A Review: Inorganic Nanoparticles in Bone Targeted Drug Delivery System

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1. Introduction

Out of various strategies, advancement in the field of nanotechnology has reformed traditional therapies by improving the effectiveness of drug delivery strategies (1). Out of various strategies, nanoparticles (NPs) appear as promising resources for diagnoses and treatments (2). Human tissues comprise of structures at the nanoscale thus, nanomaterials (ranging from 1 to 100 nm in size) have the advantage of size similarity to interact with and modulate biological components (1,3). Because of their small size, shape, and surface properties, the NPs have gained interest in targeted delivery, contrast imaging, combination therapies, tissue engineering, bone and dental repair, and hyperthermia (4,5,6). NPs offer advantages such as; increased drug-loading capacity with large surface area, increased drug solubility in conjugation with delivery vehicles, increased drug stability by providing a protective shield to increase drug retention time, targeted delivery and reduced systemic adverse effects on other tissues or organs, it mimics the bone structure thus allowing the drug to pass through blood-bone marrow barrier, and can be designed to provide immediate bone strength to the diseased bone before the drug is released (7,8).

Bone tissue also known as an osseous tissue, a type of specialized connective tissue is one of the complex and essential organs of the body composed of 60% of inorganic minerals (mainly hydroxyapatite [HAP]), 30% of organic matrix (mainly proteoglycans, collagens, and lipids), and 10% of cells and blood vessels (9,10).

Bone is mainly composed of three different types of cells: osteoblasts, osteoclasts, and osteocytes. Osteoblasts (OBs) originating from local osteogenitor cells are responsible for the production of the bone matrix. Osteoclasts (OCs) originating from various hemopoietic tissues are large, multinucleated bone resorbing cells. These two cells are present only at the bone surface, but the osteocytes permeate through the mineralized bone matrix (11).
The normal maintenance and development of the skeleton requires the bone to constantly be resorbed and rebuilt to form the bone matrix. For a healthy individual, this balance is very well coordinated with the bone mass and microstructure integrity maintained in a steady state. However, disturbances of this equilibrium are seen in numerous diseases mainly osteomyelitis, osteoporosis, osteopetrosis, paget's disease, bone cancer, myeloma related bone disease, rheumatoid arthritis, cancer bone metastasis (1,7,11,12). As discussed earlier, bone tissue comprises of inorganic minerals and organic matrices that can be assembled at nanoscale (13,14). Thus, the intracellular targeting drug delivery based on nanotechnology can enhance the treatment efficiency of bone diseases with the precise delivery of drugs to subcellular regions.

Thus, functionalized nanomaterials can deliver therapeutic medicines to the pathological region with great efficacy and specificity. They can precisely aggregate damaged bones and target cells and then translocate to target organelles (15,16). The types of NPs for drug delivery in bone diseases can be classified into organic and inorganic NPs. Because of their customizable biodegradability and release kinetics, polymeric NPs are a common choice among organic NPs for drug delivery applications. Chitosan, lipid NPs, and poly(L-lactide-co-glycolide) (PLGA) NPs are a few examples of organic NPs for bone drug delivery (17). Inorganic NPs mainly include mesoporous silica NPs, titanium nanotubes, gold NPs, nano diamonds and calcium phosphate NPs

2. Inorganic NPs in bone treatment

Inorganic NPs have gained a lot of importance due to their unique physicochemical properties for novel applications in drug delivery. Moreover, as compared to organic materials, inorganic NPs are highly stable, hydrophilic, and biocompatible. Inorganic NPs as drug or gene delivery carriers have gained potential interest due to their high cellular uptake capacity, nonimmunogenic response, and low toxicity (18).

2.1 Mesoporous silica nanoparticles (MSNs)

They have unique mesoporous structure (up to 10–20 nm pore size), (19) allowing efficient drug loading due to their high surface area, (20) a medication carrier and a bone bioactive agent, making them a suitable therapeutic agent for the treatment of osteopetrosis (21). MSNs acts by increasing OB activity to speed up bone production and decreasing OC activity to slow down bone resorption are two strategies (22). MSNs that have been loaded with doxorubicin (DOX), a layer of poly (acrylic) acid (PAA), and a target ligand, such as concanavalin A, were found to boost pH sensitivity and biocompatibility. As a result of NPs affinity for cell-surface glycans, which are abundant in cancer cells, the therapy of tumor cells is highly targeted.According to the study's findings, when compared to free medicine, this method might maintain the viability of healthy cells and enhance therapeutic efficacy against malignant cells (23).

Mesoporous bioactive glass nanospheres (MBGs) can be created by combining MSNs with calcium ions using well-known sol-gel and supramolecular surfactant chemical processes. The study found the release of calcium ions has been proven to boost OB proliferation and differentiation thus, these MBGs can aid in bone production (24).

2.2 Calcium phosphate nanoparticles

Owing to their superior biocompatibility, Due to their structural resemblance to the inorganic makeup of bone minerals and applications in the field of bone science, CPNs have attracted particular attention (25). As they can stabilize DNA or RNA through electrostatic interactions between the positive calcium ions and negatively charged nucleotides of these molecules, they have been widely exploited for applications in gene transport (26). As a result, it increases the internalization of nucleotides into cells and stops plasma nucleases from degrading them (25). Porous scaffolds have been created using different stages of calcium phosphate for bone tissue engineering applications. Porous structures speed up bone formation by inducing bone ingrowth within the pores, even though excessive porosity reduces the mechanical strength that affects the possible clinical applications (27). Using a soft template technique, Zhou et al. created a porous HAP framework and loaded it with reduced graphene oxide. T

hese porous scaffolds improved the adhesion of BMSCs, promoted cell proliferation, and significantly accelerated bone growth in the scaffold in vivo.

2.3 Nano diamonds (NDs)

Due to their great surface area, simplicity in surface functionalization, and outstanding biocompatibility, NDs, which are octahedral nanoscale carbon allotropes, have drawn interest in regenerative medicine. (28) Similar to GNPs, NDs have been shown to promote osteoblast development and proliferation. (29) To increase bone cell activity and tissue regeneration, Ryu et al. created ND conjugated with alendronate (Alen). (30) They performed affinity tests to determine the suitability of NDs for bone drug delivery and found that Alen ND could bind favorably to the bone mineral HA through interaction with HA and Alen, along with that they also bind to MC3T3-E1 murine OBs in comparison to HepG2 hepatocytes or NIH3T3 fibroblasts, and that this enhanced the OBs expression of alkaline phosphatase (ALP). Alen-NDs were also deposited in bone tissue with great targeting effectiveness when administered intravenously into the rat tail vein. The buildup of NDs in bone to boost mechanical strength and the delivery of Alen, according to the scientists' hypothesis, could encourage synergistic bone development for OP treatments in the future.

3. Metallic inorganic nanoparticles for bone regeneration and bone repair therapy

3.1 Gold Nanoparticle (AuNPs)

They have the potential to deliver pharmaceuticals to the bone because they are simple to functionalize with medications, targeting molecules, and polymers on gold-thiol links (31), because they naturally can increase OB activity (32) and decrease OC differentiation.(33,34) OCs development may be downregulated by GNPs (35).

By inhibiting osteoclast differentiation through suppression of the RANKL-induced signaling pathway, the curcumin cyclodextrin complex loaded in AuNPs core had demonstrated possible anti osteoporotic therapeutic action. The self-assembly method of functionalizing AuNPs by bisphosphonates (alendronate & pamidronate) exhibits superior activity on OCs compared to free bisphosphonates in a concentration-dependent way, indicating use in the treatment of osteoporotic bone diseases (36,37).

3.2 Platinum Nanoparticles

The primary use of platinum NPs is in catalysis, and they are created using a variety of physical and molecular techniques. The use of these particles in bone tissue is explained by their capacity to neutralize anionic radicals and hydrogen peroxide in a way that is comparable to superoxide dismutase (SOD) and catalase (CAT), pointing to their function as antioxidants. By reducing OC quantity and activity in vivo, these particles aid in averting bone loss (38,39).

3.3 Titanium nanotubes

Nowadays, titanium metals are utilized to create bone implants in the form of screws, plates, and pins due to their great mechanical strength, excellent biocompatibility, and resistance to corrosion (40). Because a lack of osseointegration can result in bone infection that necessitates surgery or amputation, osseointegration of the bone implant with the surrounding tissue is essential for tissue recovery. Titanium bone implants can be customized with hierarchical structures using nanofabrication techniques to generate nanoscale surface roughness, increasing the contact with surface adhering cells and so promoting osseointegration (41). By

encouraging cell adhesion, proliferation, spreading, and osteoblast differentiation, this nanoscale design can further enhance the development of bone tissue (42). TNTs loaded with Alen were indicated in a study by Shen et al. to enhance osseointegration and bone production for conditions such osteopetrosis (43). According to the in vitro findings, the Alen-loaded TNT-nHA substrate could maintain the release of Alen for more than 500 hours (about 3 weeks), which in turn encouraged OB proliferation and/or differentiation and downregulated OC differentiation.

3.4 Cerium Oxide Nanoparticles

The primary applications for cerium oxide NPs are in catalysis, luminescence, fuel cells, cosmetics, and pharmaceuticals. By reducing the quantity of free reactive oxygen species, they function as antioxidants (44). When OBs are exposed to hydrogen peroxide, nanoceria protects them from the oxidative harm it causes (45). Reactive oxygen species (ROS) are reduced, and the incidence of cell apoptosis is decreased, which has protective effects. According to research on mouse stromal cells, these particles may have therapeutic utility for diseases associated with ROS, such as Osteopetrosis, where oxidative stress is the primary cause of disease (46). The proliferation, differentiation, and survival of these NPs are significantly influenced by their size, concentration, and culture duration.

4. Global market status of targeted drug delivery systems

The global drug delivery system market was valued at approximately US$ 510 billion in 2016 and is projected to expand at compound annual growth rate (CAGR) of over 6.9% to reach approximately US$ 900 billion by 2025 (Market, 2018) (47). The global market for nanotechnology-enabled drug delivery systems was valued at USD 134 billion for 2016, USD 6,960 million for 2021 (48). The market will be found growing at a CAGR of 16% from 2021 to 2030. The global targeted drug delivery market is expected to reach USD 26,468 million by 2030 (49).

5. Conclusion

There has been a lot of focus on the rising incidence of bone ailments. While conventional pharmacological therapies can offer some comfort, there are several restrictions on how the drugs are delivered and side effects that have also slowed down research on bone illnesses. Based on their superior targeting and delivery efficiency, nanomaterial-based drug delivery systems continue to be a promising strategy for treating bone disease despite the many obstacles in the way of clinical translation. The key benefit of using nanomaterials is that precise functional moieties may be engineered and created to deliver to the bone microenvironment and subcellular compartment. In the coming decades, nanotechnology will remain a rapidly expanding field and more promising outputs will be translated. The present review discussed the latest ongoing research and development on inorganic NPs utilized as drug carriers and tissue engineering. Nanomaterial-based drug delivery systems will also be paired with a variety of ligands thanks to consistently developing breakthrough technologies, and they could one day be used to treat bone disorders that are presently incurable. Thus, designing the right size of NPs, surface modification for cellular-specific targeting,

selecting a suitable route of administration, and optimum dose can generate safe and effective inorganic NPs for drug delivery, tissue engineering, sensing, and imaging applications.

6 References

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