiltrate the body via several routes: Inhalation, ingestion, absorption through the skin or injection during medical procedures. Once nanoparticles have entered the body, their high mobility may allow them to traverse the blood-brain barrier. Nanoparticles may affect the body's immune system by overloading the phagocytes. Inflammation and stress reactions may be triggered, leading to a weakened defence against other harmful challenges. They could interrupt the physiological and biological processes in the body (Singh, 2018; Chandarana et.al., 2018 and Dreher, 2004) as enzyme regulatory mechanisms by adsorbing onto the surface of the cells or fluids they encounter in attributed to their large surface area.

**Conclusion**

Nanomedicine and nano delivery systems are a relatively new but rapidly developing science where materials in the nanoscale range are employed to serve as means of diagnostic tools or to deliver therapeutic agents to specific targeted sites in a controlled manner. Nanotechnology offers multiple benefits in treating chronic human diseases by site-specific, and target-oriented delivery of precise medicines.

Nanotechnologies are making a compelling contribution in this area through the development of novel modes for drug delivery, and some of these methods have proven effective in a clinical setting and are clinically used.

Nanocarriers serve as revolutionary platforms to minimize toxicity, improve efficacy and achieve targetability of drugs. The development of hundreds of nanocarrier formulations over the last decades has introduced numerous in vitro and in vivo characterisation techniques. Consequently, it has become more challenging to standardize the safety and manufacturing protocols that control the regulatory approval of those revolutionary systems.

Nanocarriers improve the bioavailability and therapeutic efficiency of antitumor drugs while providing preferential accumulation at the target site. A number of nanocarriers have been developed; however, only a few are clinically approved for the delivery of antitumor drugs for their intended actions at the targeted sites.

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