REVIEW ARTICLE

Therapeutic Potential of Nanomaterial-based Drug Delivery

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ABSTRACT

The medical market for sophisticated therapeutic medicine delivery systems is growing at a breakneck pace. There are many benefits to using nanotechnology and nanomaterials in treating chronic human illnesses, such as the ability to target the delivery of drugs to particular areas. Improving the therapeutic effectiveness of current and future medications might be as simple as creating new drug delivery methods. The prime applications related to nanomaterial drug delivery include immunotherapeutic agents, diagnostic testing, cancer therapy and nutraceutical delivery. Nanotechnology has the capacity to collaborate with physics, biologists, chemists and pharmaceutics to form a multidisciplinary contribution in the rise of novel diagnostic and therapeutic technology. Nanomaterials can be used in specific sites targeted by drugs for brain illnesses. These nanodrugs can cause lesser immune response and maintain low inflammatory conditions compared to heavy drug particles. Along with this, nanodrugs can cause damage at the genetic level, create oxidative stress and inhibit cell death according to their particle size, shape, surface and its composition. In this current review various applications, current trends and recent developments in nanomaterials are elucidated. The detailed mechanism and cutting edge nanomaterial based drug delivery were explained along with this.

Keywords: Nanotechnology, Nanomaterial, Drug delivery, Immunotherapeutic agents, Nutraceutical delivery, Chronic.

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INTRODUCTION

The term nan pertains to the Greek prefix, which denotes dwar or extremely little, representing one millionth of a meter. In the 5th century BC, nanoscience was present during the Democritus and Greek periods.[1] The oldest object related to nanomaterials is Lycurgus Cups, currently present in the British Museum. When these cups are tested using transmission electron microscopy (TEM), the dichromic mechanism is observed due to nanoparticles (50–100 nm). These cups display different colors with the different light effects.[2] Nanoparticles' synthesis and mode of interaction were called as nanoscience and these nanoparticles have at least 1 to 100 nm in range. This unique and novel size made nanoparticles more versatile to study and to understand it behavior.[3] The reaction and interaction of biology with nanotechnology is always an intricate and complex procedure that can initiate the development of potential and therapeutic nanotechnology medicine.[4] The major factors responsible for the development of nanotechnology-related drugs are i) Physicochemical characteristics of a nanoparticle, such as its shape, surface chemistry, size, design and surface area. ii) The biochemical and biological environment, including pH and other biochemical factors: iii) Kinetics of biology and nanoparticle interactions.[5] Metal nanoparticles can develop nanoshells, and these nanoparticles are used against different diseases that decrease the quality of life. The metals used in the nanoparticle development is gold, copper, silver, cadmium, iron, zinc and titanium.[6]

The nanoparticles, mainly AuNPs and AuNPs (gold and silver) have potential antifungal, antibacterial and antiviral properties.[7] When these nanoparticles are developed using gold, has a high tendency to enter the specific cancer cells and deliver the drug/medicine at specific regions. These can easily enter the cell membrane and plasma membrane to initiate the programmed cell death.[8] In the same way related to maxillofacial surgery (oral region), the silver nanowere used in apical surgeries, removal of harmful bacteria, dental implants, oral cancer and wound healing.[9] Targeting is a strategy used

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to improve the therapeutic effect's delivery specificity to reach the desired area most effectively, minimizing any adverse consequences from unspecific accumulation in other organs or cellular compartments. A highly developed targeting technique would utilize all of the advantages of the nanoscale stated above. In order to lengthen the targeted particle's duration in circulation and simultaneously get access to endogenous transport and trafficking pathways, one would, therefore want to trick the immune system; few drugs are available that can be helpful. Doxile, abraxane, caelyx, and abraxane are the few therapeutic drugs present on the market to treat cancer. Due to its noninvasive nature, administrating orally is the best choice, and delivering protein-related drug will not reach the infected region due to its acidic stomach. To overcome this, nanotechnology is used for the better delivery by encapsulating the drug and this encapsulation of drug by the nanoparticles will have strong site-specific drug delivery, accumulation of more drug and less toxic effects.[10] Targeting ligands, such as monoclonal antibodies and their Fab fragments, on the surface of nanoparticles allow them to target cancer cells in tumors. Mice show a reduction in tumor growth and metastasis when nanoparticles encoding targeting peptides are used to target tumor cells.[11,12]

For medical approaches in a variety of clinical processes, such as atherosclerosis, inflammation, and thrombosis, the vascular endothelium is a possible target. The delivery of drug to these areas will always be a complicated process, and the nanocarriers can overcome this. Endothelial cells are exposed to dynamically changing mechanical stresses brought on by blood flow because of the topography of their intravascular environment. Tumor necrosis factor (TNF) therapy, or the use of a small amount of Triton X-100 concentration to compromise cell membranes, was used to replicate vascular inflammation and the concomitant endothelial damage. Nanocarriers could be employed for targeted medication delivery to post-capillary veins and vascular compartments with shear stress of 0.05 Pa. Additionally, the potential for giving medications to lessen shear stress in the vascular compartments may make it easier for nanoparticles to be taken up and delivered specifically to the inflammatory areas.[12,13] A fundamental change occurred in the study of lubricants and lubricant additives, and nanotechnology was also involved in the development of lubricant technology. Due to their unique qualities, nanomaterials and nanoparticles have lately been investigated as lubricants or lubricant additives rather than conventional materials.[14] "Because nanoparticles fall off of the contact spot during loading and shearing, they do not provide any tribological benefit to the shearing surfaces. In the first scenario, where the feature roughness duration scale of shearing surfaces is smaller than the nanoparticles' radius, the ratio of the nanoparticles' root mean square (RMS) roughness to their radius is an indicator of the amount of lateral force required to push the nanoparticles out of the asperity barrier.[15] Hence, insufficient lubrication might result from too large and non-adherent nanoparticles, as they could easily fall away from the interface site." In the two-dimensional situation, when the length scales of the function roughness are much larger than the debris's radius, nanoparticles may fill the valleys between the worn shearing surfaces. This enhances the tribological characteristics and artificially smoothes the shearing surfaces.[16] In total these nanoparticles are used in wide varieties like textile, food, industries, pharmaceuticals, delivery of drugs, biosensor fields, and molecular imaging.[17] In this current review, we tried to explain the different nanoparticles, the behavior nature of nanoparticles towards the cells and drug deliver by the nanoparticles.

The bio-system itself is a powerful biota unit. The cellular, acellular, multicellular and unicellular type of cells, which serves as both the functional and structural basis of the bio-system and a well-organized structure that, displays a wide range of responsibilities that are essential to the bio-system's survival. Bio-systems and nanomaterials communicate in a very unusual way and the majority of the physicochemical characteristics of nanoparticles affect associating material whether it is chemical, organic, or biological. Activities of nanomaterials depend on the controlled interaction of the environment's biota and abiota.[17] There are two basic importation processes that may take place, either a non-energy-dependent contact with the plasma membrane[18] or a power endocytotic pathway[19] that is, subject to the cellular surface structure and the physicochemical characteristics of the nanocarrier. The following characteristics of nanomaterials, including thickness, structure, hydrophobicity, charge density, surface energy, and polarity determine how cells interact with them. Cells first come in contact with the nanoparticle surface. Due to nanoparticle charge, electrostatic forces, Van der Waals forces, solvation, dipole-dipole interactions, depletion forces, etc., interactions can have inadvertent biological impacts. Another crucial element that affects a nanoparticle's structural, physical, and chemical characteristics is its shape. The electronic, optic, and mechanical properties are influenced by a variety nanoparticle forms.

Cellular Uptake of Nanoparticle (Endocytosis-Based)

The cell membrane (CM) of the cell maintains cell homeostasis and safeguards the intracellular components from the outer environment. The CM manages the ion concentration, delivers support and maintain the entry exit of nutrient and charged molecules.[20] The nanoparticles engage with plasma membrane and pass through it and enter the cell by endocytosis mechanism. This process of endocytosis involves engulfment of nanoparticles and the formation of endocytic vesicles by a number of different processes, including phagocytosis, caveolin-mediated endocytosis, clathrin-mediated endocytosis, and a combination of the two.[21]

In clatrin-mediated endocytosis the nanoparticles enter in to the cell by the process of binding and clustering. Nanoparticle size and surface ligands cluster and bind to the appropriate cell membrane receptors to begin the principal pathway for nanoparticle cellular penetration in clatrin-mediated endocytosis. Low-density lipoprotein receptors, β2 adrenergic receptors, epidermal growth factor receptors, and

transferrin receptors are the major receptors involved in the clathrin-mediated endocytosis.[22] By the help of opsonization process nanoparticle phagocytosis occurs and opsonins like complement protein, fibronectin, and immunoglobulins were adsorbed. The phagocytes identified the adsorbed nanoparticles through the ligand-receptor, leading to the signal cascade (actin assembly was triggered) and cell surface extension. The receptors involved in this process are complement receptor, fructose receptor, Fc receptors, and scavenger receptor.[23] The heavier molecule movement or inward movement will be highly effective through phagocytes, and albumin nanoparticles with 200-1500 nm size have more efficient uptake by the phagocytic process when treated with blood cells.[24] In the same way for the Nanoparticles related to polystyrene with size 460 to 2100 nm has good efficient inside movement in mouse macrophages.[25] Macropinocytosis refers to a collection of non-specific cellular process which distinguishes by the engulfment of extracellular fluids through actin-stabilized plasma membrane extensions. This process results in capturing nanoparticles and other consumed substances inside vesicular structures known as macropinosomes.[26] In contrast to many other endocytosis mechanisms membrane ruffling and actin signaling leads to macropinocytosis. Such vesicles can be anywhere from 0.5 to 1.5 m in size. According to the reports, macropinosomes leak intracellular vesicles that could allow nanoparticles to exit until they are degraded by lysosomes.[27] A further significant receptor-specific route for assimilating nanoparticles is caveolin-dependent endocytosis, dependent on infoldings of the plasma membrane known as caveolae loaded with caveolin.[28] Caveolin-coated vesicles are transferred across the cytoplasm after ingestion and initiation of a complicated signaling cascade. Vesicles containing caveolin often pass *via* the cell's golgi apparatus and endoplasmic reticulum.[29] A second optimal pathway for cell nanoparticle absorption is endocytosis mediated by clathrin and caveolin. This region of the sphingo lipids is important in endocytosis, according to Lajoie and Nabi (2007). According to Foerg *et al*. (2005),[30] nanoparticles may be brought into cells by lipid raft mediated endocytosis, which involves the modification of nucleotides and cell penetrating peptides based on the current state of affairs (Figure 1).

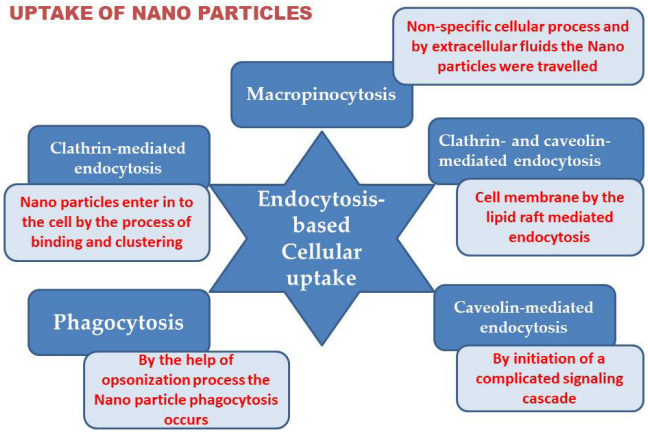

Figure 1: Different endocytosis based cellular uptake of nanoparticles

Nanomaterial Based Drug Delivery System

Extensive research focus has been given to nanomaterials with enzyme-like characteristics, or "nanozymes." Chinese researchers by the help of this nanozyme deactivated the severe acute respiratory syndrome (SARS) COVID-19 up to 99%. Typically administered in a stable colloidal state, these nanoparticles are engineered to decrease toxicity by minimizing drug exposure to healthy cells and tissues. Simultaneously, they are engineered to increase the therapeutic index of anticancer therapies by passive or active targeting. With the ability to transport large quantities of medicine *via* metal-based particles, the half-life of the drug in the bloodstream might be extended. Research on nanoparticles relies heavily on carbon-related polymers, particularly carbon dots, nanoforms, fullerenes, and nanodiamonds.[31] Potential conjugative and cell-penetrating polymers containing carbon bonds are used for targeted medication delivery in living organisms.[32] Both single-walled and double-walled nanotubes activate the traditional route of the serum complement system in patients. Peptides C3a, C5a, and C4a are produced when these single-walled carbon nanotubes (SWNTs) and double-walled carbon nanotubes (DWNTs) activate the serum complement system.[33] In a roundabout way, this triggers receptor ligand exchange events, which in turn promote beta cell proliferation, antigen presentation, and immunoglobulin production (Fearson and Carroll 2000). Graphene oxide, a compound made of carbon atoms arranged in a single sheet, is a drug delivery method and an effective antibacterial agent utilized in ophthalmology.[34,35] Solid lipid nanoparticles (SLNs) are unique in nature and have the tendency to intake the drug and can be loaded in particular shell.[36,37] These SLNs will carry the drug and by the disposition and absorption process (Pharmacokinetics) the drug delivery mechanism occurs.[38] Metal nanoparticles have strong nature of carrying the large sized drugs to have the capacity to increase the circulatory half-life and they carry drug and help in lowering or eradicating the disease (Table 1).

Polymeric Nanoparticles and its Drug Delivery

Many different types of pharmacological compounds have their pharmacodynamic and pharmacokinetic properties altered or improved by the use of particle technologies, such as nanoparticles. The dissolved medicine trapped, encapsulated or linked to nanoparticle network through the biodegradable and biocompatible polymer size ranging between 10 to 1000 nm to develop the polymeric nanoparticles (PNPs).[39] In a variety of fields, including biotechnology, conducting materials, electrical, optoelectronic, sensors, medicine, environmental technology, and pollution management the study of PNPs is rapidly growing.[40] Because of their small size, PNPs may be able to cross cell membranes and remain stable in blood flow. Their nanometer-size enhances their stability in the

Table 1: The different Drugs delivered at helped against different disease by the Nanotechnology

S. No	*Nanoparticle*	*Drug*	*Used in*	*Reference*
1	zirconium phosphate (ZrP) nanoplatelets	Doxorubicin	enhanced cytotoxicity in MDA-MB-231 cancer cells	Saxena *et al*., 2013
2	Gold Nanoparticles	TPPS	inhibition of cellular metastasis, and angiogenesis in the cancer cells	Bera *et al*., 2018
3	carbon nanomaterials	dental implants	Diabetic patients	Vijay *et al*., 2021
4	PLGA	Dexamethasone	Anti-inflammatory	Kim *et al*., 2006
5	PBCA	Temozolomide	Anticancer drug	Tin *et al*., 2011
6	PBCA	Rivastigmine	Anti-Alzheimer's	Wilson *et al*., 2008
7	PLGA	paclitaxel	Anticancer drug	Sahoo *et al*., 2004
8	SLN	Retinoic acid	Anticancer drug	Wong *et al*., 2007
9	Gold Nanoparticles	Dihydromyricetin	anti-inflammatory	Guo *et al*., 2014
10	Gelatin	Rifampicin	Antitubercular drug	Saraogi *et al*., 2010

bloodstream and efficient penetration across cell membranes. Utilizing polymers is a breeze, and the results may be endlessly varied molecular patterns that can be integrated into unique nanoparticle formations that have several potential medicinal applications.[41] Albumin, gelatin, chitosan and sodium alginate were the natural polymers used in the development of PNPs.[42]. In the same way there are different varieties of synthetic polymers like poly acrylamide, poly malic acid, polycaprolactone, polyglycolides (PGA), polylactides (PLA), poly (methacrylic acid), poly (acrylic acid), poly (vinyl alcohol), polycyanoacrylates , poly(lactide co-glycolides) (PLGA) and polyglycolides (PGA).[43] By the help three major physic-chemical properties the PNPs can carry the drug and deliver at specific region and the methods are, 1) Diffusion, in this hydration induced swelling of the PNPs, which then led to the release of the drug. 2) The enzyme reaction leads to cleaving the polymer at a specific delivery site and drug release in the inner core of the entrapped area; 3) Adsorption of the nanoparticle near the plasma membrane.[44,45.]

Drug Delivery by Nanoparticle in Oral Cancer

According to the 2011 statistics oral squamous cell carcinoma (OSCC) accounted for total 3% cases all over the globe. The malfunction of the cell division represents cancer and id wide varieties of cancer oral stand in top five.[46] Human papillomavirus (HPV) has emerged as a novel risk factor for squamous cell carcinoma (SCC) of the oropharynx. Oral leukoplakia is the most common disorder that might be malignant. The development of cancer in the mouth (mouth cancerogenesis) involves a cascade of events involving several cellular and genetic abnormalities. Another possible role is an imbalance of VEFG, EGF, and PDGF caused by gene alterations associated with tobacco use and/or HPV 16 and 18 infection.[47] Cisplatin (CDDP) is one the prime drug in chemotherapy against the neck and head squamous cell carcinoma. The CDDP (NC-6004) was developed and tested against the OSCC. This NC-6004 is a nanoparticle related to cisplatin prepared using by the cutting-edge micelle nanotechnology. In both *in-vivo* and *in-vitro* the NC-6004 exhibited strong antitumor activity and developed apoptosis in renal cells.[48] Drugs taken orally *via* SLNs are mostly released through the solid lipid matrix of the stomach through a breakdown and/or diffusion mechanism.[49] The mangiferin-phospholipid compound exhibited 10.1 fold greater in permeation when compared with solution mangiferin.[50] Ayurvedic practitioners rely on nanostructured lipid carriers (NLCs) and SLNs for their potent tumor-inhibiting properties, stable encapsulation, and oral bioavailability.[51] With the increasing prevalence of cancers, gene therapy has become an important tool for treatment. Recently, researchers have found a way to target human oral cancer cells—KB cells—by transferring DNA using folate-linked NPs. This is a first. It is worth considering the potential use of these NPs as vectors to convey genes to oral cancer cells, as suggested by Hattori *et al*. (2004).[52] Jeong *et al*. (2004).[53] found that nanoparticles made of a hydrophilic-hydrophobic diblock copolymer including poly(g-benzyl-l-glutamate) (PBLG) and poly(ethylene glycol) (PEG) had certain useful properties that might be put to use in a drug delivery system for the treatment of oral cancer. Perovskite-poly(g-benzyl-l-glutamate) NPs researchers found that nanoparticles carrying the Herpes simplex virus thymidine kinase (HSV-TK) gene were able to inhibit the growth of oral cancer cells produced by DMBA and in the tongue area. The potential for PEG-PBLG nanoparticles to outperform other gene carriers in the future is due to their enhanced gene-transfer efficiency and DNA preservation. In a study conducted by Wang *et al*. (2008),[54] it was shown that the HSV-TK/GCV suicide-gene system had an effective anticancer effect on OSCC.

Significance of Nanoparticle Size

Different sized and shaped nanostructured materials connect with cells in diverse ways. The majority of research on the impact of nanomaterial size has used spherical size. The lack of standard techniques to assess size makes determining how nanoparticle size affects interactions with cells a special problem. There are numerous methods for determining

nanoparticle size, each of which has inherent drawbacks. Nanoparticles may be studied in a controlled environment by suspending and quantifying them in the same solvent or medium that will be used in the biological experiment.[55] It was only very lately that the surface area toxicity of AuNP was found, casting doubt on their once innocent reputation. Worryingly, nothing is known about the effects of AuNP on cellular physiology, although their safety has been widely assumed. Researchers have shown that NP ranging in size from 1 to 100 nm may change processes essential for basic biological functions, including as active and passive cell death. Most research has identified the tiniest nanoparticles with sizes below 2 nm as harmful to cells. Nanoparticles can actively mediate biological effects and therefore no longer be considered only carriers for biomedical applications.[56,57]

When a nanomaterial's diameter is bigger than 6 nm, the kidneys cannot remove it unless it is made of substances that can break down, like lipids, hydrogels and polymers. Over 200 nm-size nanoparticles build up in the spleen and liver, where mononuclear phagocyte system (MPS) cells break them down.[58] When injected into the blood, the majority of nanomaterials are ingested by the MPS's phagocytic cells within seconds or hours. Polyethylene glycol (PEG) coatings on nanoparticles may slow or stop their rapid clearance. All nanomaterials, regardless of charge density, have their blood half-lives greatly extended by PEG because it prevents opsonization. Extending PEG causes the protective barrier to thicken, which in turn extends the half-life of gold nanoparticles in the circulation. Make these long "stealth" nanoparticles, and they'll stick to the target tissue better. "In addition to PEGylation, a nanoparticle's size, shape, and surface chemistry can affect blood split. As an example, rod-shaped micelles have a circulation lifespan that is ten times longer than spherical micelles. A nanoparticle's pharmacokinetics and biodistribution after intravenous delivery are heavily influenced by its size, as the inter endothelial pores that line the blood arteries vary in size. The rapid elimination of nanoparticles smaller than 6 nm is attributed to their ability to be excreted by the kidneys.[59,60] The process of tumor penetration into the biological cell is always passive, allowing the particle to pass *via* the extremely permeable tumor vasculature and diffuse throughout the tumor interstitial space. The addition of targeted ligands makes the particles much larger and more biologically reactive, making transport over these barriers even more difficult. The nanoparticle's size and shape constantly influence the treatment's efficacy and the drug's ability to enter the cell. Coating abraxane with the lyp-1 or irGD peptide improved drug penetration.[61-65]

CONCLUSION

This nanoscale version of nanoparticle will help in transporting the drug of interest and genes to the cellular parts. Nanoparticles can carry the medicine or drug up to intra- and intercellular components, which can interact and modify according to our interests. In the developing discipline of nanomedicine, materials with nanoscale dimensions are used for therapeutic and disease-diagnosis purposes. One of the biggest obstacles to treating many illnesses is getting therapeutic chemicals to specific locations in living organisms. Targeted distribution using metal nanoparticles is one method that has recently grown in popularity. Biocompatible magnetic nanoparticles are connected to medicinal compounds using these technologies, which concentrate externally generated magnetic fields on specific *in-vivo* targets. Improved delivery to the target place is the outcome of the particle complex being caught by the fields. One example is the development of nanotechnology-based methods and materials for cancer cell identification and elimination. There is a lot of promise and recent success in combining nanotechnology with pharmaceutical research for practical applications. Many different types of nanoparticles, both organic and inorganic, as well as metal nanoparticles including micelles, dendrimers, carbon nanotubes, solid lipid nanoparticles (SLNs), and liposomes, are used in controlled and targeted drug delivery systems. Recently, we have learned more about the ways in which nanoparticles interact with living things. Nevertheless, many questions, such the results of particle immunomodulation, remain unanswered. To understand nanoparticles' unique interaction and physicochemical properties, we need more in-depth studies and a better grasp of mechanistic investigations. An overview of the fundamental link between cells (the biological system) and the drug delivery via nanoparticles is given in this publication. Traditional medications may have their therapeutic and physiological effects amplified via the use of drug delivery methods that use nanocarriers. Nanocarriers may shield drug molecules from degradation, allow for regulated release, and target specific drug molecules. Due to their diminutive size, nanocarriers may traverse the blood-brain barrier (BBB) and carry out molecular-level functions. Compared to traditional medication formulations, nanocarrier-drug conjugates provide superior efficacy and selectivity. By increasing medicine concentrations at targeted locations, they may reduce toxicity and other negative side effects in healthy tissues.

AuNPs or gold nanoparticles are potent radio-sensitizers used in cancer treatment and drug delivery in medicine. Image-guided nanoparticle-enhanced radiation has potential uses in biomedicine and cancer treatment where AuNPs may act as a contrast agent and dosage enhancer. The latest research included accessing a membrane-bound compartment in HeLa cells using a cell penetrating peptide and Au NP coated with mycobacterium. The linking agent couples AuNPs with peptides. A study demonstrates that surface functionalization affects the uptake of AuNPs by cells depends on its molecular weight, ligand, and graft density which indirectly acts on cellular absorption. This knowledge is crucial for scientists in designing nanoparticles with defined pharmacokinetics and pharmacologic performance for improved cellular absorption and internal transport. More research is required to translate nanotechnology concepts into real-world applications and to determine the appropriate medicine concentrations and distribution from these processes for the treatment of various tumors with various cellular and molecular pathways.

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