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Nanotechnology in Pharmacology: Advances and Applications in Drug Delivery

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Abstract

Nanotechnology has transformed pharmacology by allowing the development of more efficient drug delivery systems with fewer side effects. The present review aims to present an overview of the recent advances and applications of nanotechnology in drug delivery, highlighting its potential to improve the diagnosis and treatment of diseases. Different applications of nanoparticles and nanocarriers are analyzed for the treatment of various diseases, where technology is combined with medicine to explore advanced delivery systems and understand at the molecular level the mechanisms that govern cells. Nanotechnology has allowed the development of more efficient drug delivery systems with fewer side effects. Nanomedicine uses nanotechnology to improve drug delivery to specific organs, allowing doctors to achieve the best possible effectiveness and safety of the medications they administer. Nanoparticles are one of the most used tools in nanotechnology for the delivery of drugs and advanced treatments. These nanoparticles, due to their size, shape and surface chemistry affect all aspects of the interaction between the body and the drug.

Keywords: Blood-brain barrier; Drug delivery; Medicine; Nanoparticles; Nanotechnology; Pharmacology

Abbreviations: VEGF: Vascular Endothelial Growth Factor; PDGF: Platelet-Derived Growth Factor; FGF: Fibroblast Growth Factor; NSAID: Nonsteroidal Anti-Inflammatory Drugs; ApoE: Apolipoprotein E; PEG: Polyethylene Glycol

Introduction

Conventional treatment or therapy causes the medication to be normally distributed throughout the body without any selectivity; As a result, only a small fraction of the administered dose reaches the affected organ or tissue, again requiring higher doses, running the risk of producing undesirable side effects. A clear example in this regard are some viral and bacterial diseases whose resistance to antibiotics is becoming increasingly dangerous. The alternative to conventional therapies is nanotechnology, which refers to the manipulation of materials at the nanoscale (10-9 meters) to develop systems and technologies with various applications, including medicine. In the field of pharmacology, nanotechnology has led to the development of new drug delivery systems, such as controlled and sustained release, that can improve the effectiveness of a treatment and reduce unwanted adverse effects [1]. Additionally, nanotechnology has facilitated the creation of biocompatible nanoparticles capable of transporting pharmaceutical agents throughout the body. By transporting drugs across biological barriers [2] and directly to target tissues or cells, these nanoscale carriers can increase therapeutic bioavailability, the amount of drug reaching the systemic circulation, and the site of action [3]. As a promising new discipline, nanomedicine has potential for transformative progress through technologies such as molecularly targeted nanoparticles, which can act as personalized drug delivery vectors in response to the disease state or tissue environment. These advances exemplify how nanotechnology is revolutionizing pharmaceutical research by refining drug formulation and transport mechanisms to maximize clinical benefit with reduced harm.

Nanotechnology and Medicine

To understand the influence of nanotechnology on medicine, we look at the human organism from a molecular point of view. Any type of disease originates when there is a nonlinear thermodynamic state change or entropy in the molecular

structure of a cell, whether due to a viral or bacterial infection, degeneration, or trauma. Nanotechnology aims to rearrange atoms and put them back in their place, proposing a new revolution in medicine, by using structures and devices on a nanometric scale, with applications in the diagnosis of diseases, treatment, and prevention. - Wouldn't it be ideal for the body's cells to warn when the person is starting to get sick, long before symptoms appear? Also, manufacture devices for identification of entities of vital medical importance, as well as biological systems that may have important clinical applications. There are numerous nanotechnological drug delivery systems, from those in the research stage to consolidated products already on the market. For example, colloidal systems such as liposomes and microemulsions, which have given rise to products that improve the therapy of numerous pathologies, such as some types of cancer [4] and degenerative diseases. Also, there are virosomes; systems that combine lipids with viral proteins with adjuvant action, which allow the marketing of vaccines for influenza and hepatitis. Within colloidal systems, micelles stand out those of the polymeric type such as di-block or tri-block, which have promoted their study due to their potential use in numerous medical applications.

The importance of micelles lies in the modifications of their structural DNA, which makes them an ideal system for transporting drugs to localized areas of the diseased body, and then releasing them. These micelles, like the natural ones, act like soap bubbles, isolating their content from the outside, so they can penetrate the cancer cells without interacting with them to their core, and once there release the drug, with a maximum effect, stopping the tumor growth [5,6]. This is another alternative in conjunction with the dendrimer technique to treat diseases such as cancer, which claims hundreds of thousands of lives per year around the world, and which is expected to be applied routinely in humans within a few years. Likewise, there are very advanced developments in solid lipid nanoparticles, archaeosomes, microsomes, liposomes or nanospheres and nanocrystals; each with its differential characteristics for the treatment of chronic diseases. For example, a recent development using nanoparticles that act as a delivery vector for chemotherapy drugs for the treatment of glioblastoma can overcome the blood-brain barrier by transporting specific molecules coated with peptides that attack tumor cells, killing them specifically [7]. Under this approach, the aim is to develop new models of nanoparticles to treat other types of brain tumors.

Parallel to nanomedicine, there is nano instrumentation, nanoparticles and nano capsules, which could be effective intelligent delivery systems for an endless number of drugs and genetic therapies. Nanostructures offer new meanings for the set of images inside the human body. Nano tweezers and small surgical tools are already in use and others are in development. Nanoparticles are larger than typical molecules and similar in size to many proteins, which allow monitoring the biological impact, including, of the radiation that astronauts' bodies receive.

A method like nanoparticles are aquasomes, which have direct application in the pharmaceutical and medical field. The aquasome acts as a container that contains a drug designed to act directly on the organ that requires it, that is, by vectorization or targeting; in such a way that it remains long enough to be effective in the treatment of a certain disease. Aquasomes operate as targeted or "smart" medicine, visibly reducing the toxicity of the drug [8], since the dosage is ideal and, most importantly, it is local, increasing its effectiveness on the organ or tissue. Due to the nanometric size of aquasomes, they can contain poorly soluble drugs, including natural and artificial proteins, which can easily infiltrate through the cell membrane and play the role of a specific vector in the treatment of a disease at the molecular level. To do this, its design is based on an inorganic core covered with a polymer, whose function is to serve as a bridge with the molecule that will be transported; Vectorization or targeting to the target organ or tissue is obtained by incorporating a substance that allows the cells of the specific organ or tissue to be recognized.

Advances in drug delivery Nanotechnology has had a profound impact on the diagnosis and treatment of diseases. The development of biosensors that can detect disease biomarkers has facilitated early diagnosis and monitoring of chronic diseases [9,10]. Furthermore, nanoparticles have been used to treat diseases such as cancer by selectively delivering drugs to diseased cells, thereby minimizing the adverse effects of standard therapies [11].

These advances have the potential to revolutionize the field of medicine and improve the quality of life of millions of people around the world [12]. Future research could focus on the development of more efficient and specific biosensors that can detect a broader range of biomarkers, as well as the use of nanoparticles in the treatment of other diseases [13]. Table 1 shows some potential treatments that combine nanotechnology and pharmacology. Some of these treatments are still in the experimental stages and more research is needed to fully understand their safety and effectiveness. As a complement to the above, recently, new forms of nanoparticle structures densely modified with small fragments of DNA or RNA have been developed, which interact with living systems in ways never observed [14-17]. These structures, known as spherical nucleic acids, have the potential to revolutionize genetic medicine and gene therapy. The CRISPR-Cas9 biological gene editing nanomachine has been identified [18,19] isolated and reconstituted as drugs, enabling rapid development for a variety of different targets. These nanomedical tools have a high modularity that allows them to be adapted to different needs and objectives, opening new possibilities for the treatment of a wide range of diseases [20]. The ability of these spherical nucleic acid structures to access and penetrate tissues is one of their main advantages, as it makes it easier to be used as new and powerful

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genetic medicines. Furthermore, its interaction with living systems allows greater efficiency and precision in genetic editing, reducing the incidence of side effects and improving the effectiveness of treatment. To conclude this section, it is important to evaluate the safety and toxicity of nanomaterials used in diagnosis and treatment to ensure that they do not cause any harm to patients [21,22]. By continuing to explore the potential of nanotechnology in medicine, researchers can help improve the health status of people regardless of their economic status.

Table 1: Treatments where nanotechnology is combined with pharmacology.

Treatment	Nanotechnology Used	Pharmacology Used
Cancer Chemotherapy	Nanoparticles to deliver drugs directly to cancer cells.	Chemotherapy drugs
Cancer	Nanotechnology and ultrasound therapy in drug delivery.	Ultrasound-sensitive nanomaterials used in drug delivery.
Chronic Pain Management	Nanoparticles to deliver pain medication directly to the affected area.	Opioids, nonsteroidal anti-inflammatory drugs (NSAIDs).
Rheumatoid arthritis	Disease-modifying antirheumatic drugs (DMARDs). New Drug Delivery Systems (NDDS).	Targeted biological and synthetic DMARDs aim to control inflammation and prevent joint destruction.Nanoparticles, dendrimers, and liposomes, offering expanded bioavailability and improved stability for targeted drug delivery.
Diabetes Management	Nanoparticles to deliver insulin or other glucose-lowering medications.	Insulin, metformin and sulfonylureas
Breast cancer	Nanoparticles based on acetalated dextran (AcDEX). It has pH sensitive properties and is not harmful to living organisms.	Imaging and treatment of breast cancer through drug administration [14]. Combination therapy, including CMD-conjugated trimethyl NIK/STAT3- and BV6-specific siRNA [15].
Cardiovascular Disease	Nanoparticles to deliver drugs that lower cholesterol or blood pressure.	Statins, beta-blockers, ACE inhibitors.
Neurological Disorders	Nanoparticles to deliver drugs that treat neurological conditions.	Antidepressants, anti-anxiety drugs, anti-seizure drugs.
Ophthalmic Disorders	Nanoparticles to deliver drugs that treat eye conditions.	Antibiotics, anti-inflammatory drugs, anti-vascular endothelial growth factor (VEGF) drugs.
Wound Healing	Nanoparticles to deliver growth factors or other molecules that promote wound healing.	Growth factors, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF).
Osteoarthritis	Nanoparticles and nanocarriers for transdermal administration.	Microfluidic-based 3D cell culture models. Hydrogels based on microemulsions for the topical administration of therapeutic agents. Liposome and transfersome delivery systems.Cubosomes for drug delivery [16].
Immunological Disorders	Nanoparticles to deliver drugs that modulate the immune system	Immunosuppressants, immunomodulators, vaccines
Chronic diseases	Long-acting nanocarriers	Administration of long-acting parenteral drugs. Treatments using Triptorelin, Trelstar®, Aripiprazole lauroxil, OT (leuprolide acetate for depot suspension), Paliperidone palmitate, Pasireotide, AVEED (testosterone undecanoate) injection [17].
Drug Delivery	Nanoparticles to deliver drugs across the blood-brain barrier	Drugs for treating brain tumors, neurodegenerative diseases, and other conditions

New Materials and Technologies

Nanotechnology has also led to the development of new materials and technologies for drug delivery, including implantable devices that provide sustained drug release over time and inhalation systems, which improve drug efficacy by reducing the side effects of diseases. respiratory. Nanotechnology has led to the development of new materials and technologies for drug delivery, including:

a) Implantable devices: These devices are designed to be implanted in the body and provide sustained drug release over time [23]. They can be used to treat a variety of conditions, including cancer, diabetes, and cardiovascular diseases [24].

b) Inhalation systems: These systems use nanoparticles to deliver medications directly to the lungs, where they can be absorbed into the bloodstream. This can improve the effectiveness of medications and reduce the side effects of respiratory diseases [25].

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c) Targeted drug delivery: Nanotechnology has enabled the development of targeted drug delivery systems that can be selectively delivered to specific cells or tissues [26,27]. This type of treatment reduces the risk of side effects and improves the effectiveness of the drug [17].

d) Drug delivery through the skin: Drug delivery systems have been developed that can penetrate the skin and deliver drugs directly to the body. This type of treatment is useful for treating conditions such as skin cancer [28].

e) Administration of medications through the eyes: Consists of the development of ocular medication administration systems for the treatment of conditions such as macular degeneration and glaucoma [29].

f) Drug delivery through the intestine: Involves administering drugs directly to the intestine to treat conditions such as inflammatory diseases.

g) Drug delivery through the brain: These are drug delivery systems that can be administered directly to the brain to treat neurodegenerative conditions such as Alzheimer's disease [30].

Several personalized treatments using cutting-edge technologies are currently being developed to address a wide variety of diseases and conditions. Some examples of personalized treatments that are currently being developed are summarized in Table 2.

Table 2: Personalized treatments using nanotechnology.

Personalized treatment	Description
Cancer vaccines	It uses messenger RNA tailored to each patient to combat cancer in an effective and personalized way.
RNA therapies	It uses ribonucleic acid (RNA) to treat a wide variety of diseases, including cancer, genetic and autoimmune diseases.
Genomics-based medicine	It uses DNA information to develop personalized treatments that adapt to the specific needs of each patient.
Cellular therapies	It uses patient stem cells to treat a wide variety of diseases, including cancer, autoimmune diseases, and degenerative diseases.
Implantable devices	Medical devices that are designed and manufactured to fit the specific needs of each patient may include bone implants, artificial joints, and cardiac support devices.
Diagnostic tests	It uses cutting-edge technologies to identify diseases in a precise and personalized way, which may include analysis of DNA, proteins, and other biological markers.
Virtual and augmented reality therapies	It uses virtual and augmented reality technologies to create personalized environments that help patients overcome their health problems, which may include autism spectrum disorders, depression, anxiety, and chronic pain.
Drug nanoparticles	These nanoparticles can be designed to release the drug in a sustained manner or to target a specific site in the body.
Nanocarriers	They are drug transport systems that use nanoparticles that move through the blood to reach target cells. This improves the effectiveness of the drug and reduces side effects.
Drug delivery nanosystems	They are systems that release the drug in a controlled and sustained manner, thereby improving the effectiveness of the drug and reducing side effects. These systems can be designed to release the drug at a specific location in the body or to release it sustainably over time.
Nanostructured drugs	Drug nanostructuring can improve drug efficacy by allowing greater absorption and specificity at the site of action. This can be achieved by creating drugs in the form of nanoparticles, nanocrystals, or nanotubes.
Nanosensors	They are devices that can detect the presence of drugs in the body and monitor their concentration. This can help optimize drug dosing and minimize side effects.
Conjugated drug nanoparticles	They are nanoparticles that are conjugated with drugs to improve their effectiveness and reduce side effects. These nanoparticles can be designed to release the drug in a sustained manner or to target a specific site in the body.
Nanoparticulate drugs	They are drugs that come in the form of nanoparticles. This may improve the efficacy of the drug by allowing greater absorption and specificity at the site of action.

These are just some examples of the personalized treatments that are currently being developed, where disciplines such as nanobiotechnology, nanomedicine, proteomics, molecular biology, and tissue engineering, among others, are combined to achieve unprecedented developments in the field of personalized medicine and pharmacology. Technology and science are advancing at a dizzying pace, and personalized medicine is expected to become increasingly common in the coming years to treat diseases such as: cancer, diabetes, arthritis, Alzheimer's, Parkinson's, Huntington's, Crohn's, Gaucher, Niemann-Pick, Tay-Sachs, Fabry, Pompe, Sandhoff, Krabbe and Duchenne, among many others. It is evident that nanotechnology has the potential to revolutionize the field of drug delivery by enabling the development of new materials and technologies that can improve drug efficacy, reduce side effects, and increase drug safety and effectiveness. Nanoscale dimensions and surface engineering allow both passive and active transport

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modes to safely overcome biological barriers [31] that often block the free permeation of drugs. Advances in personalized drug delivery have advanced in recent years, so much so that the development of edible microchips could soon release drugs into the body at sequential intervals to treat diseases, which could lead to a "pharmacy in one chip". Additionally, we are seeing more personalized treatments, such as vaccines to treat cancer that use messenger RNA, and RNA therapies that use nanoparticles for delivery.

Discussion

There are a few keyways that nanoscale carriers can move drugs across biological barriers that are critical to ensuring the treatments outlined above, including:

i. Size effect: Nanoparticles in the range of 10 to 100 nm can passively diffuse and cross biological barriers more easily than larger drug molecules due to their smaller size. This size range coincides with some pathways, such as fenestration in the vasculature [32].

ii. Surface properties: targeted ligands are fixed on the surface of the nanoparticles that allow active transport by binding and interacting with transport processes/receptors. This includes binding to transporters/receptors on the blood-brain barrier or cell membranes.

iii. Cellular uptake: Functionalized nanoparticles can take advantage of endogenous absorption mechanisms (e.g., endocytosis, phagocytosis) to be transported intracellularly, facilitating transcytosis across barriers such as the intestinal epithelium.

iv. Interactions with barrier components: properties such as surface charge can influence the partitioning of nanoparticles into barrier layers (e.g., mucus) or cells, modulating permeation rates through barriers such as the skin or tract gastrointestinal.

v. Prevent drug efflux: Drugs transported intracellularly via nanoparticle carriers can bypass barrier-active efflux transporters that would normally pump out free drug molecules.

Nanosized drug carriers can cross biological barriers through functionalized nanoparticles [33], which act with specific binding ligands that can use active transport mechanisms, such as receptors or transporters, to cross barriers such as blood-brain barriers. This can direct the drug directly to the target cells. Another aspect to take into account is the nanometric size, which allows the particles to be incorporated into the cells through endocytosis or phagocytosis, thereby facilitating their transit through barriers such as the intestinal epithelium. In this process, the surface charge of the nanoparticles can affect their interaction with barrier components, allowing greater penetration through it such as the skin or mucous membranes. Properties such as polyethylene glycol (PEG) ligands can help evade the active efflux pump mechanisms present in some barriers, which would normally remove free drug molecules. By transporting drugs intracellularly, some metabolic and solubility limitations that hinder the absorption of non-encapsulated drugs can be overcome [34]. Some examples of ligands used in nanoparticles to facilitate crossing the blood-brain barrier are apolipoprotein E (ApoE), which binds to low-density lipoprotein receptors expressed on brain endothelia, promoting their transport. Another receptor is transferrin that facilitates endocytosis across the blood-brain barrier. There are also p-Glycoprotein ligands of ABC efflux pumps which, when bound, can prevent drug elimination, and promote internalization. RGD peptides bind to alpha-V-beta-3 integrins expressed in epithelia, which increases adhesion and transcellular passage. Insulin ligands bind to receptors on the glucose transporter GLUT1, facilitating receptor-mediated endocytosis. Finally, there is folic acid which binds to the folate receptor overexpressed in some brain cancers, targeting nanoparticles to specific tumors.

The development of new ligands is also an active area of research leading to optimizing the crossing of this important physiological barrier [35]. Optimizing blood-brain barrier crossing is extremely important for the effective delivery of drugs targeting the central nervous system [36]. Some key points to take into account about nanodrug delivery systems are:

a) The blood-brain barrier restricts the passage of most drugs to the brain, limiting the treatment of many neurological diseases [37].

b) Improving brain penetration capacity through functionalized nanoparticles allows drugs to be directed directly to the site of action.

c) Increase the cerebral bioavailability of drugs, with the aim of allowing lower doses to be used and reducing unwanted systemic effects [38].

d) It also facilitates the treatment of tumors or other brain pathologies by being able to overcome the intact blood-brain barrier [39].

e) Administering drugs directly to the brain improves their therapeutic efficacy in conditions such as epilepsy, Alzheimer's, Parkinson's, tumors, etc.

f) Optimizing the crossing of this physiological barrier is a key challenge for the future of nanomedicine and therapeutics aimed at the central nervous system.

g) Like any pharmacological treatment, there are disadvantages or risks associated with optimizing the crossing of the blood-brain barrier [40] that are important to consider:

h) The risk of brain toxicity increases if the dosage and release of the drug once inside the brain is not effectively controlled.

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i) It can facilitate the entry of unwanted molecules that bind to ligands, such as toxins.

j) Active transport mechanisms through receptors can become saturated or down regulated with repeated use.

k) Nanoparticles are distributed heterogeneously in the brain and may not reach specific regions.

l) Its elimination from the brain after treatment is a challenge as it could affect its detoxification.

m) The long-term effects of brain accumulation of nanoparticles are uncertain.

n) Complex functionalization increases the risk of unforeseen adverse reactions.

It is important to thoroughly evaluate the potential side effects of nanoparticles through preclinical studies and clinical trials before widespread application in humans [41]. Safe optimization requires a careful balance between risks and benefits [42]. For example, some of the most common preclinical studies and clinical trials to evaluate the potential side effects of drug delivery systems [43] that cross the blood-brain barrier include:

i. In vitro studies use cultures of central nervous system endothelial cells to evaluate toxicity, biocompatibility, integrity, and transport mechanisms [44].

ii. In vivo studies in small animal models (mice, rats) to determine pharmacokinetics, brain biodistribution, short- and long-term acute and chronic toxicity.

iii. Phase I clinical trials in a few of healthy volunteers to evaluate safety, tolerability, pharmacokinetics, and initial efficacy signals. These human trials include brain imaging tests such as PET/CT to corroborate transport to the CNS.

iv. Phase II clinical trials with larger cohorts of patients to determine safe doses and preliminary effectiveness, as well as identify adverse events [45]. In this phase, neuropsychological and cognitive functioning tests are performed to detect subtle side effects.

v. Randomized, controlled, double-blind phase III clinical trials to confirm efficacy and safety in a large population. This phase allows clinical parameters to be correlated with cerebrospinal fluid analysis to understand intracranial pharmacokinetics.

vi. Post-marketing surveillance to detect any rare or long-term adverse effects. This surveillance includes a scan of safety databases to identify emerging adverse events early.

vii. Neuroimaging studies to evaluate possible accumulation or abnormal distribution in the brain. The challenge is to characterize the long-term effects of repeated brain exposure to nanoparticles, so preclinical studies include extended periods.

The goal of these types of studies is to fully characterize the risk-benefit profile before approval and widespread clinical use. Consequently, a multidisciplinary approach that integrates different levels of evidence is essential to guarantee the safety of each stated procedure. A helpful tool in this context is artificial intelligence, which has become an invaluable technological resource that helps plan each phase of in vitro and in vivo study and exploration, in a relatively short time compared to traditional research techniques.

Conclusion

The field of pharmacology has experienced significant advances in recent years, thanks to innovative applications of nanotechnology. The development of new drug delivery systems, nanoparticles for drug transport, biosensors for disease diagnosis and new materials and technologies open countless applications in personalized medicine. Nanotechnology-mediated drug delivery methods have contributed to improving the efficacy and reducing side effects of medications. These advances have the potential to improve the quality of life of patients. Further research and development in this field is warranted to fully explore the potential of nanotechnology in pharmacology. Future studies could focus on developing more efficient and specific drug delivery systems that can be delivered directly to specific cells or tissues in the body. Additionally, researchers could investigate the use of nanotechnology in the development of new diagnostic tools for early detection of diseases. Finally, the safety and toxicity of nanomaterials used in drug delivery and diagnosis must be carefully evaluated to ensure that they do not cause any harm to patients. By continuing to explore the potential of nanotechnology in pharmacology, researchers can help improve the lives of millions of people around the world.

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