Nanotechnology is a multidisciplinary branch of science which involves the manipulation and control of matter at the nanometer scale to produce new structures, materials, and devices. The concept of nanotechnology was first introduced by Richard P. Feynman[1] in 1959. Since then, nanotechnology has become a research area which promises advancements in many aspects of human life, including electronics, agriculture, transportation, food industry, communication, energy, biological sciences, and medicine. Nanomedicine, the application of nanotechnology in the field of medicine, has the potential to make a great impact on human health and has already impacted and reshaped many aspects of clinical practice and research. Nanotechnology-based materials with unique physical, chemical, and biological characteristics offer a variety of new approaches for clinical practices ranging from prevention to treatment and diagnosis of many diseases and conditions.[2-5] Among all the applications of nanotechnology in medicine, nano-based drug delivery systems have attracted a significant research interest thanks to its great translational value.[6-10] Owing to the rapid developments in nanotechnology, research in the field of controlled drug delivery has experienced an extraordinary progress. Nano drug delivery systems provide a new drug delivery method for the treatment of various diseases and demonstrate numerous advantages over traditional drug delivery systems. The nanoscale manipulation provides site-specific targeting and delivery, as well as the controllable release of drugs, genes, and imaging agents.[11,12] A variety of nano-based drug delivery systems have been recently developed from different materials such as lipids, polymers, metals, inorganic materials, and small molecules.[13] Among the broad spectrum of nano-based drug delivery applications, orthopedics is one of the most active areas.

**ABSTRACT**

In recent years, nanotechnology has led to significant scientific and technological advances in diverse fields, specifically within the field of medicine. Owing to the revolutionary implications in drug delivery, nanotechnology-based drug delivery systems have gained an increasing research interest in the current medical field. A variety of nanomaterials with unique physical, chemical and biological properties have been engineered to develop new drug delivery systems for the local, sustained and targeted delivery of drugs with improved therapeutic efficiency and less or no toxicity, representing a very promising approach for the effective management of diseases. The utility of nanotechnology, particularly in the field of orthopedics, is a topic of extensive research. Nanotechnology has a great potential to revolutionize treatment, diagnostics, and research in the field of orthopedics. Nanophase drug delivery has shown great promise in their ability to deliver drugs at nanoscale for a variety of orthopedic applications. In this review, we discuss recent advances in the field of nanostructured drug delivery systems for orthopedic applications.

**Keywords:** Drug delivery, nanomedicine, nanotechnology, orthopedics.
In the past few decades, the emergence of nanotechnology has affected and reshaped every aspect of orthopedic research and practice. Nanotechnology has an exceptional potential for orthopedic applications owing to its unique ability to create materials and devices with extraordinary physicochemical, mechanical and biological properties. It has been utilized in a number of novel approaches including tissue engineering for bone regeneration, targeted drug delivery, surface modification of prostheses and implants, and diagnostics in orthopedics. In particular, nanotechnology-based drug delivery systems have influenced many areas of orthopedics. In the current review, we discuss recent advances on nano-based drug delivery systems in the field of orthopedics.

**NANO-BASED DRUG DELIVERY SYSTEMS AND THEIR USES IN ORTHOPEDICS**

Drug delivery systems are engineered structures used to protect, transport, and release a pharmaceutical compound in a controlled manner. Compared to traditional drugs, nanotechnology-based drug delivery systems have several advantages, including high surface area-to-volume ratio for efficient drug loading, improved targeting due to their small size allowing them to overcome biological barriers, enhanced drug solubility and physical stability in biological media, ease of surface functionalization to sense, image, diagnose and deliver pharmaceuticals by the conjugation of biological targeting moieties, controlled dissolution rates/drug bioavailability, reduced adverse side effects, and size similarity to interact with, and modulate biological component.

Various nanotechnology-based drug delivery vehicles, including polymeric nanoparticles, lipid nanoparticles, dendrimers, quantum dots, carbon nanotubes, and metallic nanoparticles have brought great advancements in the field of drug delivery, as well as the entire medical field. These delivery strategies have been applied for the treatment of bone-related diseases for increasing treatment efficiency and specificity of conventional clinical therapies. Nanoparticles and nano-based scaffolds have been widely used for the treatment of bone-related diseases including osteoarthritis, osteosarcoma, cancer bone metastasis, osteoporosis, bone infections and inflammatory diseases, as well as for bone tissue repair and regeneration.

**Osteoarthritis**

Osteoarthritis is one of the most common joint diseases and a leading cause of disability, with a growing rate in prevalence worldwide. Current treatment options for osteoarthritis are limited, and many of these primarily focus on pain relief rather than modifying the disease progression. The major limitations for systemically administered osteoarthritis drugs are rapid clearance after intra-articular injection, limited cartilage targeting, and severe side effects due to multiple injections of high-dose drugs. Nanotechnology-based drug delivery systems have been explored for improving the pharmacodynamics and pharmacokinetics of osteoarthritis drugs through targeted and sustained therapeutic action with fewer systemic adverse effects and longer-term benefits.

Maudens et al. developed kartogenin nanocrystal-polymer particles for effective treatment of osteoarthritis with a very high drug loading over an extended period of time as a controlled drug release system. Kartogenin is a small heterocyclic molecule with the ability of cartilage protection and regeneration. Polymeric particles loaded with kartogenin nanocrystals demonstrated a higher bioactivity than kartogenin solution in a murine mechanistic osteoarthritis model, representing a novel and innovative extended drug delivery system. In a study by Kang et al., thermostressive nanospheres based on chitosan oligosaccharide conjugated pluronic F127 grafting carboxyl group were synthesized for the simultaneous and independent dual release of kartogenin and diclofenac in a single system for combined osteoarthritis therapy. The nanospheres demonstrated initial burst release of diclofenac and sustained release of kartogenin in response to temperature change independently. In vitro and in vivo experiments suggested that these thermostressive nanospheres provide a dual function of anti-inflammatory and chondroprotective effects in the treatment of osteoarthritis. A cationic multi-arm avidin nano-construct was also designed and reported by He et al. for intra-cartilage delivery of a broad array of small molecule osteoarthritis drugs and their combinations to chondrocytes. Its small size and optimal positive charge enable avidin to penetrate deep into the cartilage. Avidin nano-construct as an intra-cartilage drug delivery system may have potential to deliver combination of drugs with only a single injection eliminating toxicity issues and maintain sustained drug release within the joint for efficient and safe osteoarthritis treatment.

**Orthopedic oncology**

Osteosarcoma is the most common primary malignant bone neoplasm. Chemotherapy is an important treatment of osteosarcoma, but limited for
severe side effects and drug resistance.[44] Advances in nanotechnology have led to the development of multifunctional nanomaterials as diagnostic and therapeutic agents which can target bone tumor and deliver drugs and genes selectively to the targeted cells.[15,45] Targeted delivery and controlled release of chemotherapeutic agents by nanocarriers prevent rapid clearance of the drug, prolong blood circulation time, enhance intra-tumoral accumulation, thereby, improving therapeutic efficacy and minimizing side effects.[46]

A cisplatin-crosslinked, doxorubicin-loaded hyaluronic acid nanogel was reported for the effective treatment of osteosarcoma.[46] This codelivery system exhibited a prolonged circulation time owing to the enhanced stability of the nanogel, compared to free drugs. Synergistic apoptosis-inducing effects of doxorubicin and cisplatin were observed following valid tumor accumulation, indicating its great potential for the chemotherapy of osteosarcoma.[47] In another study by Au et al.,[47] pH-responsive nanoscale metal-organic frameworks were developed for the delivery of calcium zoledronate for the treatment of cancer bone metastasis. Folate, a targeting ligand, was incorporated to facilitate the tumor uptake of nanoparticles.[15] The authors demonstrated the increase in direct antitumor activity of zoledronate by 80 to 85% in vivo, compared to free drug, which could be explained by the improved tumor uptake and the prolonged drug release kinetics.[47] Similarly, an intelligent nano drug delivery system composed of functional graphene oxide conjugated with folic acid, polyethylene glycol, and photosensitizer indocyanine green was developed for the delivery of MutT homolog 1 inhibitor and doxorubicin. This nano drug delivery system responding to low pH environment within a tumor and having photothermal and photodynamic transformation abilities showed combined chemo-photodynamic effects to inhibit osteosarcoma.[47]

**Osteoporosis**

Osteoporosis is a degenerative and progressive bone disease, affecting hundreds of millions of aged individuals worldwide, with a consequent increase in the bone fragility and susceptibility to fracture.[48-50] Systemically administered anti-osteoporotic drugs lead to side effects, due to off-target tissue effects. Therefore, novel drugs with higher therapeutic efficacy, less adverse side effects, and more convenient administration routes are needed. On the other hand, nanostructured drug delivery systems, which are able to allow specific drug release kinetics, increase local drug concentration, reduce side effects and enhance bone regeneration, represent innovative and alternative treatment methods for osteoporosis.

A controlled drug release system consisting of simvastatin-loaded poly(N-isopropylacrylamide) brush-modified mesoporous hydroxyapatite nanoparticles was developed for the repair of osteoporotic local defects.[51] This system provided a sustained release of simvastatin to inhibit osteoporosis along with mesoporous hydroxyapatite nanoparticle promoting the osteogenesis as a novel strategy. Ryu et al.[52] designed alendronate-conjugated nanodiamonds and investigated for potential treatment of osteoporosis to obtain a synergistic effect as a bone-targeted delivery system. Specific accumulation to the bone tissue, high affinity to hydroxyapatite, positive synergistic effect for alkaline phosphatase activity, and in vivo bone targeting ability demonstrated the potential of alendronate-conjugated nanodiamonds for osteoporosis treatment. In another study by Nagai et al.,[53] transdermal formulations containing raloxifene solid nanoparticles were designed to improve the low bioavailability of raloxifene by using a permeation enhancer and evaluated them for osteoporosis treatment in an ovariectomized rat model. In this study, a high rate of skin penetration of raloxifene through the transdermal route and high therapeutic effects on osteoporosis were observed.

**Orthopedic infections**

Nanotechnology has demonstrated a great potential for the treatment and prevention of bone infections with the development of antibacterial nanomaterials to improve antibiotic efficacy and to overcome bacterial resistance in selected cases. Nanotechnology-based antibiotic delivery systems offer many advantages over free antibiotics, including controlled and sustained drug release kinetics, ease of surface modification for bacteria or bone targeting, high local bioactivity, low systemic side effects, ability to deliver multiple antibiotics and, enhanced drug solubility and stability.[54,55]

Some nanostructures such as metallic nanoparticles have intrinsic antibacterial activities. Qadri et al.[56] utilized antibacterial activity of silver-copper-boron composite nanoparticles to eradicate *Staphylococcus aureus* bone infection in a mouse osteomyelitis model and demonstrated a potential inorganic route as an antibiotic free and effective alternative approach which could be used for the treatment of osteomyelitis.[56]

Mesoporous silica nanoparticles decorated with concanavalin A and loaded with levofloxacin were
designed as a new class of targeted delivery device. Covalent grafting of concanavalin A to nanoparticles provided an effective penetration in Gram-negative bacteria biofilm, leading to an increased antibacterial efficacy of levofloxacin. Synergistic combination of biofilm internalization and antibacterial agent resulted in a remarkable antibacterial effect against bacterial biofilm.

The combination of antibacterial nanomaterials with implants provides the possibility of osseointegration and elimination of infection simultaneously. Similarly, antibacterial nanomaterials can be also conjugated with bioactive matrix materials to form dual functional composites which are able to both eradicate infection and provide a scaffold for enhanced osteogenesis. Combination of scaffolds with nano-based drug delivery systems stands out as a successful strategy both to improve tissue regeneration and eradicate infection.

The bone cements which have been currently used have several limitations including antibacterial performance and elution of antibiotics from polymethylmethacrylate matrix. A variety of nanotechnology-based antibiotic delivery systems have been explored to improve the drug release profile from polymethylmethacrylate bone cement including polymeric nanoparticles, carbon nanotubes, liposomes, clay nanotubes, and hydroxyapatite nanorods.

**Bone regeneration**

Despite the advances in pharmacological and surgical interventions over the last years, bone regeneration and reconstruction still represent a major concern in the field of orthopedic medicine. Bone tissue engineering is considered a promising approach for bone tissue repair and regeneration using a variety of bioactive materials. Nanotechnologies appear to have an important and promising role in bone tissue engineering. The use of nanostructured scaffolds provides an appropriate environment for cell proliferation, differentiation, adhesion, and bone formation by mimicking the biological micro- and nano-environments, as well as controlled delivery of drugs and growth factors in the lesion site. Nanoparticles can be also combined with scaffolds to further facilitate the bone regeneration.

Many studies in the literature reports the use of three-dimensional nanostructured scaffolds with drug delivery capabilities for bone tissue regeneration. A mesoporous silicate nanoparticle incorporated-nanofibrous gelatin scaffold was designed for the dual delivery of bone morphogenic protein 2 and deferoxamine serving as a biomimetic osteogenic environment. The results showed that the designed scaffold had the ability to control the dual drug delivery of bone morphogenic protein 2 and deferoxamine at distinct release rates, while maintaining their osteogenic and angiogenic abilities, respectively.

A hybrid nanoparticle/hydrogel small interfering ribonucleic acid (siRNA) delivery system was developed for bone fracture healing as an injectable formulation. The results revealed that the formulated system was able to increase bone formation and accelerate healing significantly, which make them potential materials for fracture healing.

Carbon nanotubes are employed in tissue engineering owing to their mechanical, structural and biological properties and also used as delivery vehicles for drugs and genes. Sharmeen et al. reported a controlled drug-releasing matrix using multi-walled carbon nanotubes. The multi-walled carbon nanotube incorporated gelatin-chitosan nanocomposite films were designed and loaded with ciprofloxacin, a common antibiotic. Improved drug release capacity, as well as mechanical and thermal properties were reported by the incorporation of carbon nanotubes, compared to non-incorporated nanocomposite films.

**NANOTOXICOLOGY**

On the other hand, the rapid development of nanotechnology research and production of wide range of new nanomaterials for diverse applications have led to concerns regarding their potential risks on human health. Although a significant amount of research has been carried out to assess the safety of nanomaterials, there is still a need for further studies to reach the knowledge about the interaction of nanomaterials with living organisms, as well as cellular responses and long-term clinical safety. Extensive toxicological studies, in vivo investigations, and clinical trials are required to accelerate the translation of nanotechnology-based drug delivery systems into clinical practice.

In conclusion, nanotechnology-based drug delivery systems have the potential to significantly improve the treatment of various bone-related diseases. Recently, there is a number of outstanding nano-based drug delivery system applications in the treatment of bone related-diseases. Despite the considerable progress in the field of nano-based drug delivery systems for use in orthopedics,
further extensive studies and clinical trials should be performed to demonstrate their efficacy and to evaluate their long-term safety profiles before the results are translated to the clinical practice. A close collaboration among researchers and clinicians is also essential for the achievement of an effective clinical translation.

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