Nanotechnology and its use in imaging and drug delivery (Review)

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Abstract. Nanotechnology is the exploitation of the unique properties of materials at the nanoscale. Nanotechnology has gained popularity in several industries, as it offers better built and smarter products. The application of nanotechnology in medicine and healthcare is referred to as nanomedicine, and it has been used to combat some of the most common diseases, including cardiovascular diseases and cancer. The present review provides an overview of the recent advances of nanotechnology in the aspects of imaging and drug delivery.

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1. Introduction

Nanoscience is the study of the unique properties of materials between 1-100 nm, and nanotechnology is the application of such research to create or modify novel objects. The ability to manipulate structures at the atomic scale allows for the creation of nanomaterials (1-3). Nanomaterials have unique optical, electrical and/or magnetic properties at the nanoscale, and these can be used in the fields of electronics and medicine, amongst other scenarios. Nanomaterials are unique as they provide a large surface area to volume ratio. Unlike other large-scaled engineered objects and systems, nanomaterials are governed by the laws of quantum mechanics instead of the classical laws of physics and chemistry. In short, nanotechnology is the engineering of useful objects and functional systems at the molecular or atomic scale (4).

Nanotechnologies have had a significant impact in almost all industries and areas of society as it offers i) better built, ii) safer and cleaner, iii) longer-lasting and iv) smarter products for medicine, communications, everyday life, agriculture and other industries (5). The use of nanomaterials in everyday products can be generally divided into two types. First, nanomaterials can be merged or added to a pre-existing product and improve the composite objects' overall performance by lending some of its unique properties. Otherwise, nanomaterials such as nanocrystals and nanoparticles can be used directly to create advanced and powerful devices attributed to their distinctive properties. The benefits of nanomaterials could potentially affect the future of nearly all industrial sectors (6).

The beneficial use of nanomaterials can be found in sunscreens, cosmetics, sporting goods, tyres, electronics and several other everyday items (6). Additionally, nanotechnologies have revolutionized advances in medicine, specifically in diagnostic methods, imaging and drug delivery. Table I illustrates the areas where nanotechnologies have had a significant impact.

Nanomaterials allow mass-creation of products with enhanced functionality, significantly lower costs, and greener and cleaner manufacturing processes, to improve healthcare and reduce the impact of manufacturing on the environment (7).

2. Nanotechnology in medicine and healthcare

Nanomedicine is the term used to refer to the applications of nanotechnologies in medicine and healthcare. Specifically, nanomedicine uses technologies at the nanoscale and nano-enabled techniques to prevent, diagnose, monitor and treat diseases (8). Nanotechnologies exhibit significant potential in the field of medicine, including in imaging techniques and diagnostic tools, drug delivery systems, tissue-engineered constructs, implants and pharmaceutical therapeutics (9), and has advanced treatments of several diseases, including cardiovascular diseases, cancer, musculoskeletal conditions, psychiatric and neurodegenerative diseases, bacterial and viral infections, and diabetes (10).
3. Types of nanoparticles

To date, several nanoparticles and nanomaterials have been investigated and approved for clinical use. Some common types of nanoparticles are discussed below.

Micelles. Micelles are amphiphilic surfactant molecules that consist of lipids and amphiphilic molecules. Micelles spontaneously aggregate and self-assemble into spherical vesicles under aqueous conditions with a hydrophilic outer monolayer and a hydrophobic core, and thus can be used to incorporate hydrophobic therapeutic agents. The unique properties of micelles allow for the enhancement of the solubility of hydrophobic drugs, thus improving bioavailability. The diameter of micelles ranges from 10-100 nm. Micelles have various applications, such as drug delivery agents, imaging agents, contrast agents and therapeutic agents (11).

Liposomes. Liposomes are spherical vesicles with particle sizes ranging from 30 nm to several microns, that consist of lipid bilayers. Liposomes can be used to incorporate hydrophilic therapeutic agents inside the aqueous phase and hydrophobic agents in the liposomal membrane layer. Liposomes are versatile; their surface characteristics can be modified with polymers, antibodies and/or proteins, enabling macromolecular drugs, including nucleic acids and crystalline metals, to be integrated into liposomes (10,11). Poly(ethylene glycol) (PEG)ylated liposomal doxorubicin (Doxil®) is the first FDA-approved nanomedicine, which has been used for treatment of breast cancer, and it enhances the effective drug concentration in malignant effusions without the need to increase the overall dose (10,11).

Dendrimers. Dendrimers are macromolecules with branched repeating units expanding from a central core and consists of exterior functional groups (10-12). These functional groups can be anionic, neutral or cationic terminals, and they can be used to modify the entire structure, and/or the chemical and physical properties. Therapeutic agents can be encapsulated within the interior space of dendrimers, or attached to the surface groups, making dendrimers highly bioavailable and biodegradable. Conjugates of dendrimers with saccharides or peptides have been shown to exhibit enhanced antimicrobial, antiprion and antiviral properties with improved solubility and stability upon absorption of therapeutic drugs (13). Polyamidoamine dendrimer-DNA complexes (called dendriplexes) have been investigated as gene delivery vectors and hold promise in facilitating successive gene expression, targeted drug delivery and improve drug efficacy (14,15). dendrimers are promising particulate systems for biomedical applications, such as in imaging and drug delivery (16,17), due to their transformable properties.

Carbon nanotubes. Carbon nanotubes are cylindrical molecules that consist of rolled-up sheets of a single-layer of carbon atoms (graphene). They can be single-walled or multi-walled, or composed of several concentrically interlinked nanotubes (17). Due to their high external surface area, carbon nanotubes can achieve considerably high loading capacities as drug carriers. Additionally, their unique optical, mechanical and electronic properties have made carbon tubes appealing as imaging contrast agents (18,19) and biological sensors (20).

Metallic nanoparticles. Metallic nanoparticles include iron oxide and gold nanoparticles. Iron oxide nanoparticles consist of a magnetic core (4-5 nm) and hydrophilic polymers, such as dextran or PEG (17-20). Conversely, gold nanoparticles are composed of a gold atom core surrounded by negative reactive groups on the surface that can be functionalized by adding a monolayer of surface moieties as ligands for active targeting (17-20). Metallic nanoparticles have been used as imaging contrast agents (21), in laser-based treatment (12), as optical biosensors (12) and drug delivery vehicles (22).

Quantum dots. Quantum dots (QDs) are fluorescent semiconductor nanocrystals (1-100 nm) and have shown potential use for several biomedical applications, such as drug delivery and cellular imaging (17,23,24). Quantum dots possess a shell-core structure, in which the core structure is typically composed of II-VI or III-V group elements of the periodic table. Due to their distinctive optical properties and size, with high brightness and stability, quantum dots have been employed in the field of medical imaging (10,23).

4. Nanotechnology in imaging and diagnosis

Diagnosis of a disease is one of the most crucial steps in the healthcare process. All diagnoses are desired to be quick, accurate and specific to prevent ‘false negative’ cases. In vivo imaging is a non-invasive technique that identifies signs or symptoms within a patient’s live tissues, without the need to undergo surgery (24). A previous improvement in diagnostic imaging techniques is the use of biological markers that can detect changes in the tissues at the cellular level. The aim of using a biological marker is to detect illnesses or symptoms, thereby serving as an early detection tool (25). Notably, some of these high precision molecular imaging agents have been developed through the use of nanotechnologies. In addition to diagnosis, imaging is also vital for detecting potential toxic reactions, in controlled drug release research, evaluating drug distribution within the body and closely monitoring the progress of a therapy. Potential drug toxicity can be reduced with the possibility of monitoring the distribution of drugs around the body and by releasing the drug as required (26).

Diagnostic imaging. Imaging techniques such as X-ray, ultrasound, computed tomography, nuclear medicine and magnetic resonance imaging are well established, and are widely used in biochemical and medical research. However, these techniques can only examine changes on the tissue surface relatively late in disease progression, although they can be improved through the use of contrast and targeting agents based on nanotechnologies, to improve resolution and specificity, by indicating the diseased site at the tissue level (27). Currently used medical imaging contrast agents are primarily small molecules that exhibit fast metabolism and a non-specific distribution, and can thus potentially result in undesirable toxic side effects (10). This particular area is where nanotechnologies make their most significant contribution in the field of medicine, by developing more powerful contrast agents for
almost all imaging techniques, as nanomaterials exhibit lower toxicity, and enhanced permeability and retention effects in tissues. The size of the nanoparticles significantly influences its biodistribution, blood circulation half-life, cellular uptake, tissue penetration and targeting (17,28). Table II summarises some examples of nanoparticles used as contrast agents in the biomedical field.

<table>
<thead>
<tr>
<th>Nanoparticle</th>
<th>Application</th>
<th>Refs.</th>
</tr>
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<tbody>
<tr>
<td>Perfluorocarbon</td>
<td>Imaging of angiogenesis, cancer metastases and blood clots.</td>
<td>(65)</td>
</tr>
<tr>
<td>Gadolinium complexes</td>
<td>CT imaging of thrombi as a contrast agent.</td>
<td>(66)</td>
</tr>
<tr>
<td>Fullerenes</td>
<td>Used in MRI to enhance contrast.</td>
<td>(67)</td>
</tr>
<tr>
<td>Quantum dots</td>
<td>Specific cellular imaging.</td>
<td>(68)</td>
</tr>
<tr>
<td>Silicon particles</td>
<td>Coated with conductive layers to enhance MRI.</td>
<td>(69)</td>
</tr>
<tr>
<td>Iron oxide</td>
<td>Imaging of tumours.</td>
<td>(70)</td>
</tr>
<tr>
<td>Gold particles (core shell structure)</td>
<td>Ultrasound.</td>
<td>(71-73)</td>
</tr>
<tr>
<td>Gold particles</td>
<td>X-ray/CT scan.</td>
<td>(71-73)</td>
</tr>
</tbody>
</table>

Table II. Examples of nanoparticles used as contrast agents in the biomedical field.

CT, computed tomography; MRI, magnetic resonance imaging.

The use of nanoparticles in X-rays has some limitations. In order to enhance the contrast, a number of heavy atoms must be delivered into the target site without causing any toxic reactions. This can be achieved using stable and inert surface atoms, such as gold and silver. Hence, gold nanoshells have garnered significant attention, due to its low toxicity. Gold nanoshells are heavy metal nanoparticles (dielectric core) encapsulated in gold shells and have been proposed to be one of the most promising materials in optical imaging of cancers (29,30). Gold nanoshells are cost-effective, safe due to its non-invasive property and may provide high resolution imaging. Gold nanoshells have similar physical characteristics to gold colloids, as they both possess a unified electronic response of the metal to light resulting in active optical absorption (29-32). Gold nanoshells are widely employed by researchers as contrast agents in the Optical Coherence Tomography of cancer cells, as the optical resonance of gold nanoshells can be adjusted accurately over a wide range, including near-infrared, where tissue transmissivity is higher (31). Table III shows the various types of nanomaterials used as contrast agents in pre-clinical investigations and in clinical use. Significantly more research and pre-clinical studies are required to understand and predict the effects of these nanomaterials in biological systems.

In situ diagnostic devices. In situ diagnostic devices, such as capsule endoscopy cameras, have been shown to be successful in the clinical stage. These devices can locate and image the bleeding site and other internal problems via oral ingestion. It is hypothesized that in the future, these devices will incorporate nano-scaled sensors for chemicals, virus, bacteria and pH to broaden their utility and applications. Moreover, these devices are also being developed as an alternative safe and precise means of drug-loaded capsules in drug delivery systems (33,34).

Nanotechnology in drug delivery. Therapy typically involves delivering drugs to a specific target site. If an internal route for drug delivery is not available, external therapeutic methods, such as radiotherapy and surgical procedures are employed. These methods are often used interchangeably or in combination to combat diseases. The goal of therapy is to always selectively remove the tumours or the source of illness in a long-lasting manner (35). Nanotechnologies are making a compelling contribution in this area through the development of novel modes for drug delivery, and some of these methods have proven effective in a clinical setting and are clinically used (36). For example, doxorubicin a
A drug which exhibits high toxicity, can be delivered directly to tumour cells using liposomes (Doxil®) without affecting the heart or kidneys. Additionally, paclitaxel incorporated with polymeric mPEG-PLA micelles (Genexol-PM®) are used in chemotherapeutic treatment of metastatic breast cancers (10,11,36). The success of nanotechnologies in drug delivery can be attributed to the improved in vivo distribution, evasion of the reticuloendothelial system and the favourable pharmacokinetics (36).

A perfect drug delivery system encompasses two elements: Control over drug release and the targeting ability. Side effects can be reduced significantly, and drug efficiency can be ensured by specifically targeting and killing harmful or cancerous cells. Additionally, controlled drug release can also reduce the side effects of drugs (37). Benefits of nanoparticle drug delivery systems include minimised irritant reactions and improved penetration within the body due to their small size, allowing for intravenous and other delivery routes. The specificity of nanoparticle drug delivery systems is made possible by attaching nano-scaled radioactive antibodies that are complementary to antigens on the cancer cells with drugs, and these approaches have produced desirable results (38), exhibiting improved i) drug bioavailability, ii) delivery of drugs specifically to the target site, and iii) uptake of low solubility drugs (39). Table IV summarises the advantages of nanoparticles over conventional fine particles (39,40).

5. Nanotechnology and cancer treatment

Staggering numbers of individuals suffer from cancer worldwide, highlighting the need for an accurate detection method and novel drug delivery system that is more specific, efficient and exhibits minimal side effects (41). Anticancer treatments are often regarded as superior if the therapeutic agent can reach the specific target site without resulting in any side effects. Chemical modifications of the surface of nanoparticle carriers may improve this required targeted delivery. One of the best examples of modifications at the surface of nanoparticles is the incorporation of PEG or polyethylene oxide. These modifications enhance not only the specificity of drug uptake, but also the tumour-targeting ability. Incorporating PEG avoids the detection of nanoparticles as foreign objects by the body's immune system, thus allowing them to circulate in the bloodstream until they reach the tumour. Additionally, the application of hydrogel in breast cancer is a prime example of this innovative technology. Herceptin is a type of monoclonal antibody used in breast cancer treatment by targeting human epidermal growth factor receptor 2 (HER2) on cancer cells. A vitamin E-based hydrogel has thus been developed that can deliver Herceptin to the target site for several weeks with just a single dose. Due to the improved retention of Herceptin within the tumour, the hydrogel-based drug delivery is more efficient than conventional subcutaneous and intravenous delivery modes, thus making it a better anti-tumour agent (42-44). Nanoparticles can be modified in several ways to prolong circulation, enhance drug localisation, increase drug efficacy and potentially decrease the development of multidrug resistance through the use of nanotechnologies.
There are several studies using FDA-approved nano drugs, such as Abraxane®, Doxil® or Genexol-PM® as adjuvants in combinatory cancer treatment. Abraxane®, a paclitaxel albumin-stabilised nanoparticle formulation (nab-paclitaxel) has been approved for the treatment of metastatic breast cancer (45). There are >900 ongoing clinical trials involving nab-paclitaxel as an anticancer agent, based on Clinicaltrials.gov as of August 2020. Moreover, nab-paclitaxel, in combination with 5-chloro-2,4-dihydroxypyridine, tegafur and oteracil potassium exhibited promising results when used for the treatment of HER2-negative breast cancer patients (46). Doxorubicin, daunorubicin, paclitaxel and vincristine are among the most extensively investigated anticancer agents in liposome-based drug formulations (10,11). Table V provides examples of FDA approved nanomedicines (10).

6. Nanotechnologies for the treatment of cardiovascular diseases

Cardiovascular diseases are another field where the properties of nanoparticles may be leveraged. Cardiovascular diseases are the leading cause of death globally, and the rates are increasing alarmingly, due to an increase in sedentary lifestyles (47). Common examples of cardiovascular diseases that affect several individuals includes stroke, hypertension and restriction or blockage of blood circulation in a specific area. These diseases are the most common causes of prolonged disability and death (47). Nanotechnologies offer novel avenues for therapeutic and diagnostic strategies for management of cardiovascular diseases.

Most cardiovascular risk factors (for example, for hypertension, smoking, hypercholesterolemia, homocystinuria and diabetes mellitus) are associated with impaired nitric oxide (NO) endothelial production. Impaired endothelial function is established to be the first step in atherosclerosis. Gold and silica nanoparticles have been developed to improve NO supply for possible application in cardiovascular diseases, where low NO bioavailability occurs (48). Systemic administration of the 17-βE loaded CREKA-peptide-modified-nanoemulsion system has been shown to reduce the levels of pathological contributors to early atherosclerosis by reducing lesion size, lowering the levels of circulating plasma lipids and decreasing the gene expression of inflammatory markers associated with the disease (49). Moreover, novel formulations of block copolymer micelles constructed using PEG and poly(propylene sulphide) have been demonstrated to suppress the levels of pro-inflammatory cytokines (50), and exhibited excellent potential for management of atherosclerosis (50).

Drug delivery via liposomes has been proven to be effective for prevention of platelet aggregation, atherosclerosis and thrombosis. Prostaglandin E-1 (PGE-1) exhibits a wide range of pharmacological properties, including vasodilation, inhibition of platelet aggregation, leukocyte adhesion, as well as exhibiting an anti-inflammatory effect. Liposomal drug delivery of PGE-1 (Liprostin™), is currently undergoing phase III clinical trials for the treatment of various cardiovascular diseases, such as restenosis following angioplasty (51). Additionally, the use of liposomes carrying the thrombolytic drug urokinase has also been assessed; cyclic arginyl-glycyl-aspartic acid (cRGD) peptide liposomes encapsulated with urokinase can selectively bind to the GPIIb/IIIa receptors, and this improves the thrombolytic efficacy of urokinase by almost 4-fold over free urokinase (51).

Efficacy and effectiveness of the conventional thrombolytic drugs can also be advanced via novel nano-therapeutic approaches. Drugs can be selectively targeted to vascular blockage sites through mechanical activation within blood vessels based on the high-fluid shear strains present within them. In vivo and in vitro studies have been encouraging, thus validating this approach for use in lysis of blood clots, using a significantly lower amount of thrombolytic drug (48-53). One example of this technology is the use of dendrimers. Dendrimers have been used in several diseases as a means of delivering therapeutic agents. Plasminogen activator (rtPA) has been successfully attached to dendrimers producing an alternative drug delivery system, allowing for refinement of the rtPA-dendrimer complex concentration throughout the duration of treatment using different dilution proportions of each part of the complex (53). Another potential role of nanoparticles is to decrease haemorrhaging, which is a severe side effect of

<table>
<thead>
<tr>
<th>Clinical agents</th>
<th>Formulation</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligard</td>
<td>Leoprolide acetate and polymer [poly (DL-lactide-co-glycolide)]</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Genexol-PM</td>
<td>mPEG-PLA micelle loaded with paclitaxel</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>Doxil/Caelyx</td>
<td>Liposomal doxorubicin</td>
<td>Ovarian, breast cancer, Kaposi’s sarcoma, multiple myeloma</td>
</tr>
<tr>
<td>Myocet</td>
<td>Liposomal doxorubicin</td>
<td>Combination therapy with cyclophosphamide in metastatic breast cancer</td>
</tr>
<tr>
<td>Onivyde</td>
<td>Liposomal irinotecan</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Cynviloq</td>
<td>Paclitaxel-loaded poly(ethylene glycol)-b-poly(D,L-lactic acid) block copolymers</td>
<td>Non-small cell lung cancer and metastatic breast cancer.</td>
</tr>
<tr>
<td>Nanoxel</td>
<td>Docetaxel-loaded poly(ethylene glycol)-b-poly(D,L-lactic acid) block copolymers</td>
<td>Breast cancer, non-small-cell lung cancer, prostate cancer, ovarian cancer, head and neck cancer, oesophageal cancer</td>
</tr>
</tbody>
</table>

Table V. Examples of FDA approved nanomedicines.
thrombolytic agents. Targeted thrombolysis via rtPA bound to polycrylic acid coated nanoparticles minimises the intracerebral haemorrhage, and enhances retention at the target site (11). Incorporation of nanotechnologies has assisted in reducing the side effects of drugs, whilst requiring lower doses of the drug to treat cardiovascular diseases. Table VI summarises some of the applications of nanoscale pharmaceuticals in drug delivery.

The current progress in nanotechnology research for drug delivery systems, particularly with regard to their water-insoluble properties, has enabled drugs to be delivered to target sites with higher carrier capacity, specificity and stability. The constant advancements in nanoparticle drug delivery systems have allowed researchers to develop formulations that can increase the efficiency of drugs, whilst reducing the cost (54).

7. Potential risks of nanotechnologies

Although the emerging field of nanotechnology has piqued the public’s interest at large, nanotechnologies have also resulted in extensive discussions regarding their safety and any health
risks associated with their use. New challenges arise with the use of nanomaterials, specifically in predicting, understanding and governing the potential health risks. Research has demonstrated that low-solubility nanoparticles are more hazardous and toxic on a mass by mass basis than larger particles (55). Other potential risks posed by nanoparticles include explosions and catalytic effects. It is important to note that only specific nanomaterials are considered risky, particularly those with high reactivity and mobility. Until more thorough studies can confirm the hazardous effects of nanomaterials, the mere presence of them in a laboratory setting will not in itself impose a threat to humanity and the environment (56). Potential risks of nanotechnology can be broadly grouped into three areas: Health, environment and society, as shown in Table VII.

8. Conclusion

There is no doubt that nanotechnologies have helped to improve the quality of life of patients by providing a platform for advances in biotechnological, medicinal and pharmaceutical industries. They have also facilitated healthcare procedures, from diagnosis to therapeutic interventions and follow-up monitoring. There is a constant push to create and develop novel nanomaterials to improve diagnosis and cures for diseases in a targeted, accurate, potent and long-lasting manner, with the ultimate aim of making medical practices more personalised, cheaper and safer (57,58). The prospect of nanotechnology lies within using the right nanomaterials and governing the potential health risks. Research has demonstrated that low-solubility nanoparticles are more hazardous and toxic on a mass by mass basis than larger particles (55). Other potential risks posed by nanoparticles include explosions and catalytic effects. It is important to note that only specific nanomaterials are considered risky, particularly those with high reactivity and mobility. Until more thorough studies can confirm the hazardous effects of nanomaterials, the mere presence of them in a laboratory setting will not in itself impose a threat to humanity and the environment (56). Potential risks of nanotechnology can be broadly grouped into three areas: Health, environment and society, as shown in Table VII.

Competing interests

The authors declare that they have no competing interests.

References


