Bone Disease: Recent Approach and Future Perspectives in Bone Targeted Nanoparticles



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1.Introduction

Bone is one of the most important organs of the human body which sustains and protects other organs, produces blood cells, and regulates hormones (1). It is composed of a matrix that includes proteins such as collagen, proteoglycans, and lipids, and a mineral phase, generally known as hydroxyapatite(2). Besides the mineral and protein component, cells, macromolecules, and blood vessels could also be found in bone. Bone diseases encompass a variety of skeletal-related disorders, and can be dividedinto subclasses including genetic, metabolic, degenerative, traumatic, malignant (metastatic and primary), and myeloma-related disorders. Bone disorders and their potential complications have a major impact on an individual's life, causing disability and reduced quality of life (3).

Bone-targeted delivery systems refer to methods and technologies designed to specifically target drugs or other therapeutic agents to bones, in order to treat bone-related diseases such as osteoporosis, bone cancer, and bone infections. The primary goal is to enhance the therapeutic efficacy of the drug while reducing its side effects on other tissues. This is accomplished by attaching the drug to a carrier molecule that selectively binds to the bone matrix, allowing the drug to accumulate in the bone tissue and remain there for a longer duration. Some common approaches for bone-targeted drug delivery include the use of bisphosphonates, another approach is the use of bone-seeking peptides. Other strategies include the use of liposomes, hydrogels, and other materials that can be engineered to target the bone tissue. Overall, bone-targeted drug delivery is an important area of research that holds great promise for the treatment of bone-related diseases (4).

Nanosystems used as vehicles should observe a particular affinity for bone inorganic material but should also be able to target the site of bone disease and prolong drug release. The material forms used for this aim include a range of nanoscale compounds like polymers, ceramics, semiconductors, metals, and self-assembled molecular complexes (6-7). Nanoparticles as drug delivery systemshave been extensively applied for many different diseases, from tumours to regenerative inflammatory pathologies. since they can

develop stable interactions with different ligands, increase drug loading efficiencyof both hydrophilic and hydrophobic molecules, and control delivery of micro and macromolecules (8-9).

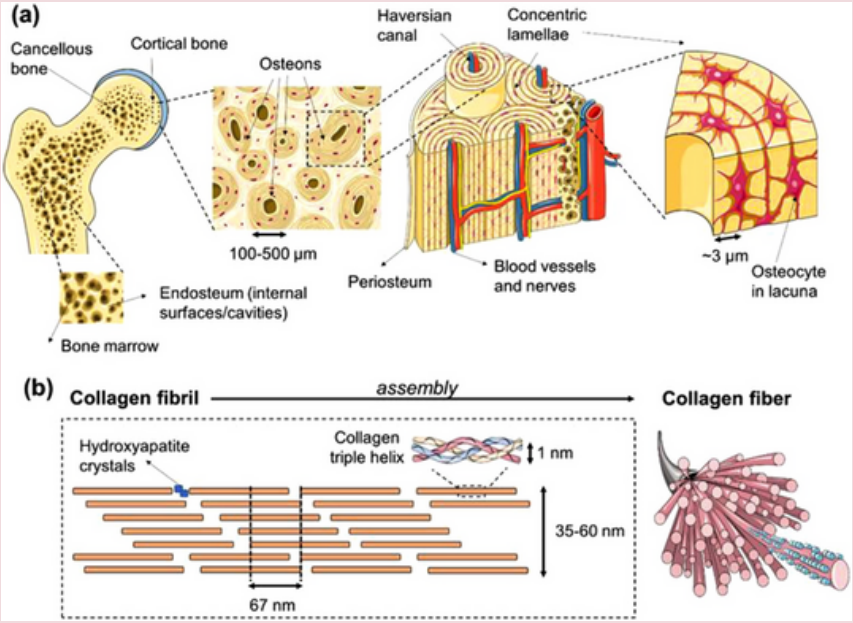

Figure 1. Schematic representation of bone structure. Reproduced with permission [5] Copyright 2018, Elsevier B.V

In particular, nanoparticles assure

1. Increased drug solubility
2. Prolonged drug stability as a result of the protective shield that reduces drug metabolism after administration and avoids fast clearanceby filtering organs
3. Enhanced transport ability across cell membranes
4. Reduction of drug resistance mediated by extrusion pumps;

Nanomedicine has brought forth numerous successful formulations that have reached different stages of clinicaltrials or approvalby the U.S. FDA, includingthe recent successful vaccine formulations againstSARS-COV-2 by Pfizer (10).

2. Drug delivery systems for bone diseases

Among the broad spectrum of nanotechnology-based drug delivery. There are several approaches to bone-targeted drug delivery including:

- Extracellular vehicles: proposed for their ability to load proteins and nucleic acid in various fields such as oncology and regenerative medicine.
- Liposomes: spherical vesicles with an aqueous core surrounded by a single or multiple bilayer membrane, proven to be suitable tools also in several bone diseases.
- Microspheres: generally made of natural, semisynthetic, and synthetic polymers, frequently applied in anticancer therapy.
- Nanoparticles: solid, colloidal particles of different materials which can be functionalized or coated to improve stability and receptor binding.
- Dendrimers: nanosized synthetic polymeric macromolecules composed of a central core with branching units that can provide cytotoxicity. Conjugates: especially polymer-drug and lipid-drug types, exploited in bone diseases.

- Cements: obtained by mixing solid and liquid parts until a viscous paste is formed, used both as bone filler during surgery and as drug carrier.
- Ceramics: inorganic non-metallic solids obtained by heating, including β-tricalcium phosphate (TCP), HA, and mesoporous silica.
- Nanodiamonds: carbon-based nanomaterials which exhibit a large surface area and could be functionalized to conjugate various compounds or drugs, suitable as photoluminescent probes.
- Nanocrystals: usually stabilized by surfactants and/or polymers to prolong the circulating time in the blood and facilitating tumor accumulation.
- Nanohybrids: which combine the mechanical and thermal stability of the inorganic component and the ease of processability of the organic one (e.g., clay-based, carbon-based or metal/metal oxide based nanohybrids).
- Nano capsules: systems with a liquid/solid core with a protective coating which delays the release of the entrapped active compounds.
- Scaffolds: biocompatible templates which are similar to a platform and promote the attachment and the growth of cells, thus used for tissue regeneration and surgical repairs.
- Antibody-based targeting: Antibodies can be engineered to target specific molecules on the surface of bone cells. By attaching a drug to the antibody, it can be delivered specifically to the bone tissue.
- Bisphosphonates: These are a class of drugs that are used to treat osteoporosis and other bone diseases. They work by binding to the bone tissue and inhibiting bone resorption. Bisphosphonates can be delivered orally or intravenously (11-15)

Nanotechnology-based therapeutic agents concern those known as “first generation agents” which are composed by liposomes or polymers, with no active targeting, and containing only one type of drug. The goal of bone-targeted delivery systems is to improve drug efficacy, reduce side effects, and increase patient compliance. Traditional drug delivery systems often result in systemic distribution, leading to off-target effects and toxicity. Several bone-targeted delivery systems have been developed, including nanoparticle-based systems, liposome-based systems, and hydrogel-based systems. These delivery systems can be designed to target specific cell types in bone tissue, such as osteoclasts or osteoblasts, or to target specific molecules involved in bone metabolism, such as the receptor activator of nuclear factor kappa-B ligand (RANKL) or the bone morphogenetic proteins (BMPs). Bone-targeted delivery systems are still in the early stages of development and have not yet been widely used in clinical practice Bones are highly vascularized, but the structure of the vascular network can vary greatly depending on the skeletal site, age, and presence of pathologic conditions, affecting the diffusion of the drug from the bloodstream to the target site. The absence of a basal membrane in some bone blood vessels makes them especially permeable to large molecules. This physiological feature can favour nanoparticles accumulation within the targeted bone, similar to the enhanced permeability and retention effect present in many tumours (Figure 2).
This system involves the use of nanoparticles, which are tiny particles with sizes ranging from 1 to 100 nanometres, to deliver drugs specifically to the bone tissue. The bone-targeted nanoparticles drug delivery system works by modifying the surface of the nanoparticles with bone-targeting molecules, such as bisphosphonates, which have a high affinity for the bone

tissue. These bone-targeting molecules help to increase the accumulation of nanoparticles in the bone tissue and reduce their accumulation in other organs, which can reduce the risk of side effects. The nanoparticles can also protect the drug from degradation and clearance by the immune system of the body, which can prolong the half-life of the drugs and increase its bioavailability. Overall, the bone-targeted nanoparticles drug delivery system has the potential to revolutionize the treatment of bone-related diseases by improving drug efficacy, reducing side effects, and providing a more targeted and controlled drug delivery approach. These nanoparticles are engineered to have a high affinity for bone tissue by incorporating specific ligands, such as bisphosphonates or calcium-binding proteins, on their surface. Once they reach the bone tissue, the nanoparticles are internalized by the bone cells, where they release the therapeutic agents.

The advantages of bone-targeted nanoparticles drug delivery systems include:

1. Improved drug efficacy: By targeting the drug to the site of action, higher drug concentrations can be achieved in the bone tissue, resulting in improved therapeutic efficacy and reduced systemic toxicity.
2. Enhanced drug stability: Encapsulation of the drug in nanoparticles can protect it from degradation and increase its stability, resulting in a longer half-life and improved pharmacokinetics.

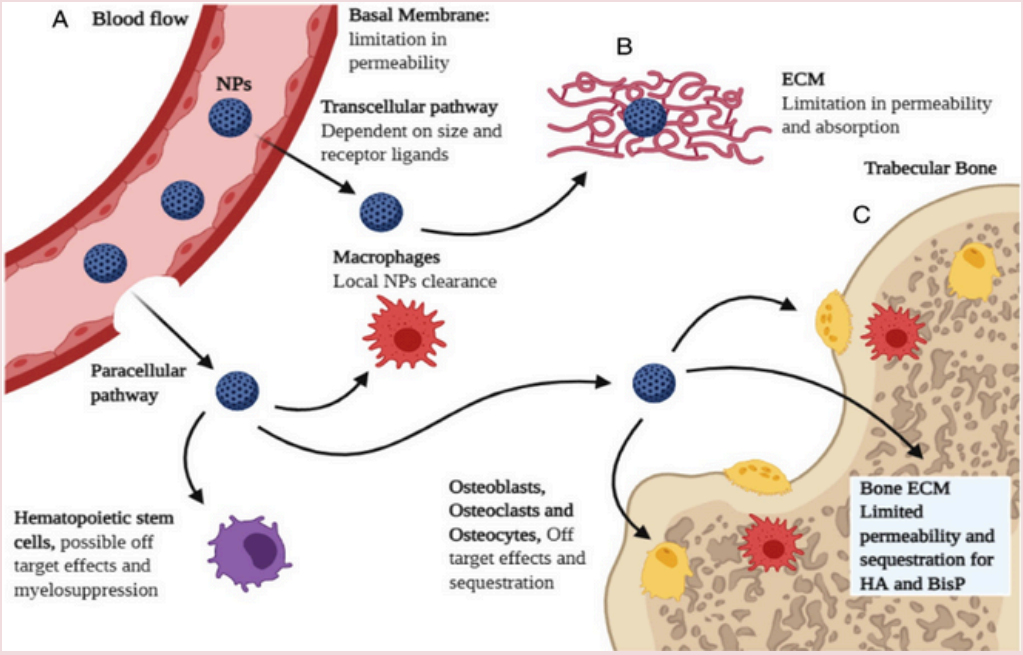

Figure 2. Schematic representation of IV administered nanoparticles path from the blood flow through the bone tissue

3.Conclusion

The various nanoparticles are often used as new therapeutic tools for bone-related diseases. Despite all the progress that has been made in developing various multifunctional drug delivery platforms, these nanoparticles are not yet ready for the clinic. Most are still in the cellular and animal experimental stage and will undergo a long transition period before clinical application. The advantages of the system for targeted drug delivery to bone road nanoparticles include increased drug efficacy, reduced side effects and improved patient

compliance. The system allows a lower drug dose to be administered, which reduces the risk of systemic toxicity. In addition, targeted drug delivery to bone tissue increases the local concentration of the drug, resulting in a higher therapeutic effect. We believe that combined therapies may provide a synergistic therapeutic effect, a larger therapeutic window, lower drug resistance, limited side effects, and systemic exposure of healthy tissues in the near future. Bone-targeted nanoparticles could be used in combination with immunotherapy to target checkpoint inhibitors, antibodies, and immunomodulatory agents to increase their therapeutic effect.

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