A REVIEW OF NANOPARTICLE DRUG DELIVERY SYSTEM

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ABSTRACT:

In the last four decades, nanotechnology has gained momentum with no sign of slowingdown. The application of inventions or products from nanotechnology has revolutionised all aspectsof everyday life ranging from medical applications to its impact on the food industry. Nanoparticleshave made it possible to significantly extend the shelf lives of food product, improve intracellulardelivery of hydrophobic drugs and improve the efficacy of specific therapeutics such as anticanceragents. As a consequence, nanotechnology has not only impacted the global standard of living but hasalso impacted the global economy. In this review, the characteristics of nanoparticles that confers themwith suitable and potentially toxic biological effects, as well as their applications in different biologicalfields and nanoparticle-based drugs and delivery systems in biomedicine including nano-based drugscurrently approved by the U.S. Food and Drug Administration (FDA) are discussed. The possibleconsequence of continuous exposure to nanoparticles due to the increased use of nanotechnology and possible solution is also highlighted.

KEYWOREDS-*Target drug delivery, Nanocarriers, Pharmacokinetics, Pharmacodynamics, Nanomedicine, Smart drug delivery*

INTRODUCTION

There are e advent of nanotechnology has revolutionized various fields of science, with medicine being one of the primary beneficiaries. Nanoparticle-based drug delivery systems have emerged as a transformative approach in targeted therapy, offering unique solutions to challenges in traditional drug delivery methods. These systems, typically ranging from 1 to 100 nanometers in size, allow for precise control over the pharmacokinetics and biodistribution of therapeutic agents.

Nanoparticles can be engineered to improve the solubility, stability, and bioavailability of drugs, thereby enhancing therapeutic efficacy while minimizing systemic side effects. Their ability to be functionalized with targeting ligands further enables them to selectively accumulate in diseased tissues, such as tumors or inflamed regions, reducing off-target toxicity. Additionally, nanoparticles can protect encapsulated drugs from premature degradation or clearance, enabling prolonged circulation times.

The versatility of nanoparticles extends beyond drug delivery; they also serve as platforms for combination therapies, diagnostic imaging, and even theranostics – a combination of therapy and diagnostics. Materials commonly used in nanoparticle construction, such as lipids, polymers, metals, and proteins, each offer unique properties, allowing for a broad spectrum of applications in oncology, infectious diseases, cardiovascular conditions, and neurodegenerative disorders.

Despite the promising advancements, challenges such as biocompatibility, potential toxicity, large-scale manufacturing, and regulatory hurdles remain. This review aims to provide a comprehensive overview of the current landscape of nanoparticle drug delivery systems, highlighting recent advancements, challenges, and future directions in this rapidly evolving field.

TYPES OF NANOPARTICLES

The classes of nanoparticles listed below are all very general and multi-functional; however, some of their basic

properties and current known uses in nanomedicine are described here.

1) Solid lipid nanoparticles (SLNs)

2) Liposomes

3) Nanostructured lipid carriers (NLC)

4) Fullerenes

5) Nanoshells

6) Quantum dots (QD)

(1)Solid lipid nanoparticles

SLNs mainly comprise lipids that are in solid phase at the room temperature and surfactants for emulsification, the mean diameters of which range from 50 nm to 1000 nm for colloid drug delivery applications SLNs offer unique properties such as small size, large surface area, high drug loading, the interaction of phases at the interfaces, and are attractive for their potential to improve. Typical methods of preparing SLNs include spray drying high shear mixing ultra-sonication and high pressure homogenization (HPH) Solid lipids utilized in SLN formulations include fatty acids (e.g. palmitic acid, decanoic acid, and behenic acid), triglycerides (e.g. trilaurin, trimyristin, and tripalmitin), steroids (e.g. cholesterol), partial glycerides (e.g. glyceryl monostearate and gylceryl behenate) and waxes (e.g. cetyl palmitate). Several types of surfactants are commonly used as emulsifiers to stabilize lipid, including soybean lecithin, phosphatidylcholine, poloxamer 188, sodium cholate, and sodium glycocholate Advantages of these solid lipid nanoparticles (SLN) are the use of physiological lipids, the avoidance of organic solvents in the preparation process, and a wide potential application spectrum (dermal, oral, intravenous).

(2)Liposomes

Liposomes are vesicular structures with an aqueous core surrounded by a hydrophobic lipid bilayer, created by the extrusion of phospholipids. Phospholipids are GRAS (generally recognized as safe) ingredients, therefore minimizing the potential for adverse effects. Solutes, such as drugs, in the core cannot pass through the hydrophobic bilayer however hydrophobic molecules can be absorbed into the bilayer, enabling the liposome to carry both hydrophilic and hydrophobic molecules.The lipid bilayer of liposomes can fuse with other bilayers such as the cell membrane, which promotes release of its contents, making them useful for drug delivery and cosmetic delivery applications. Liposomes that have vesicles in the range of nanometers are also called nanoliposomes. Liposomes canvary in size, from 15 nm up to several lm and can have either a single layer (unilamellar) or multiple phospholipid bilayer membranes

(multilamellar) structure. Unilamellar vesicles (ULVs) can be further classified into small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) depending on their size rangeStudies included in this review involved adult patients diagnosed with pancreatic cancer, irrespective of stage or treatment history. Data from clinical trials, retrospective studies, and meta-analyses were included to provide a comprehensive overview.

(3)Nonstructured lipid carriers

Nanostructured Lipid Carriers are produced from blend of solid and liquid lipids, but particles are in solid state at body temperature. Lipids are versatile molecules that may form differently structured solid matrices, such as the nanostructured lipid carriers (NLC) and the lipid drug conjugate nanoparticles (LDC) that have been created to improve drug loading capacity. The NLC production is based on solidified emulsion (dispersed phase) technologies. NLC can present an insufficient loading capacity due to drug expulsion after polymorphic transition during storage, particularly if the lipid matrix consists of similar molecules. Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. In some cases it might be desirable to have a controlled fast release going beyond diffusion and degradation. Ideally this release should be triggered by an impulse when the particles are administered. NLCs accommodate the drug because of their highly unordered lipid structures.

A desired burst drug release can be initiated by applying the trigger impulse to the matrix to convert in a more ordered structure. NLCs of certain structures can be triggered this way. NLCs can generally be applied where solid nanoparticles possess advantages for the delivery of drugs

(4)Fullerenes

A fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid, or tube. Spherical fullerenes are also called buck balls, and cylindrical ones are called carbon nanotubes or buck tubes. Fullerenes are similar in structure to the graphite, which is composed of stacked grapheme sheets of linked hexagonal rings, additionally they may also contain pentagonal (or sometimes heptagonal) rings to give potentially porous molecules. Buckyballclusters or buck balls composed of less than 300 carbon atoms are commonly known as endohedral fullerenes and include the most common fullerene, buckminsterfullerene, C60.

(5)Nanoshells

Nanoshells are also notorious as core-shells, nanoshells are spherical cores of a particular compound (concentric particles) surrounded by a shell or outer coating of thin layer of another material, which is a few 1–20 nm nanometers thick Nanoshell particles are highly functional materials show modified and improved properties than their single component counterparts or nanoparticles of the same size. Their properties can be modified by changing either the constituting materials or core-to-shell ratio Nanoshell materials can be synthesized from semiconductors (dielectric materials such as silica and polystyrene), metals and insulators.

Usually dielectric materials such as silica and polystyrene are commonly used as core because they are highly stable

(6)Quantum dots (QD)

The quantum dots are semiconductor nanocrystals and core shell nanocrystals containing interface between different semiconductor materials. The size of quantum dots can be continuously tuned from 2 to 10 nm, which, after polymer encapsulation, generally increases to 5–20 nm in diameter. Particles smaller than 5 nm are quickly cleared by renal filtration. Semiconductor nanocrystals have unique and fascinating optical properties; become an indispensable tool in biomedical research, especially for multiplexed, quantitative and long-term fluorescence imaging and detection. QD core can serve as the structural scaffold, and the imaging contrast agent and small molecule hydrophobic drugs can be embedded between the inorganic core and the amphiphilic polymer coating layer. Hydrophilic therapeutic agents including small interfering RNA (siRNA) and antisense oligodeoxynucleotide (ODN)) and targeting biomolecules such as antibodies, peptides and aptamers can be immobilized onto the hydrophilic side of the amphiphilic polymer via either covalent or non-covalent bonds. This fully integrated nanostructure may behave like magic bullets that will not only identify, but bind to diseased cells and treat it

Mechanisms of Drug Delivery Using Nanoparticles

Nanoparticles can enhance drug delivery through various mechanisms that improve targeting, absorption, and release of therapeutic agents. Here are the key mechanisms by which nanoparticles deliver drugs:

1. Passive Targeting

Enhanced Permeability and Retention (EPR) Effect:

Tumors and inflamed tissues often have leaky vasculature and poor lymphatic drainage. Nanoparticles (NPs) can exploit these features to accumulate passively in these areas.

This is known as the *EPR effect*, where nanoparticles preferentially accumulate in tumor tissues due to their small size (10-200 nm), which helps them pass through abnormal blood vessels more easily than normal cells.

Example: Liposomal doxorubicin (Doxil) uses this passive mechanism for tumor targeting in cancer therapy.

2. Active Targeting

Ligand-Receptor Binding Active targeting involves modifying the surface of nanoparticles with ligands (such as antibodies, peptides, or small molecules) that bind specifically to receptors on target cells. By recognizing specific receptors that are overexpressed on diseased cells (e.g., cancer cells), the nanoparticles can deliver the drug more precisely to the desired site, reducing side effects on healthy cells.

Example: Nanoparticles functionalized with folic acid target cancer cells overexpressing folate receptors.

3. Stimuli-Responsive Systems

Nanoparticles can be designed to release their drug cargo in response to external stimuli like temperature, light, or magnetic fields

Example : Thermo-sensitive nanoparticles release drugs at higher temperatures, which can be useful for localized hyperthermia treatments for cancer.

Nanoparticles can also be designed to respond to internal physiological triggers, such as:

pH-Sensitive Nanoparticles: Tumors or inflammatory sites often have a lower pH (acidic environment). Nanoparticles engineered to be pH-sensitive can release their drug load when exposed to this acidic environment

Enzyme-Sensitive Nanoparticles : Some nanoparticles are designed to degrade or release their contents when exposed to certain enzymes that are overexpressed in diseased tissues (e.g., proteases in cancer cells)

Example: pH-sensitive micelles that disassemble in acidic environments to release chemotherapy drugs in tumors.

4. Controlled Releases

Sustained Drug Release:

Nanoparticles can be engineered for slow, controlled release of drugs over a prolonged period. This helps maintain therapeutic drug levels in the bloodstream and tissues for longer durations, improving treatment efficacy and reducing the need for frequent dosing

Example: Polymeric nanoparticles can encapsulate drugs and degrade slowly in the body, providing sustained drug release for diseases like diabetes or chronic infections.

Certain nanoparticle systems may allow for a rapid release of the drug initially, followed by a slower, sustained release.

5. Cellular Uptake and Endocytosis

Receptor-Mediated Endocytosis:

After binding to the cell surface receptor, nanoparticles are taken up by cells through endocytosis (cellular engulfing). The nanoparticles enter the cell inside vesicles (endosomes).

- Once inside, nanoparticles can escape from the endosomes to release the drug into the cytoplasm, allowing the drug to act on intracellular targets.

- *Example*: Polyethylene glycol (PEG)-coated nanoparticles enhance circulation time and are internalized by cancer cells through receptor-mediated endocytosis.

6. Transcytosis

Crossing Biological Barriers

One of the major challenges in drug delivery is crossing biological barriers like the blood-brain barrier (BBB) or the gastrointestinal (GI) tract.

Nanoparticles can be engineered to undergo *transcytosis*, where they are taken up by endothelial cells and transported across the cells to reach the other side (e.g., from the bloodstream into the brain).

Example: Lipid nanoparticles coated with specific peptides are designed to cross the BBB for the treatment of neurological disorders.

7. Nanoparticle-Mediated Gene Therapy

Gene Delivery:

Nanoparticles can be used to deliver genetic material (like DNA, RNA, or siRNA) into cells, which can modify gene expression for therapeutic purposes. This is a powerful tool for treating genetic disorders or for silencing harmful genes in cancer.

Example: Lipid nanoparticles used in mRNA vaccines (such as COVID-19 vaccines) deliver genetic material into cells to induce an immune response.

8.Magnetic Targeting

Magnetic Nanoparticles :

In magnetic drug targeting, magnetic nanoparticles (like iron oxide) are loaded with drugs and guided to the target site using an external magnetic field.

This method enhances drug accumulation in specific tissues and organs, allowing for more localized and efficient therapy.

Example: Magnetic hyperthermia in cancer therapy, where magnetic nanoparticles are directed to the tumor site and heated by an external magnetic field to destroy cancer cells.

Methods of Preparation Of Nanoparticles

Nanoparticles can be prepared from a variety of materials such as proteins, polysaccharides and synthetic polymers.

The selection of matrix materials is dependent on various factors which include:

a. Size of nanoparticle required

b. Inherent properties of the drug, e.g., aqueous solubility and stability

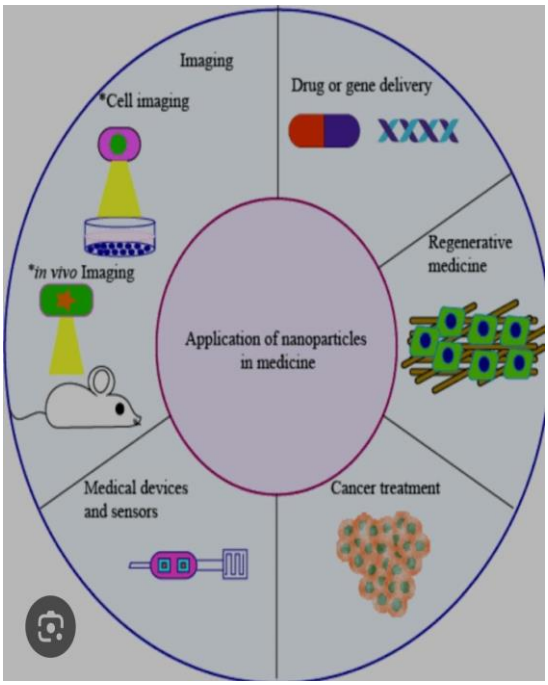
c. Surface characteristics such as charge and permeability

d. Degree of biodegradation, biocompatibility and toxicity

e. Drug release profile desired

f. Antigenicity of the final product.

Applications of Nanoparticles:



Tumor targeting using Nanoparticulate delivery system

The rational of using nanoparticles for tumor targeting is based on

(1) Nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced

permeability and retention effect or active nanoparticles.

(2) Nanoparticles will reduce the drug exposure of health tissues by limiting drug distribution to target organ.An experiment demonstrated in mice treated with doxorubicin incorporated into poly (isohexylcynoacrylate) nanospheres that higher concentration of doxorubicin manifested in the liver, spleen and lungs than in mice treated with free doxorubicin.

Nanoparticles for Gene delivery

Polynucleotide vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both humoral and cell-mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system.

Nanotechnology in Medicine Application:

Anti-Microbial Techniques

One of the earliest nanomedicine applications was the use of nanocrystalline silver, which is as an antimicrobial agent for the treatment of wounds, A nanoparticle cream has beenshown to fight staph infections. The nanoparticles contain nitric oxide gas, which is known to kill bacteria. Studies on mice have shown that using the nanoparticle cream to release nitric oxide gas at the site of staph abscesses significantly reduced the infection. Burn dressing that is coated with nanocapsules containing antibotics. If an infection starts the harmful bacteria in the wound causes the nanocapsules to break open, releasing the antibotics. This allows much quicker treatment of an infection and reduces.

Nanotechnology in Medicine Application: Cell Repair

Nanorobots could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes. Read about design analysis for one such cell repair nanorobot in this article.

The Ideal Gene Delivery Vector: Chromallocytes, CellRepair Nanorobots for Chromosome Repair Therapy.Nanoparticles for drug delivery into the brain

The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. Relatively impermeable endothelial cells characterize the BBB with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of water-soluble molecules from the blood circulation into the CNS, and can also reduce the brain concentration of lipid-soluble molecules by the function of enzymes or efflux pumps. Consequently, the BBB only permits selective transport of molecules that are essential for brain function. Strategies for nanoparticle targeting to the brain rely on the presence of and nanoparticle interaction with specific receptor-mediated transport systems in the BBB.

ADVANTAGE OF NANO PARTICLES

The advantages of using nanoparticles as a drug delivery system include the following:

 Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.

 They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.

 Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.

 Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.

Disadvantages of Nanoparticles

Disadvantages of Nanoparticle Nanoparticle drug delivery systems (NDDS) hold promise in improving the effectiveness and targeting of drugs, but there are several disadvantages that need to be addressed in research and clinical use. Here's a review of the key disadvantages:

1. Toxicity and Biocompatibility

- Some nanoparticles (NPs), especially those made from metals (e.g., gold, silver), can induce toxicity at both cellular and systemic levels. They may cause oxidative stress, inflammation, and cellular damage.

- The long-term accumulation of non-biodegradable NPs can pose serious health risks, including organ damage.

2. Production Challenges

- The manufacturing of NPs with consistent size, shape, and surface characteristics is difficult and can lead to batch variability. Scaling up the production of nanoparticles for commercial use remains a challenge.

- The stability of nanoparticles during storage and their behavior in physiological conditions may lead to aggregation, reducing effectiveness.

3. High Cost

- Producing NPs with precise characteristics, including surface modifications for targeting, is expensive. The cost of raw materials, equipment, and quality control in production contributes to the overall high cost of NDDS.

- For large-scale clinical use, the economic burden of NDDS needs to be weighed against its potential benefits.

4. Complex Regulatory Approval

- The regulatory landscape for nanoparticle-based drugs is still evolving. Gaining regulatory approval for NDDS is more complex due to the need for detailed studies on toxicity, safety, and long-term effects.

- Different regulatory bodies may have different standards for nanomedicine, creating challenges for global market approval.

5. Rapid Clearance by the Immune System

- Nanoparticles can be rapidly cleared by the mononuclear phagocyte system (MPS), reducing their circulation time and effectiveness. Although PEGylation and other surface modifications can reduce immune recognition, these modifications are not foolproof.

- The body's immune response to NPs may vary across patients, leading to inconsistent therapeutic outcomes.

6. Challenges in Targeting and Bio-distribution

- Despite advancements in targeting techniques, ensuring that nanoparticles reach specific tissues or cells without off-target effects remains a challenge.

- The heterogeneity of tumors and other diseases can complicate the bio-distribution of NPs, limiting their therapeutic efficacy.

7.Environmental Impact

- Nanoparticles, especially those that are not biodegradable, may pose environmental hazards. Once released into the environment (e.g., during manufacturing or disposal), NPs can contaminate water and soil, potentially causing ecological harm.

8. Unclear Long-term Effects:

- The long-term effects of NDDS on human health are not yet fully understood. There is concern over the potential for chronic toxicity, unforeseen immune responses, and other adverse effects after prolonged exposure.

Conclusion

Nanoparticles represent a promising drug delivery system of controlled and targeted release. The emergence of nanotechnology is likely to have a significant impact on drug delivery sector, affecting just about every route of administration from oral to injectable. In addition, the payoff for doctors and patients should be lower drug toxicity, reduced cost of treatments, improved bioavailability, and an extension of the economic life of proprietary drugs. The foregoing show that nano particulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. The core of this system can enclose variety of drugs, enzymes, genes and is characterized by a long due to the hydrophilic shell which prevents recognition by the reticular-endothelial system To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. Further advances are needed in order to turn the concept of nanoparticles technology into a realistic practical application as the next generation of drug delivery system. This would allow earlier and more personalized diagnosis and therapy, improving the effectiveness of drug treatments and reducing side effects. In addition, nanoparticles are a promising platform technology for the synthesis of molecular-specific contrast agents.

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