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Advancements and Potential Future Applications of Medication Delivery Systems Using Nanotechnology

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Abstract:

The development in molecular pharmacotherapy and enhanced comprehension of disease mechanisms have necessitated the precise targeting of cells responsible for initiating and advancing illnesses. This is particularly true for the majority of life-threatening illnesses that need treatment medicines with many adverse effects. Therefore, precise tissue targeting is crucial to avoid systemic exposure. Modern drug delivery systems (DDS) are created utilizing cutting-edge technology to expedite the administration of drugs across the body to a particular target area, optimizing the effectiveness of treatment and reducing the build-up of drugs in unintended areas. Consequently, they significantly impact the management and therapy of diseases. Recent drug delivery systems (DDS) have significant benefits over older methods in improved performance, automation, accuracy, and effectiveness. Nanotechnology and nano-delivery techniques are emerging fields of study that focus on using materials at the nanoscale to function as diagnostic instruments or transport therapeutic drugs to particular targeted areas in a controlled way. This review provides an up-to-date overview of recent progress in nanotechnology and drug delivery methods based on nanotechnology. It thoroughly examines the use of nanomaterials to enhance the effectiveness of new and existing drugs, including natural products, and their role in targeted diagnosis using disease indicator molecules.

Keywords: Drug delivery system, Nanotechnology, Pharmacokinetics, Drug targeting

Introduction

Drug delivery mechanisms are technical systems that use advanced methods to prepare and preserve molecules of medications in appropriate formats, such as tablets or solutions, for administration (1). They expedite the delivery of medications to the precise intended location in the body, optimizing the effectiveness of treatment and reducing the buildup of pharmaceuticals in unintended body areas (1, 2). Drugs can be introduced into the body through different routes (3). The drug's physiochemical qualities are determined by its components, which also affect the changes it induces in the body when consumed (4).

Drug delivery systems (DDS) have successfully managed illnesses and enhanced health in recent decades (5). This is primarily attributed to their ability to enhance systemic circulation and regulate the pharmacological impact of the medication. The progress in pharmacological and pharmacokinetics has shown the significance of drug release in influencing the success of treatment, leading to the emergence of the idea of controlled administration (6). The approval of the controlled-release formulation

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for medicine dates back to the 1950s, and it has since garnered substantial interest owing to its notable benefits compared to traditional pharmaceuticals. It dispenses medications at a pre-established pace and for a particular duration (7).

Furthermore, regulated drug delivery methods are unaffected by physiological circumstances, allowing them to maintain their effectiveness for extended periods ranging from days to years. Furthermore, they offer spatial drug release regulation, allowing for consistent or adjustable release rates (8). Moreover, they enhance the solubility of drugs, facilitate their accumulation at the intended location, increase their effectiveness, enhance their pharmacological activity, enhance their pharmacokinetic characteristics, promote patient acceptability and compliance, and decrease medication toxicity (9).

Although organic product-based discovery of drugs and medication delivery systems have several benefits, pharmaceutical corporations are reluctant to increase their investment in this area (10). Instead, they prefer to focus on exploring the existing libraries of chemical compounds in order to identify new medications (11). There is ongoing research to evaluate the potential of natural substances in treating several significant illnesses such as cancer, diabetes, cardiovascular diseases, inflammatory diseases, and microbiological diseases (10, 11). The primary reason is that natural medications provide distinct benefits, including reduced toxicity and side effects, affordability, and significant therapeutic potential. Nevertheless, the biocompatibility and toxicity problems related to natural chemicals provide a significant obstacle to their use as medication. As a result, several natural substances are not progressing through the clinical trial stages due to these issues (10-12). Using bulky materials in drug administration presents significant obstacles, such as in vivo instability, low bioavailability, limited solubility, inadequate absorption in the human body, challenges in achieving target-specific distribution, suboptimal efficacy, and potential side effects of pharmaceuticals. Thus, using novel drug delivery technologies to target medications to particular anatomical regions might address these crucial challenges (13). Therefore, nanotechnology is crucial in developing sophisticated medicine and medication formulations and precisely targeting drugs and their controlled release and administration, achieving remarkable results (1, 13).

Nanotechnology effectively overcomes the division between biological and physical research by using nanostructures and nanophases across several scientific disciplines, particularly in nanomedicine and nano-based medicine delivery systems, where these particles are essential (14). *Nanomaterials* are defined as substances with diameters ranging from 1 to 100 nm. These materials significantly impact several aspects of nanomedicine, including biosensors, microfluidics, drug transport, microarray assays, and tissue engineering (14-16). Nanotechnology utilizes therapeutic substances at the nanoscale to create nanomedicines. Nanoparticles have played a crucial role in advancing the science of biomedicine in areas such as nanobiotechnology, delivery of medications, biological sensors, and tissue engineering (17). Nanoparticles are often nanospheres that consist of materials manufactured at the atomic or molecular scale (18). Therefore, smaller materials have more mobility inside the human body than more extensive materials. Nanoparticles have distinct characteristics in structure, chemistry, mechanics, magnetism, electricity, and biology due to their tiny size. In recent years, nanomedicines have gained recognition for their ability to serve as delivery agents by encapsulating medications or attaching therapeutic substances. They can transport these therapies to target tissues with greater precision and controlled release (14-18).

Nanostructures remain in the bloodstream for an extended duration and provide the controlled release of combined medications at a predetermined dosage. As a result, they induce fewer variations in plasma with fewer negative consequences. Due to their nanoscale size, these structures can enter the tissue system, allowing for simple medication absorption by cells, enabling effective drug distribution, and ensuring focused action at the desired site. The cellular uptake of nanostructures is much greater than larger particles measuring between 1 and 10 µm (14-18). Consequently, they interact directly to effectively treat the affected cells with enhanced efficacy and few or insignificant adverse effects.

Nanotechnology has several advantages in treating chronic human illnesses through the precise and targeted delivery of medications to specified sites. Insufficient understanding of the toxicity of nanomaterials is a significant concern that requires more study to enhance the effectiveness and safety of these medications for safer practical use (1, 13, 18). Hence, meticulously formulating these nanoparticles might be beneficial in addressing the issues linked to their use. This review aims to provide an overview of various nano-based systems for drug delivery, the critical applications of nanomedicines derived from natural compounds, and the topics of bioavailability, targeting locations, and controlled diffusion of nano-drugs. Additionally, it will address the challenges associated with using nanomaterials in healthcare.

The first phase of medication delivery systems

In antiquity, individuals relied on botanical remedies for their medical needs. Despite their advantages, these drug delivery methods were inconsistent and

lacked uniformity and specificity (19). Before the implementation of controlled medication delivery, all medicines were manufactured and preserved in tablet or capsule compositions. Upon coming into contact with gastrointestinal liquids, the substance dissolves, penetrates the wall of the intestine, and then absorbs into the circulation via blood capillaries (20). The medication's release dynamics could not be controlled due to a lack of capacity. Rhazes and Avicenna invented covered technology to mask medications' unpleasant taste. This coating technique modified the pace at which the medication was released. Gold, silver, and pearl-coated tablets were introduced in the 10th century (21).

Advanced coating technology, including enteric, pearl, glucose, keratin, and shellac, was also developed in the 20th century. However, collagen and shellac were ineffectual because of their high pH and unstable storage, making it difficult for the small intestine to dissolve properly (21, 22). Scientists developed an enteric-coating substance using polymer-based cellulose acetate phthalate that dissolves at a low alkaline pH, similar to the small intestine. This characteristic makes it ideal for use in controlled-release formulations for the intestines (21, 22).

Current advancements in medication delivery systems and their practical uses

Significant progress has been made in recent decades in the development of delivery methods for drugs employing inorganic, biological, and combination nanomaterials as transporters for targeted drug administration, particularly in the field of chemotherapy (21, 22). Modern drug delivery systems (DDS) are designed with enhanced characteristics, including reduced particle size, enhanced permeability, better solubility, effectiveness, targeted administration to particular sites, stability, reduced toxicity, and prolonged release. They have the potential to significantly enhance the effectiveness of medicinal agents compared to traditional dose forms (21, 22).

Recently, there have been significant advancements in delivery systems for administering therapeutic agents or naturally derived active chemicals to specific target locations for treating different ailments (23). Several drug delivery methods have been effectively used in recent times. However, there are still specific issues that must be addressed, and sophisticated technology must be created to ensure successful drug delivery to target areas (20-23). Currently, researchers are studying nano-based drug delivery devices to enhance the efficiency of medication delivery.

A)Principles of nanotechnology-based methodologies in developing drugs

Significant advancements have recently been made in delivery systems for administering therapeutic agents or naturally derived active chemicals to specific target locations to treat different ailments (24). Several drug delivery methods have been effectively used recently. However, specific issues must be addressed, and sophisticated technology must be created to ensure successful drug delivery to target areas. Currently, researchers are studying nano-based drug delivery devices to enhance the efficiency of medication delivery. Extensive research has been conducted on developing drugs at the nanoscale, which is currently the most advanced method in nanoparticle applications. This technology offers significant benefits, including the ability to change properties such as dissolution, drug release characteristics, diffusivity, bioavailability, and immunogenicity. As a result, this may lead to the enhancement and advancement of easy methods of administering medication, reduced toxicity, fewer adverse effects, better dispersion throughout the body, and a longer lifespan of the drug (Table 1) (23, 24). Personalized drug delivery systems may be designed to target a particular place specifically or to release therapeutic substances in a regulated

Table 1. Different stages of nanotechnology expansion and development.

Stage	Research focus	History
First nanoparticle therapeutic	Devoted to facilitating the creation of various oral and cutaneous controlled-release compositions.	1950-1980
Second generation (2G)	The researchers aimed to create drug delivery systems that maintain a consistent rate of drug release, include self-regulating capabilities, have long-term depot formulations, and are based on nanotechnology, specifically nanoparticle formulations. During this time period, researchers created formulations of peptide/protein medications that released the medication slowly over an extended period of time.	1980-2000
Third generation	The contemporary age of controlled dispensing technique. The physiochemical challenges occur because to insufficient water dissolution, the significant molecular mass of therapeutic substances such as peptides and proteins, and the difficulty in achieving precise and controlled drug release. On the other hand, the biological barrier challenges pertain to problems related to the distribution of drugs throughout the body.	2000-2024

manner at a specific spot. Their development entails self-assembly, whereby well-defined shapes or patterns are spontaneously generated from building components (24). In addition, they must overcome obstacles such as opsonization and sequestration via the mononuclear phagocyte system (24).

Nanotechnology structures may provide drugs via two mechanisms: inactive or active delivery. In the first case, medications are predominantly delivered into the internal chamber of the material via the property known as hydrophobic. While nano-structured substances are directed towards specific locations, they release the desired quantity of the medicine due to the low concentration of the pharmaceuticals enclosed in a hydrophobic microenvironment (25). In contrast, the medications meant to be released in the latter scenario are directly linked to the carrier nanostructure substance to facilitate their distribution. The timing of drug release is critical in this strategy since the drug will rapidly detach from the carrier and fail to reach the intended region. Conversely, if the drug disappears from its nano-carrier network at the appropriate moment, its bioactivity and effectiveness will be diminished. (24, 25) Drug targeting is a crucial use of nanomaterials or Nano formulations as systems for delivering drugs. It may be categorized into two types: active targeting and passive targeting. Active targeted delivery refers to the process of connecting elements, like as immunoglobulin and amino acids, to a system for delivering drugs in order to bind them to specific target complexes at the intended site. A passive targeting approach refers to the process of circulating a mix of a medication and carrier through the circulatory system, with subsequent delivery to the desired place dependent on parameters such as affinity, binding, pH, heat, molecular position, and shape. The main goals inside the human system involve the receptors situated on the outer layers of cells, the lipid components of the cell, and antigenic substances or proteins found on the outside of cells (1, 25). Most nanotechnology-based medication delivery systems are specifically designed to target and treat cancer.

B)Application of biopolymeric nanoparticles in the fields of diagnostics, detection, and imaging.

Theragnostic, a combination of therapy and diagnosis, is widely used in cancer treatment (25, 26). Theragnostic nanoparticles can aid in illness diagnosis, accurately pinpoint the disease's site, determine the disease's stage, and offer insights into the effectiveness of the therapy. Furthermore, these nanoparticles can transport a therapeutic substance to the tumor, allowing for the precise delivery of therapeutic doses by molecular and external triggers (26). *Chitosan* is a biopolymer with unique characteristics such as biocompatibility and the inclusion of functional groups (25, 26). It is used in encapsulating or coating different kinds of nanoparticles, creating particles with diverse functionalities. These particles can potentially be utilized to identify and diagnose various illnesses (25 -27).

Researchers (28) used oleic acid-coated FeO nanoparticles encapsulated in oleic acid-conjugated chitosan (oleyl-chi-tosan) to investigate the accumulation of these nanoparticles in tumor cells. This was done by studying their ability to penetrate and be retained in the cells through the enhanced permeability and retention (EPR) effect in an in vivo setting. This study aimed to explore the potential analytical applications of these nanoparticles using near-infrared and magnetic resonance imaging (MRI) techniques. Through in vivo assessments, both approaches demonstrated significant signal intensity and enhancement in tumor tissues due to a more substantial EPR effect after intramuscular administration of cyanine-5-attached oleyl-chitosan nanoparticles (Cyanine 5) (28).

Furthermore, dextran, a polymeric substance, is considered a neutral polymer and the first significant instance of microbial exopolysaccharides utilized for medicinal applications (29). An outstanding benefit of using dextran is its excellent tolerance, lack of toxicity, and biodegradability in humans without any adverse effects on the body (30). Photodynamic radiation therapy is a targeted treatment for cancer that causes little harm to healthy cells. Researchers (31) created a composite system of nano-sized particles by enclosing Fe3O4 nanoparticles inside dextran nanoparticles linked to redox-responsive chlorine 6 (C6). This system was designed for near-infrared (NIR) and magnetic resonance (MR) scanning. The nanoparticles demonstrated a redox cell reaction to the fluorescent signal that alternated between "off" and "on" states, leading to precise monitoring of the tumor (31).

Furthermore, we discovered exceptional magnetic targeting capacity both in vitro and in vivo, significantly enhancing the photodynamic treatment's effectiveness. The researchers (31, 32) synthesized theranostic nanoparticles for glioma cells in C6 mice. The particles comprise gadolinium oxide nanoparticles coated with folic acid-conjugated dextran (FA) or paclitaxel (PTX). The MTT test was used to investigate the bioprotective properties of the dextran coating and the chemotherapy impact of PTX on the C6 glioma cells. The produced nanoparticles have shown their ability to penetrate C6 tumor cells by receptor-mediated endocytosis. They also exhibit improved contrast (MR) concentration-dependent operation, which is attributed to the paramagnetic nature of the gadolinium nanoparticle. Coated gadolinium nanoparticles exhibited greater

efficacy in decreasing cell viability than uncoated ones. Consequently, using FA and PTX-coupled nanoparticles as theranostic agents with both paramagnetic and chemotherapeutic characteristics is feasible (31, 32). Furthermore, dextran, a polymeric substance, is considered a neutral polymer and the first significant instance of microbial exopolysaccharides utilized for medicinal applications. An outstanding benefit of using dextran is its excellent tolerance, lack of toxicity, and biodegradability in humans without any adverse effects on the body (33). Photodynamic radiation therapy is a targeted treatment for cancer that causes little harm to healthy cells. Researchers created a composite system of nano-sized particles by enclosing Fe3 O4 nanoparticles inside dextran nanoparticles linked to redox-responsive chlorine 6 (C6). This system was designed for near-infrared (NIR) and magnetic resonance (MR) scanning. The nanoparticles demonstrated a redox cell reaction to the fluorescent signal that alternated between "off" and "on" states, leading to precise monitoring of the tumor (30-33).

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Current commercial offerings using nanotechnology

There are many products based on medical nanotechnology available today (34-36), some of which are being used in clinical settings (Table 2). Notably, these nanomedicines are mostly created for medications with high toxicity and poor water solubility. These nano formulations may often increase the drug's pharmacokinetic qualities while lowering its toxicity. A recent assessment found that even though the FDA hasn't regulated many nanomedicines, there are several clinical trial activities underway that might soon lead to the release of many novel pharmaceuticals based on nanotechnology. Of the nanomaterials under investigation, 18 are focused on chemotherapeutics; 15 are meant to be antibacterial agents; 28 are meant for various medical applications, including autoimmune illnesses, psychiatric problems, and many others; and 30 are meant to be nucleic acid-based treatments (Figure 1) (34-36). Table 2 displays the list of nanomedicines that the FDA has authorized, sorted by the kind of carrier material utilized to prepare the formulation.

The future of medication delivery systems and nanomedicine

Nanomedicine technological advances is now among the greatest captivating areas of study. Multiple investigations done in this field over the last two decades have already led to the submission of applications and the completion of several clinical investigations (37). Carcinoma is a disease that has

Table 2. FDA approves of nanomedicine categorized according to automobile type.

Drug	Ingredient active	Carrier	Application	Approved year
Plegridy® (Biogen)	interferon-beta (IFN-β1a)	PEGylated IFN-β1a protein	Multiple sclerosis	2015
Invega® Sustenna® (Janssen Pharms)	Paliperidone palmitate	Nanocrystals	Schizophrenia schizoaffective disorder	2014
Nanotherm® (MagForce)	Iron oxide	Aminosilane-coated Iron nano-particles	Brain tumor	2010
EquivaBone® (Zimmer Biomet)	Hydroxypatite	Nanocrystals	Bone substitute	2009
Mircera® (Hoffman-La Roche)	Methoxy polyethylene glycol-epoetin beta	Chemically synthesized erythro-poiesis-stimulating agent	Anemia associated with renal failure	2007

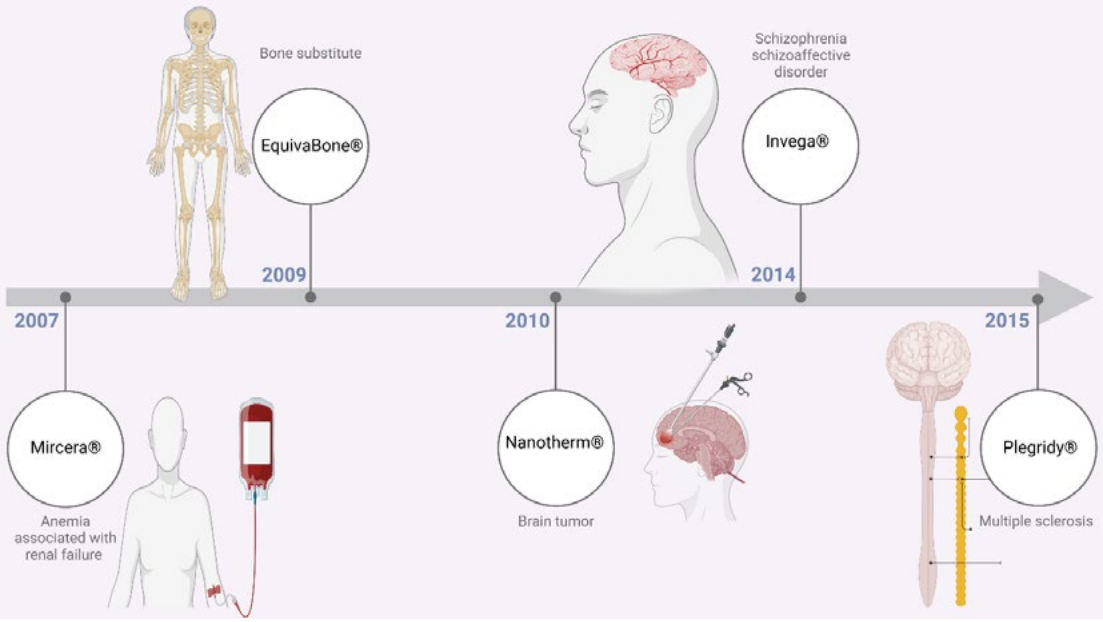

Fig 1. Schematic of some commercial drugs developed according to nanotechnology.

benefited from the use of nonmedical technology in both treatment and detection, as previously addressed in other parts. The utilization of nanotechnology and nano-drug delivery techniques is unquestionably the current state of affairs in the realm of advancement and research. These systems employ various nanoparticles to administer precise dosages of medication to specific cells, such as malignancies or tumor cells, while leaving cells that are normal unaffected. Although possible uses of nanotechnology in medicine and nanodrug methods of administration are well recognized, their impact on the medical field, particularly in the areas of cancer treatment and diagnostics, is currently limited. This is due to the fact that the discipline is still relatively young in science, having only seen two decades of serious investigation, and many important, fundamental characteristics remain unknown. Future research will primarily concentrate on studying the fundamental indications of diseased tissues, namely essential biologic indicators that allow for effective targeting without altering the normal cellular processes. Ultimately, when our understanding of diseases advances to include the molecular structure or the subcellular size of nanomaterials, with comparable biomarker identification, the area of nanotechnology will enhance, leading to the emergence of novel approaches for both detection and therapy (35-38).

Conclusion

In recent years, drug delivery and nanotechnology have drawn a lot of attention from researchers, experimenters, and clinical trials alike. It has emerged as one of the most exciting areas of study in contemporary science. The recent delivery system for drugs has a lot of potential, despite the obstacles that have prevented it from being used in clinical settings. To help achieve this efficiency, we will need to collaborate across the disciplines of academia, laboratory experimentation, medical knowledge, pharmaceutical knowledge, and excellent research. Researchers anticipate that using cell treatments will help provide an effective single dosage and address the bio-acceptability problems that drug delivery methods encounter. In actuality, cell treatments promise to dismantle intrinsic biological barriers, produce reactions that look natural inside the system, and provide a seemingly persistent stream of complicated biologics. To address some of the issues surrounding medication delivery, researchers have proposed the use of molecular imprinting polymers, micro fluids, and inorganic mesoporous nanomaterials. Researchers have found that using priming agents that can alter the biological environment in which drugs are administered—particularly those that can alter tissue structure and function to make administered drugs more advantageous without endangering patients—can increase the effectiveness of drug delivery. Additionally, since cells are a natural part of the human body, cell-based drug systems—which combine the use of cells with nanomaterials—should be taken into consideration in the field of biomaterials. This is a novel approach that is still in theory but looks to be very creative, encouraging drug delivery methods in an effort to achieve the greatest drug delivery arrangement. To support the effectiveness of these contemporary drug delivery methods and the difficulties associated with their use, a great deal of study and clinical studies are still required.

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Seyedeh Sahar Ebrahimi Hosseini and Eskandar Hoseinnzhad Lazarjani were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

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