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Drug Delivery Strategies for Treating Osteoporosis

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Abstract

Osteoporosis is characterized by a decrease in bone mass and micro architectural deterioration of bone tissue. Current treatments for osteoporosis are generally associated with many limitations, including low oral bioavailability, short half time and long-term side effects. Drug delivery systems are developed to reduce off-target side effects, protect drugs from degradation and control release of the therapeutic agents at the desired sites. This review presents current research strategies adopted for delivery anti-osteoporosis agents. Oral delivery systems were developed to facilitate the oral administration of protein drugs. Targeted delivery systems based on bone seeking agents (such as bisphosphonate) greatly enhanced the distribution of therapeutic agents to bone tissue. Local administration based on nanoparticles and hydrogels slowly released incorporated drugs and remained a sustained therapeutic effect in disease site. Though the effects of these systems have been widely approved in animal models, further researches are needed for a bench-to-bedside transition.

Keywords: Osteoporosis; Drug delivery; Nanomedicine; Bone targeting

Introduction

Osteoporosis is a progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. The pharmacological intervention of osteoporosis has substantially progressed for decades. However, the existing therapies have certain limitations including efficacy and long-term safety issues [2].

The therapeutic efficacy of a drug depends on its intrinsic specificity for the molecular target and concentration at the target site. The non-specific distribution of drugs to off-target tissues and organs generates side effects, which may limit the application of drugs, especially for long-term treatment. For example, parathyroid hormone (PTH), the only FDA approved drug, which is capable of inducing new bone formation, is limited to severe cases and can only be used for less than two years. The oral administration of bisphosphonates (BPs) has been associated with mucosal damage, including gastritis, gastric ulcer, and erosive esophagitis. Estrogen widely distributes to tissues other than bone after systemic administration. Prolonged therapy with estrogen may increase the risks of endometritis, breast and endometrial cancer, and intrauterine hemorrhage. To solve these problems, it is highly desirable to develop drug delivery systems, which might protect the incorporated drug from degradation, provide a controlled release, or effectively enhance the concentration of therapeutic agents at the disease site and therefore decrease the off-target toxicity. This review discusses the current novel drug delivery strategies for anti-osteoporotic agents.

Oral Administration

Calcitonin (CT) is a polypeptide hormone consisting of 32 amino acids. PTH is the physiological antagonist to CT. Both of them involve in the bone metabolism in the body. Currently CT is available as subcutaneous injection and nasal spray, whereas PTH is for subcutaneous injection for a two-year treatment span. Because these drugs need to be given on a daily basis over a long period of time, oral administration is a much more desirable route for the convenience of patients. However, there are many problems associated with peptide and protein drugs oral delivery, such as the susceptible for enzyme degradation and chemical instability in gastrointestinal tract, poor intrinsic permeability across the intestinal epithelium and rapid post-absorptive clearance. Drug delivery systems are developed to overcome these limitations.

Yoo et al. prepared CT poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles by loading CT-fatty acid complexes [3]. In vitro study confirmed the dose-dependent transport of the nanoparticles in Caco-2 cell monolayers, whereas the transport rate of free CT was negligible. Pharmacokinetic study in rats showed high plasma CT concentration in nanoparticles group whereas negligible amounts of CT were detected for free CT group even at a 5 times higher dosage. Moreover, mucoadhesive liposomes were prepared by coating liposomes with mucoadhesive carbopol or chitosan [4]. The mucoadhesive properties were proved using intestines isolated from SD rats. Administration of coated liposome containing CT to rats showed an enhanced and prolonged reduction in blood calcium concentration. In addition, pH sensitive microspheres containing CT were prepared using pH-sensitive polymer Eudragit P-4135F. More than 90% of CT was released within 1 hr at pH 7.4, while very slow release at pH 6.8. Oral administration of 100 μg/kg CT in microspheres resulted in a distinct hypocalcemia and a sustained release of CT in rats [5]. For the oral administration of PTH, there is no intestinal uptake of bare PTH from the digestive tract of rat. However, the incorporation of PTH in PEGylated chitosan

nanoparticles showed an oral bioavailability of PTH at 100–160 pg/mL throughout 48 hrs [6].

The mechanisms of the improved efficacy of drug delivery systems using nanocarriers have been extensively researched. Previous studies have shown that nano- and microparticles are easily taken up by a group of localized endothelial cells in the small intestine, especially by Peyer's patch [7-10]. Therefore, the drug absorption is highly increased. In addition, the incorporation of the drug into particle core could protect it against the harsh environment in the gastrointestinal tract and thus increases the stability of the peptide drug [11]. The controlled release of drug from carriers prolongs the blood circulation [12]. Though there are many oral delivery systems developed for preclinical studies, none has been approved for clinical use yet. Even so, oral delivery of anti-osteoporotic protein/peptide drugs still remains a promising possibility.

Parenteral Administration-active Targeting

The composition of bone varies with age, general health, anatomical location and nutritional status. In general, mineralized tissue accounts for about 50-70% of adult bone; the organic matrix for about 20-40% and water for about 5-10% [13,14]. The mineralized bone matrix consists of carbonated hydroxyapatite. Targeting the mineral composition of the bone presents as an ideal way to obtain osteotropicity. Various tetracyclines, BPs, acidic oligopeptides, chelating compounds and salivary proteins have been employed to target osseous tissue [15]. These compounds bind to the inorganic hydroxyapatite (HA) part of osseous tissue. Drug delivery systems based on these targeting moieties have been developed to obtain osteotropicity.

Choi et al. prepared estrogen PLGA nanoparticles modified with alendronate and polyethylene glycol. The nanoparticles had a strong and specific adsorption to HA [16]. Several other BPs modified bone-targeting nanoparticles and liposomes were developed for systemic administration and were evaluated in vitro [17-19]. Oligopeptide conjugated estradiol prodrug exhibited preferential distribution into bone, where it gradually regenerated the parent drug. As a result, weekly treatment with the prodrug showed comparable pharmacological activities with every 3-day estradiol treatment but less systemic adverse effects [20]. Zhang et al. developed a targeting system involving cationic liposomes attached to another oligoeptide (six repetitive sequences of aspartate, serine, serine) for delivering siRNAs specifically to bone-formation surfaces. Using this system, they encapsulated an osteogenic siRNA that targets casein kinase-2 interacting protein-1 (encoded by Plekho1), and this liposomal formulation markedly promoted bone formation, enhanced the bone micro-architecture and increased the bone mass in both healthy and osteoporotic rats [21].

The main component of the organic matrix of bone is type I collagen, which makes it highly interesting as another potential bone target site. Collagen binding domains (CBD) are abundant in collagenolytic proteases from microorganisms and are furthermore present in mammalian matrix metalloproteinase (MMPs) [22]. The cDNA of CBD can be added to the peptide or protein of interest by standard molecular biology techniques to produce bone-targeting fusion protein. Ponnapakkam et al. synthesized fusion proteins with CBD domain and linked it with PTH. In vivo study proved the sustained anabolic effect in bone with weekly injection [23]. In a recent study, a peptide of 7 amino acids was first used to engineer parathyroid hormone-related peptide to construct a collagen-targeting system. This peptide functioned as a CBD and specially targeted the peptide to collagen [24].

Local Administration

Though the development of active targeting delivery systems greatly enhanced the drug concentration at desired disease site after systemic administration, it is still a challenge to control the drug distribution in other organs, especially the high accumulation of nanoparticles in liver or spleen. Local delivery from a drug depot could be a viable alternative. They are especially suitable for the treatment of osteoporotic fractures. Numerous natural and synthetic polymers have been studied to employ as local delivery carriers, such as alginate, collagen, poly(lactic-acid) [25] etc. Among them, calcium phosphate (CaP) materials such as hydroxyapatite and biphasic CaP were extensively researched due to their high biocompatibility, bioactivity and osteoconductivity [26,27]. The dissolution of CaP can be controlled by adjusting the crystallinity, and thereby potentially control the release rate of bound or incorporated drugs. Verron et al. developed an injectable BP-combined CaP matrix for preventing osteoporotic fractures that was preferentially localized in the proximal femur, vertebral bodies or wrist. In vivo study proved the significantly increased relative bone content and an improvement of micro-architecture [28]. Besides CaP, HA and PLGA loaded with BP were also developed [29,30]. Local delivery of BP using these biomaterials not only minimized the gastrointestinal adverse effects but also increased the bioavailability of BP for the treatment of osteoporosis [31].

Hydrogels are another type of widely studied local delivery carriers. They are exceptionally suitable as matrices for bone regeneration due to the high tissue-like water content, generally good biocompatibility and efficient transport of nutrients [32]. In addition, some hydrogels could be injected as liquid and then form gel in situ, which is convenient for drug administration [33,34]. Various natural and synthetic polymers are used for preparing hydrogels [35,36]. Growth factors are incorporated and released with a controlled pattern from the hydrogel matrix [37]. Rey-Rico et al. developed in situ poloxamine gels for sustain the release of BMP-2 [38]. These polymers undergo sol-to-gel transition at temperature around 25-33°C. Therefore, it is able to be administrated at room temperature and then form viscoelastic gels at body temperature after injection. More information about hydrogel application in bone regeneration can be found in the reviews [2,33,39].

Miscellaneous

Nasal cavity offers a large surface area with extensive blood supply and no hepatic first-pass metabolism. These features make nasal cavity an interesting site for drug delivery. However, generally proteins and peptide drugs display a relative bioavailability of approximately 1% through nasal administration [40]. The major obstacles include the limited drug transportation across the epithelial membrane as well as the rapid mucociliar clearance [41]. To overcome these drawbacks, nasal delivery systems were developed. Ishikawa et al. developed CaCO3 dry powders as an insoluble carrier for nasal delivery of CT. In vivo study showed a rapid absorption and almost two-fold increase in bioavailability when compared with CT liquid formulation. The improvement might be based on the prolonged residence time in the nasal mucosa [42]. Other particulate nasal delivery systems were developed as well, such as ethylcellulose PTH dry powder, CT gelatin

microspheres [43,44]. Transdermal delivery represents another attractive alternative to oral delivery. Transdermal patch containing microneedles coated with CT was developed. In vivo study showed its comparable efficacy compared with subcutaneous injection. The data proved the patch without hypodermic needles is a viable alternative approach to deliver CT for treating osteoporosis [45].

Conclusion

This review presents current research strategies adopted for delivery of therapeutic agents in osteoporosis. These drug delivery modalities aim to reduce off-target side effects, protects drugs from degradation and controlled release of the therapeutic agents at the desired sites. However, treatment strategies discussed in this review need further development and discussion in future for a bench-to-bedside transition.

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