Small Molecule-Based Bone Targeted Drug Delivery Systems: An Overview

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Abstract

Bone-targeted drug delivery has received the utmost importance from the research community in the last decade since it is a major health concern among the aged population. Site-specific delivery can substantially advance the clinical treatment of bone disorders such as osteoporosis, osteoarthritis, Paget's disease, and osteosarcoma. Active moieties, including bisphosphonates, with bone-targeting capability, are studied as promising molecules in delivery systems intended to target bone tissue. Typically, bone-targeting agents can be characterized by high bone affinity, a tendency of an extended stay in bony tissues, and maintaining low concentration in the systemic circulation. Other than bisphosphonates, monoclonal antibodies and tetracyclines have shown potential as bone-targeting agents. However, proteins like antibodies-based agents can have several limitations, such as large molecular size, high manufacturing cost, and adverse immune reactions. Targeting moieties based on small molecules, such as bisphosphonates, can prove a better alternative having reduced adverse effects. This work sums up the latest findings concerning compounds having bone-targeting capabilities and the delivery approaches employing these small molecules for bone-targeted drug delivery.

1. Introduction

The bone skeleton in the body is responsible for sustaining and protecting other vital organs. It plays a major part in producing blood cells and regulating hormones and is considered one of the most crucial tissues in the human anatomy (1).

In the medical domain, bone-related disorders such as Paget's disease, osteoporosis, osteomyelitis, and osteosarcoma are often treated with traditional modes of administration of drugs. However, inefficient uptake of drugs into bones can restrict treatment efficiency and hence the therapeutic outcomes. Long-term medications are required to treat bone diseases, which can raise healthcare costs and lead to undesired adverse effects (2). For any active molecule to attain its optimum therapeutic result, it is essential that the molecule reaches and is preserved at the desired receptive site with its physiological function and chemical integrity unaffected (3). To create a sustained and desired concentration of the active drug molecule around the vicinity of bone tissue, a drug delivery system (DDS) interacting with bone architecture at the chemical and physical level is a primary need. The targeting moieties that have an affinity at bone sites can be employed in designing a DDS, resulting in a carrier system demonstrating favored affinity to the bone tissues, where they could exclusively deliver the drug load. The action can result in high therapeutic levels of the active drug component at the target site, enhancing drug treatment efficiency (4).

Systemic nanoscale-based DDS constructs can be administered orally, injected intravenously, or even by intranasal pathway. The smaller particle size grants them the ability to access the smallest blood vessels, and the restricted clearance of these nanosized vehicles from circulatory system awards them stealth-like characteristics. Thus combining targeting molecule with a nanoscale DDS can minimize the dose, imporve efficacy and significantly improve the therapueitc outcomes of the treatment.

2. **Bone Composition and Biological Targets for Bone-targeting agents:**

Bone is a matrix tissue comprised of hydroxyapatite, a mineral, and proteins such as collagen, lipids, and proteoglycans. This biological matrix generally signifies around 30% of the dry, bony mass (5). Other than mineral and protein constituents, bone tissue also accumulates various cell types, macromolecules, and blood vessels. Osteoclasts are delegated in the resorption of the bone architecture, whereas osteoblasts are implicated in the constitution of new bone material by secreting collagenous proteins. Osteocytes assist in signal transduction of mechanical stimuli. Blood vessels can transport oxygen and nutrients to the mineralized tissue through the Harversian and Volkmann's channels that are around 70 µm in diameter. The channels grant accessibility for active agents to organic bone components (6).

Collagen is a very abundantly found organic macromolecule in the body and bone tissue, and hence it could be presented as a promising target for DDS formulated with bone-targeting agents. (7). However, being the vastly present organic compound in the body (8), collagen is substantially present in other organs as well as connective tissues, turning a collagen-specific DDS into a non-specific carrier system to bone tissue. A wide range of antibodies can be used to target organic matrix proteins in the bone (9). Although such antibodies can exhibit high selectivity, the fairly minimal extent of these bone-associated macromolecules could reduce the success of the bone-binding approach. Osteocytes could possibly present as a highly exclusive target in the bone matrix (10). Nevertheless, since the bone cells are rooted in a dense inorganic bony architecture, they are poorly approachable for DDS, so they most likely are not desirable targets for DDS devices. The tissue matrix of bone is comprised almost entirely of hydroxyapatite, the most prominent constituent of the bony tissue. Since hydroxyapatite is exclusively located in bones, it proposes as an excellent target for carrier systems containing bone-specific actives.

3. Drug delivery systems for targeting therapeutics to the bone matrix

Several delivery devices conjugated with bone-seeking actives have recently been researched to direct active molecules toward the bone. A few drug delivery constructs encapsulating/ conjugated with bone-seeking agents have been summarized in Table 1.

3.1 Prodrugs

Bone-targeting prodrugs carrying bone-specific drugs have been formulated to treat bone disease in the murine model of infection (20-22). In previous studies, bisphosphonates have been linked to fluoroquinolones for bone-specific action (23-24). An in vivo investigation demonstrated that bisphosphonates-conjugated-fluoroquinolones have an advanced infection inhibition capability than the parent drug administered as a control (24).

3.2 Polymeric carriers

Natural and synthetic polymers, as carrier systems, are methodically studied materials to target the drug to desired tissue. The physiological characteristics of polymer-drug vehicles' could be attuned with a comprehensive range of biocompatible and biodegradable polymers. The major apprehension with polymeric drug carriers is chemically modifying the components, which may impact the bone-specific drug compound's affinity and/or alter the anticipated characteristics of the polymer itself. Alendronate, a second-generation bisphosphonate, has high reactivity and is commonly utilized as a bone-targeting molecule conjugated with polymer structures. The drug-carrying polymer structures are often submicron-sized units or micellar assemblies functionalized using selected bisphosphonates (25, 26).

3.3 Microspheres and Nanospheres

Bioactive drug delivery particles, such as micro and nanospheres, are generally produced by incorporating the drug in the polymer matrix. Nanoprecipitation (27), emulsion (28), solvent displacement (29), and electrospraying techniques (30) are among the common techniques which are generally used to develop the tiny particles containing homogeneously distributed the drug throughout the bulk of the particles. Bioactive molecules such as bisphosphonates (26), peptides (31), and tetracyclines (32, 33) can functionalize the polymers by surface grafting (34, 35).

Nanospheres loaded with alendronate, a nitrogen-containing bisphosphonate, were fabricated using copolymers like PLGA and mPEG with a dual-copolymer approach. It was hypothesized that the presence hydrophilic surface on mPEG copolymer could enhance the systemic circulation period of the delivery system due to the larger hydrodynamic diameter, and also alendronate could enhance the site exclusivity towards the bone tissue (26). Developing such particles involved the covalent functionalization of alendronate to PLGA and then preparing PLGA-mPEG dual-copolymer.

3.4 Microcapsules and Nanocapsules

A limited quantity of research has been available on microcapsule and nanocapsule conjugates. The nanocapsules assembled using calcium phosphate and coated with sodium dodecyl sulfate have been reported earlier (36). The nanocapsules were incubated with dentin discs to investigate in vitro affinity of the system, which revealed distinct adsorption of the bisphosphonate-conjugated nanocapsules.

3.5 Dendrimers

The research by Ouyang et al. fabricated naproxen-loaded dendrimers functionalized using several 2nd and 3rd-generation poly(Asp) copolymers (37). The hydroxyapatite binding assay revealed the greater affinity (>60%) of the dendrimers in the first two hours, highlighting bone-targeting efficiency.

Table 1. Bone-targeting agents and drug delivery applications thus far.

Bone Targeting Agent	Carrier / Drug Delivery Approach	Active Agent	References
Bisphosphonate	HPMA copolymer	TNP-470	(11)
Bisphosphonate	Solid lipid NPs	N/A	(12)
Bisphosphonate	PLGA NPs functionalized with PEG	Bortezomib	(13)
Bisphosphonate	Liposomes	Doxorubicin	(14)
Tetracyclines	3-amino-2,6-dihydroxybenzamideconjugated estradiol	Estrogen	(15)
Dasatinib derivative	PEG 3400-distearoylphosphatidylethanolamine	N/A	(16)
Bisphosphonate	PEG conjugated nanoparticles	Chloroquine	(17)
Bisphosphonate	Metal-organic framework	Doxorubicin	(18)
DDS6 peptide	Polymeric nanocarrier encapsulated nanocrystals	Arsenic-Manganese complex	(19)

4. Conclusions

Nitrogen-containing bisphosphonates, oligopeptides such as poly(Asp) and poly(Glu), and tetracyclines are commonly reported bone-seeking molecules. The therapies for the pathologies, for instance, osteoporosis, osteomyelitis, Paget's disease, and osteosarcoma, could be optimized efficiently with the help of the stated functionalized delivery devices. Developing the described drug delivery constructs can facilitate the accumulation of various forms of systemically administered active agents/ molecules at the desired site. Numerous therapies have been advanced from such innovative bone-targeting drug carrier systems. A few biomedical applications have been approved by FDA and are under evaluation with clinical trials. With the great amount of encouraging preclinical study outcomes, an expansion in bone therapeutics can be envisioned with the delivery systems entering the clinical setup in the upcoming years to relieve affected patients by alleviating the limitations of current bone therapies.

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