International Journal of General Practice Nursing, 2024, Volume 2, Issue 2
https://ojs.bbwpublisher.com/index.php/IJGPN
ISSN Online: 2981-9423
ISSN Print: 2981-9415

Application of Nanotechnology for Targeted Drug Delivery and Nontoxicity

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Abstract: Nanotechnology has applications in various fields of medicine. The health and biomedical fields can apply nanotechnology to treatment and drug delivery, enabling the targeted and controlled delivery of drugs and therapeutic compounds. Normally, the body quickly metabolizes drugs upon their entry, potentially affecting their efficiency. Additionally, drugs are often unable to specifically target cells, leading to harmful effects on healthy cells. Nanotechnology is currently being used to address these issues. Nanoparticles, which are tiny particles made up of either synthetic or semi-synthetic polymers, have introduced targeted drug delivery by allowing accurate and regulated secretion of therapeutic agents at specific activity sites. Their efficiency depends on features such as size, shape, surface, charge, and loading techniques. By utilizing their distinct attributes, nanoparticles can overcome biological barriers, improving the bioavailability of drugs and decreasing systemic toxicity. However, excessive use of nanotechnology also raises concerns about its potential nanotoxicity. The interaction between biological systems and nanoparticles can lead to hazardous effects such as genotoxicity, oxidative stress, inflammation, and neurotoxicity. Thus, it is important to examine the nanotoxicity of nanoparticles and develop various ways to diminish their toxic effects. This review aims to summarize the use of nanoparticles for drug delivery to specific sites, as well as their nanotoxicity.

Keywords: Drugs; Nanoparticles; Nanotoxicity; Barriers; Oxidative stress

Online publication: July 3, 2024

1. Introduction

The primary goal of the pharmaceutical industry is to develop therapeutic agents that can specifically target sites in the human body. Various drugs used to cure specific diseases have both beneficial and detrimental

effects. Many drugs exhibit inferior physicochemical characteristics, leading to inappropriate solubility and biodistribution, which affects their interaction with the targeted site. A carrier is the best strategy for delivering drugs to the affected site. Current studies focus on the use of nanotechnology to achieve vital improvements in disease therapy [1]. Different types of biodegradable components, such as lipids, metals, and synthetic or natural polymers, combine to form nanoparticles suitable for drug delivery [2]. Nanoparticles are usually less than 100 nm in dimension [3].

The term "nano" originates from the Greek word meaning "billionth." Cells utilize nanoparticles more effectively than large-sized micromolecules, making them an efficient drug delivery system [4]. To achieve this goal, drugs are attached to the surface of nanoparticles. An efficient drug targeting system must be able to regulate the specific drug's fate at the affected site. Properties like quantum features, the ability to bind and convey specific compounds like proteins or drugs, and the ratio of surface area to mass, which must be greater than that of other particles, determine the use of nanoparticles in drug delivery systems [5]. The structure and formation of different nanoparticles may vary. Instead of using engineered particles, we can formulate drugs at the microscopic level to use them as carriers [5].

Understanding various drug barriers, such as the therapeutic medication's strength inside the living cell, is also important [6]. Decreased drug efficiency may be due to drug uncertainty within the cell, a lack of targeting features of carrier molecules, changes in the genetic composition of various receptors present on the cell surface, and alterations in the signaling pathway with disease advancement. Exaggerated DNA methylation in cancer development can lead to the blockage of various agents, such as doxorubicin. To improve the carrier's efficiency, it is important to acknowledge the processes of uptake, preservation, and defense against deterioration inside the cell. This review paper aims to discuss the role of nanoparticles in efficient drug delivery.

2. Nanoparticles as carriers for delivering medication

Nanoparticles primarily evolved nearly 35 years ago. They were first developed as carriers for vaccines and chemotherapeutic agents [7]. Nanoparticles vary in dimension from 10 to 1000 nm and are stable, solid particles made up of biodegradable plastics [8]. Therapeutic drugs can be incorporated into the matrix of particles, adsorbed onto the surface of the particles, or trapped within the polymer. Most research focusing on the use of nanoparticles as a drug delivery system is in the area of oncology [9]. Nanoparticles can concentrate in tumor masses, sites of inflammation, and sites of infection, with the capability of improving retention and permeability [10].

It is also possible to manufacture various distinct drugs and preferentially transfer the specific drug to neoplastic tissue. A drug against cancer can be embedded in a biodegradable colloidal shell that is also surrounded by an antiangiogenesis drug in a lipid layer [11]. When this nanoparticle is delivered intravenously, the cancer cells absorb the nanoparticle. The antiangiogenesis drug is first released to suppress the intermediaries for the production of blood vessels. After this, the anticancer drug is released, efficiently killing cancer cells. All of this can be forged in a nanocell, which is an efficient carrier of the anticancer drug to the neoplastic site [12].

Figure 1 illustrates the untargeted delivery of drugs, where drugs also affect normal cells instead of targeted cells, altering the activity of normal cells. However, nanoparticles in targeted drug delivery contain a specific ligand for the receptor on the targeted cell, thereby not affecting normal cells.

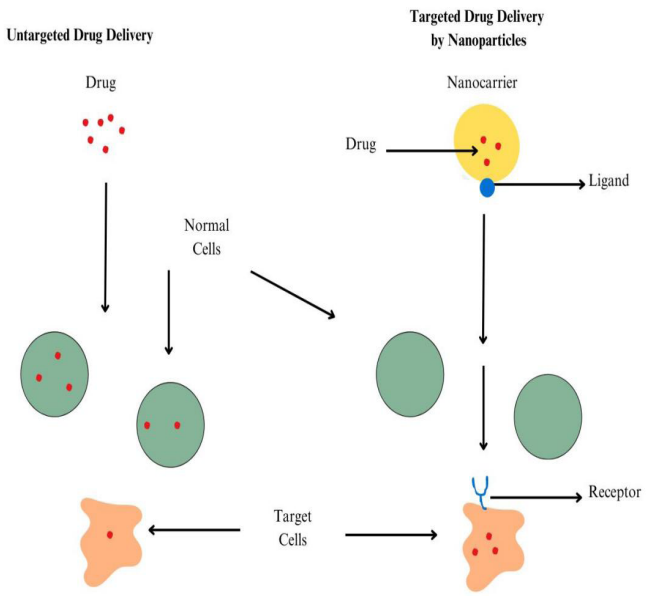

Figure 1. Comparison of drug delivery methods

3. Different types of nanoparticles used in drug delivery system

The different types of nanoparticles that can be used in drug delivery are listed in **Table 1** [13].

Table 1. List of different types of nanoparticles with their composition and applications

No.	Types of nanoparticles	Composition	Applications
1	Solid lipid nanoparticles	Melted lipid diffused in aqueous surfactant	Less toxic, firm colloidal carrier as a substitute for polymer
2	Polymeric nanoparticles	Decomposable polymer	Regulated and targeted delivery of drugs
3	Polymeric micelles	Amphiphilic block copolymer	Regulated and organized delivery of hydrophobic drugs
4	Magnetic nanoparticles	Magnetite Fe_2O_3, maghemite covered with dextran	Drug targeting and diagnostics in medication
5	Carbon nanoparticles	Metals, semiconductors, or carbon	Regulated transfer of drugs to DNA and genes
6	Liposomes	Phospholipid vesicles	Regulated delivery of drugs
7	Nanoshells	Dielectric core and metal shell	Targeted drug delivery to tumors
8	Ceramic nanoparticles	Silica, alumina, titania	Delivery of drugs and biomolecules
9	Nanopores	Aerogel created by sol-gel chemistry	Carriers for focused drug release
10	Nanowires	Silicon, cobalt, gold, or copper-based nanowires	Carries electrons in nanoelectronics

4. Cell-based targets

For effective drug delivery, it is essential to target not only specific cells or organs but also to ensure that nanoparticles function properly within the cell [14]. Nanoparticles typically end up in lysosomes or endosomes inside the cell, where they are degraded [15]. For the drug to be effective, it must be released from the nanoparticle into the cell's cytoplasm. Although nanoparticles smaller than 20 nm can be taken up by cells

without any endocytic mechanism, their fate can also be influenced by characteristics such as surface charge. Nanoparticles functionalized with PEG show more effective incorporation into endosomes and the cytosol [16].

Through endocytosis, nanoparticles are internalized by cells. A change in the surface charge of these nanoparticles from negative to positive triggers the release of the integrated drug into the cytoplasm. Modifying the surface of nanoparticles offers various applications, including uptake, intracellular transport, and cellular targeting. Specific immunologically directed targeting can be achieved by binding specific proteins, like antibodies, to the surface of the nanoparticle [17].

Figure 2 shows how drugs on nanoparticles enter cells through invagination, forming endosomes. The endosomes then deliver the drug and remain in the cell.

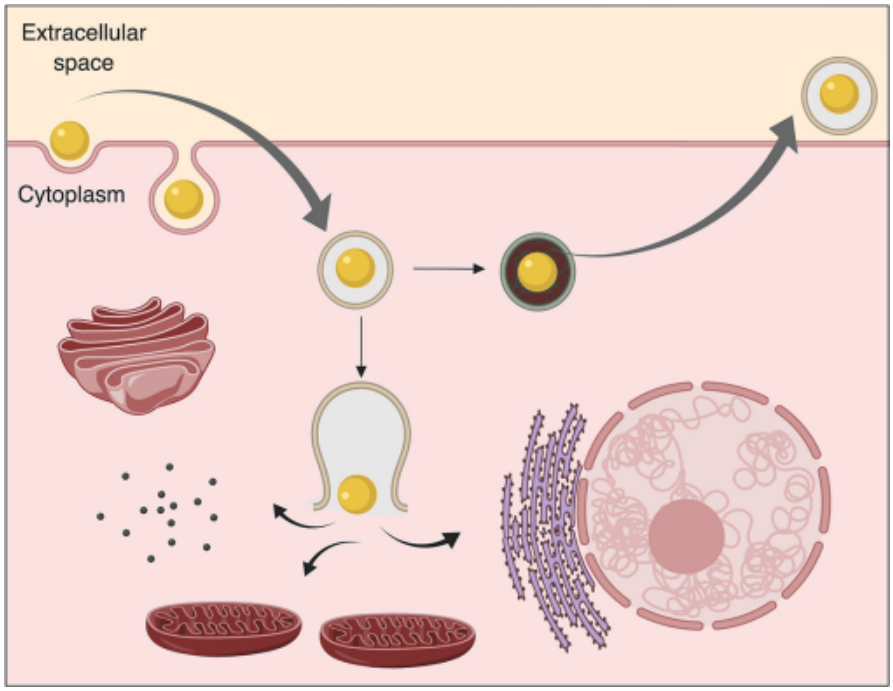

Figure 2. Illustration of the process by which drugs on nanoparticles enter cells through invagination, form endosomes, and subsequently release the drug within the cell.

5. Targeted drug delivery to the brain by nanoparticles

The brain is a challenging organ for drug delivery [18]. Firstly, the possibility of degenerative diseases increases in the elderly population. Secondly, the blood-brain barrier (BBB) acts as a guardian against exogenous substances in the body. Blood-brain barrier transporters help transport most drugs, even those small in size, across the BBB [19]. Researchers have suggested using nanoparticles to transport drugs across the BBB. For the targeted delivery of drugs to the brain using nanoparticles, the physical association of the specific drug with the nanoparticle is important [20]. Examining different nanoparticles based on their surface properties revealed that neutral nanoparticles and those with low anionic charges do not affect the BBB; on the other hand, nanoparticles with high anionic and cationic charges are toxic to the BBB. As a result, the nanoparticle's surface charge can be used to determine the toxicity and distribution profiles in the brain [21].

By coating nanoparticles with a polysorbate surfactant, they can be transported across the BBB effectively [22]. Endocytosis by the LDL receptor of endothelial cells, following the uptake of lipoproteins from the blood plasma, facilitates this transport process. Identification and interaction with the receptors of the endothelial cells in the brain are critical for drug uptake. P-glycoprotein, an ATP-dependent transporter, plays a vital role in the delivery

of drugs into the brain, acting as a gatekeeper that allows the transport of specific drugs [23]. Other ways for drugs to reach the brain, bypassing the BBB, include movement across the olfactory nerve (**Figure 3**) [24]. The olfactory nerve has demonstrated the transfer of nanoparticles, like manganese oxide, to the brain. However, both the BBB route and the olfactory nerve route only account for 2% of nanoparticle uptake, highlighting the need for further improvements to ensure efficient drug delivery to the brain [25].

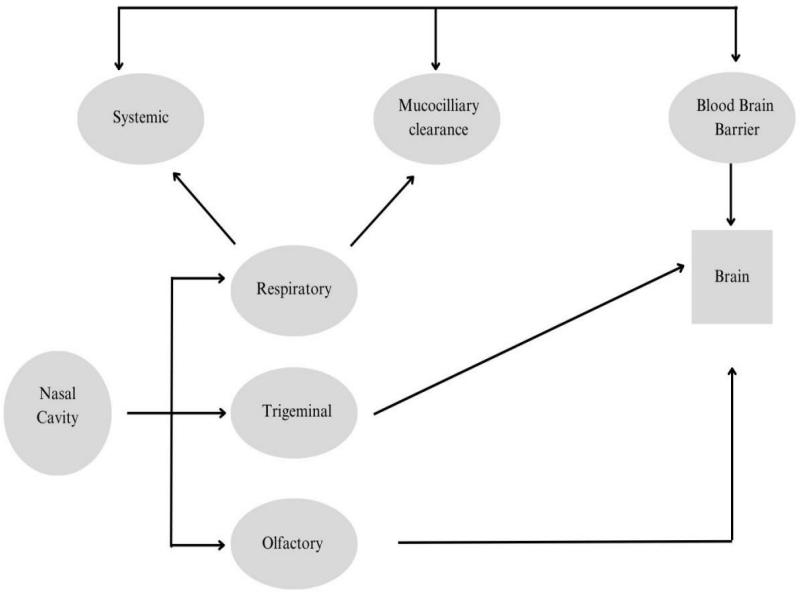

Figure 3. Schematic diagram representing the passage of drug delivery from the nasal cavity to the brain

6. Targeted drug delivery for angiogenesis by nanoparticles

Extensive tumor growth occurs due to angiogenesis [26]. Therefore, inhibiting angiogenesis is crucial for controlling tumor cell growth. Angiogenesis is regulated by various intermediates, with current studies highlighting the vital roles of Vascular Endothelial Growth Factors (VEGFs) and integrin αvβ3. Thus, targeting VEGF and αvβ3 is an effective strategy for treating various types of tumors. Recently, nanoparticles coated with peptides that specifically attach to VEGF and αvβ3 integrin receptors have been used [27]. These peptides, consisting of Arg-Gly-Asp (RGD), specifically attach to integrin and suppress tumor growth. After hydrophobic modification, glycol chitosan can create nanotubes [28]. These nanotubes are filled with FITC-GRGDS, which can be used for observing or targeting angiogenic tissue [29]. Rosette nanotubes (RNT) are a type of nanotube that is water-soluble after synthesis [30]. One of the primary characteristics of rosette nanotubes is their capability to accept a wide range of functional groups at the G/C motifs, presenting functional versatility for specific biological or medical applications. Thus, these rosette nanotubes can be modified to target a wide range of therapeutic molecules for cancer treatment [31].

7. Targeted drug delivery to control inflammation by nanoparticles

The ability of macrophages to swiftly eliminate foreign particles has facilitated macrophage-specific targeting using nanoparticles [32]. Macrophages secrete various inflammatory mediators that control inflammation in various diseases. Thus, macrophages are the optimal target to overcome inflammation. Even though macrophages can eradicate many microorganisms, some microbes have developed resistance. In this situation, targeted delivery of an antimicrobial agent in a nanoparticle would be the best strategy [33]. For example, polyalkylcyanoacrylate (PACA) nanoparticles can deliver antileishmanial drugs to macrophages [34]. PACAs can encapsulate a specific drug and

protect it from degradation. Macrophages absorb PACAs when they enter the body. Once inside macrophages, PACAs release the antileishmanial drug, which then exerts its therapeutic effect. Additionally, utilizing various receptors present in macrophages for therapeutic purposes would be a more effective way of controlling inflammation [35].

8. Toxicology of nanoparticles

Nanotoxicology is the study of the detrimental impact and toxicity of nanoparticles [36]. All types of nanoparticles interact with different cells, tissues, and organs in the body. Therefore, exposure to nanoparticles encourages unwanted and hazardous interactions, resulting in harmful effects and nanotoxicity [37]. The toxicity of nanoparticles is determined by their quantity and intensity. In addition to conventional parameters, various factors may impact their toxicity, such as physicochemical properties like size, surface chemistry, material composition, and shape [38]. These physicochemical properties complicate nanotoxicology evaluation. For instance, a small change in surface chemistry can result in distinct nanotoxicology, biodistribution, and disposition patterns [39]. A thorough understanding of the structure of nanoparticles is essential for accurately evaluating their toxicity [40]. Below, we describe the various detrimental impacts of nanoparticles.

8.1. Oxidative stress triggered by nanotoxicity

Most commonly, nanoparticle immersion at the cellular level causes oxidative stress [41]. Oxidative stress can be described as an imbalance between the generation of oxidants and the activity of antioxidants. Overproduction of reactive oxygen species (ROS) compared to antioxidants leads to oxidative stress. ROS caused by nanoparticles can alter genetic material, resulting in DNA strand disruption and genetic mutations [42]. Nanoparticles, either directly or indirectly, cause oxidative stress, which eventually leads to severe effects and cytotoxicity [43]. Researchers have identified that iron oxide nanoparticles, widely used as drug delivery carriers in cancer treatments, cause oxidative stress and alter iron homeostasis levels. Silver nanoparticles, commonly used for their antimicrobial activity, have also been shown to possess cytotoxic features that lead to oxidative stress. Experiments conducted on mice administered with silver nanoparticles revealed changes in gene and DNA expression in various tissues [44].

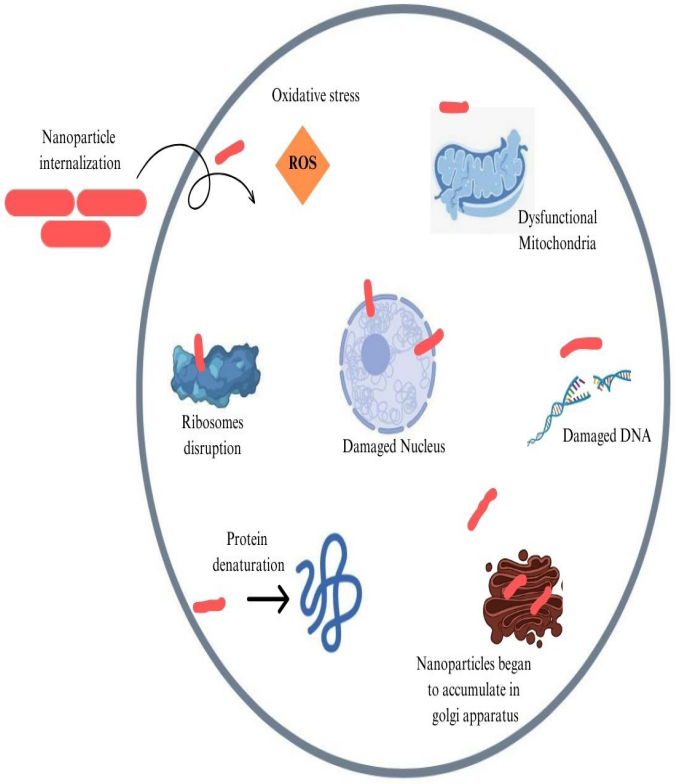

Figure 4. Effect of nanoparticles on cellular organelles

Figure 4 illustrates that nanoparticles have different effects on various organelles within the cell. For example, they damage the nucleus, disrupt its function, impair the mitochondria, degrade proteins, accumulate in the Golgi apparatus, damage DNA, interfere with ribosomes, and cause oxidative stress.

8.2. Suppression of cell cycle due to nanotoxicity

Cell division consists of two processes: mitosis, in which the nucleus divides, and interphase, which includes the G1, G2, and S phases. Researchers have discovered that nanoparticle cytotoxicity not only causes cell death but also inhibits cell propagation at any phase of the cell cycle [45]. Nanoparticles can cause apoptosis by blocking mitochondrial function, leading to the secretion of cytochrome c and activation of caspases, which trigger apoptosis [46]. Nanoparticle nanotoxicity can suppress the cell cycle by inhibiting cell signaling pathways and disrupting spindle fibers and the cytoskeleton. The interaction between cells and nanoparticles causes DNA damage. Nickel oxide nanoparticles slow down certain cell types and stages of the cell cycle [47]. For instance, these particles slow down the G0/G1 phase of the cell cycle. Similarly, CuO nanoparticles in T cells suppress the G2/M phase, while exposure to TiO_2 suppresses only the S phase [48].

8.3. Nanoparticles-induced genotoxicity

The major cause of genotoxicity induced by nanoparticles is the increased formation of reactive oxygen species and reactive nitrogen species, leading to elevated oxidative stress and subsequent oxidative damage to genetic material [49]. The excessive production of these reactive species is due to the extreme interaction of nanoparticles with target cells, resulting in adverse inflammatory reactions. Damage to genetic material occurs due to either primary or secondary toxicity [50]. Primary toxicity arises from the direct interaction of nanoparticles with DNA, while secondary toxicity occurs from the overproduction of reactive oxygen or nitrogen species by nanoparticles, leading to genetic mutations [41]. Numerous studies on nanoparticle-induced genotoxicity have reported that carbon nanotubes cause DNA abrasion in fibroblasts via oxidative stress. Similarly, high concentrations of silver nanoparticles were found to cause significant DNA damage in *Saccharomyces cerevisiae*. The genotoxicity of silver nanoparticles was also observed in various plants and microbes [51].

8.4. Nanoparticles-induced neurotoxicity

Neurotoxicity refers to the process that alters the structure, chemistry, and function of neurons in the nervous system [52]. Numerous studies have shown that neurotoxicity occurs due to oxidative stress caused by nanoparticles [53]. When nanoparticles enter the bloodstream, they can cross the blood-brain barrier and reach the brain, where they trigger oxidative stress and damage nerve cells [54]. Due to their tiny size, nanoparticles interact with various subcellular elements, interrupting normal cellular activities and altering neurotransmitter levels. Additionally, nanoparticles can activate microglial cells, leading to the secretion of inflammation-promoting cytokines and increasing neurotoxicity [55]. The specific pathway of neurotoxicity induced by nanoparticles depends on factors such as the shape and size of the nanoparticles and the duration of exposure. A list of the neurological toxicity of specific nanoparticles is provided in **Table 2**.

Table 2. List of nanoparticles with their neurotoxic effects

No.	Nanoparticles	Neurotoxic Effects
1	Carbon nanotubes	They initiate the synthesis of reactive oxygen species, escalate oxidative stress, restrain cell growth, and cause apoptosis.
2	Silver nanoparticles	They cause a decline in the antioxidant capability of antioxidative enzymes and escalate oxidative stress.
3	Titanium oxide nanoparticles	They initiate oxidative stress, cause inflammation of neurons, induce genotoxicity, imbalance neurotransmitters, and suppress signaling pathways.
4	Iron oxide nanoparticles	They cause inflammation of neurons, apoptosis, and the infiltration of immune cells.
5	Silica	They cause intellectual disruption, synapse alterations, and increase oxidative stress.
6	Organic nanoparticles	They cause oxidative stress, inflammation, and apoptosis in nerve cells.

There are various mechanisms by which nanoparticles induce nanotoxicity affecting the nervous system [56]. One general mechanism is oxidative stress, where nanoparticles can synthesize ROS, which harm neurons and affect their function. Nanoparticles can also cause brain inflammation, leading to the secretion of pro-inflammatory molecules that damage neurons. They can directly interact with neuronal proteins or membranes, disrupting their function. The presence of some nanoparticles in the nervous system can suppress neurotransmitter levels, leading to behavioral changes. Additionally, some nanoparticles serve as carriers for contaminants such as pathogens, further contributing to neurotoxicity [57].

9. Conclusion

Nanotechnology has a wide range of capabilities for drug delivery, including the potential to revolutionize the field. Soon, all routes of drug administration will benefit from the pharmaceutical advantages of nanotechnology. The delivery of implantable drugs presents numerous opportunities for the application of nanoparticle technology. While the future of nanotechnology is promising, it is essential to consider the toxicological effects of nanoparticles. We must assess the nanotoxicity of nanoparticles using oxidative stress assays, cytotoxicity assays, inflammation assays, cell-based assays, biochemical assays, and analyses of shape, size, and surface chemistry.

After identifying the mechanisms of nanotoxicity, scientists can develop approaches to mitigate the toxic effects of nanoparticles. While some research focuses on controlling the core composition of nanoparticles, most studies aim to improve the surface properties and chemistry of nanoparticles.

As medicinal innovation progresses, the use of nanoparticles for drug delivery will become more prevalent. We anticipate that nanoparticle-mediated drug delivery will enhance bioavailability and regulate secretion, thereby improving medical responses. Nanotechnology's use in diagnostics will also become increasingly significant. The primary goal of nanotechnology-acquired devices is to mimic the release of hormones, insulin, and other isolated systems using micro-electromechanical systems (MEMS). Furthermore, nanotechnology will improve drug solubility, absorption, controlled release, and reduce adverse effects.

The technique of drug delivery via nanoparticles is still evolving. The continued evolution of nanotechnology necessitates various strategies from both general and medical research to achieve sustainable innovations. Nevertheless, there is a strong probability that nanotechnology will be the next frontier of clinical research.

Author contribution

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Writing – review & editing: Muhammad Zubair, Maria Riaz, Muhammad Naeem Kiani, Ata E Zohra Fatima, Hafiz Muhammad Sultan, Aziz Ur Rehman

Disclosure statement

The authors declare no conflict of interest.

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