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Review

Drug carriers in osteoporosis: Preparation, drug encapsulation and applications

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ABSTRACT

Carriers are largely used to enhance therapy efficiency *via* the encapsulation of active molecules. The encapsulation enhances the stability of drug molecules, improves the targeting properties and prolongs pharmacological activity *via* continuous local release of active molecules. The aim of this review is to report the carrier systems used in osteoporosis therapy. This state of the art research has mainly focused on describing all types of carriers used in this area, their elaboration and properties, the drug characteristics used in such specific application, and drug release and efficiency. In this field, various processes have been used in order to obtain well-defined capsules, spheres and more complex carriers. In this exhaustive review, each process is described, illustrated and discussed.

Contents

1. Introduction

Osteoporosis is by far the most frequent metabolic disease affecting the bone. This debilitating chronic disease is characterized by a low bone mass and a microarchitectural deterioration of bone tissue. This leads to an enhanced bone fragility and risk of fracture, particularly the long bones and the vertebrae. Osteoporosis represents also a serious public health problem as all osteoporotic

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fractures are linked with increased morbidity and also because fractures of the hip and the vertebrae are associated with a significant mortality (Holroyd et al., 2008).

Osteoporosis may affect both sexes but women are more vulnerable for the disease because of an acceleration of bone loss after the menopause. In addition to general nonpharmacological measures (such as ensuring adequate dietary calcium and vitamin D intake, lifestyle modifications like smoking cessation, and exercises and reduction of alcohol intake), conventional treatment options for the disease include the use of antiresorptive therapy or anabolic agents. Antiresorptive therapy include essentially bisphosphonates (BP), hormone replacement therapy (HRT), selective estrogen receptor modulators (SERM) and calcitonin (CT), while anabolic agents comprise parathormone (PTH) and its analogs (Lecart and Reginster, 2011; MacBane, 2011; Roush, 2011; Gennari et al., 2009). The goals of treatment are to prevent fracture, preserve structural bone integrity and to decrease morbidity and mortality related to fractures (Follin and Hansen, 2003).

All the therapies mentioned above present some bioavailability concerns. In order to overcome this shortcoming, many approaches were used to obtain more convenient formulations with either better oral bioavailability or providing better patient compliance such as injectable sustained drug delivery systems. Therefore, attention was paid to deliver drugs in carrier systems.

Processes used for the preparation of these carriers include multiple techniques such as emulsion solvent process, spray drying, emulsion polymerization, emulsion solvent diffusion, rapid expansion of supercritical solutions, and ionic gelation. These various techniques led to the obtaining of a multitude of pharmaceutical forms ranging from polymeric microparticles and nanoparticles to nanocrystals and liposomes. Recently, an oral formulation of CT (Ostora® developed by Tarsa Pharmaceuticals) achieved all of the efficacy endpoints in a phase III clinical trial. Obtained results showed that reductions in bone resorption markers with the novel oral formulation were greater than those observed in nasal spray or placebo. This revolutionary event may open wide horizons for the development of other oral pharmaceutical forms of peptides as, to our knowledge, few peptides reached successfully this advanced clinical phase as oral drug delivery systems (Binkley et al., 2012).

2. Challenges in osteoporosis therapy

Therapeutic options that can be used in osteoporosis include antiresorptive agents and anabolic therapy. Antiresorptive agents include BP, HRT, SERMs and CT. BP are still used first-line for treatment and prevention although they present very low oral bioavailability and many side effects related especially to the gastrointestinal tract, with esophageal irritations being the most frequent manifestation. In fact, oral absorption ranges from about 0.7% (for alendronate and risedronate) to only 6% (for etidronate and tiludronate). Furthermore, drug absorption is reduced by food and by products containing calcium or polyvalent cations (Cremers et al., 2005).

HRT comprises the use of estrogens or progestins. Again, oral bioavailability is poor for natural estrogens and progestins because of the important first pass metabolism exerted by the liver and the gastrointestinal tract (Brar, 2010; Zaghloul et al., 2005; Christiansen, 1996). Raloxifene, a SERM which is given orally as tablets presents a low bioavailability (absolute bioavailability less than 2%) due to its poor solubility in biological fluids and its extensive first pass metabolism. High-fat meal can increase absorption but without actual clinical impact (Thakkar et al., 2011; Pickar et al., 2010; Wempe et al., 2008; Hochner-Celnikier, 1999). CT is given either by subcutaneous injection or intranasally as a spray. Following parenteral administration, CT has a short half-life (15–20 min) which needs frequent administrations. On the other hand, nasal spray provided a bioavailability of only 10–25% compared with the parenteral form.

Anabolic therapy represents another pharmacological approach for osteoporosis management. It includes PTH and its analog teriparatide. The latter is administered by subcutaneous daily injections which may compromise patient compliance because of the chronic nature of osteoporosis. Thus, development of an oral drug delivery system of teriparatide will be interesting but must challenge the acid-induced hydrolysis of the active pharmaceutical ingredient (API) in the stomach and its poor membrane permeability (Goldberg and Gomez-Orellana, 2003).

3. What are the main advantages of using carriers compared to conventional aspect based on use of molecules solution?

The shortcomings of pharmacological therapy and the crucial achievements related to the formulation of carrier systems, especially, the enhancement of the bioavailability of various active molecules (Raffin et al., 2012; Vural et al., 2011; Sahoo et al., 2007), led to attempts to investigate their application in osteoporosis. The use of carriers as drug delivery systems provides advantages over a simple solution of active molecules as they can protect drug from inactivation (by light or enzymatic attack) and also reduce its toxicity (Khachane et al., 2011; Mazzaferro et al., 2012; Tammam et al., 2012; Barratt, 2003). Moreover, encapsulation allows the masking of unpleasant taste of some drugs. Enhancement of the therapeutic efficacy may also be obtained as biodistribution of the active molecule depends no longer on its own physicochemical properties but on carrier's ones (Gagliardi et al., 2012; Heneweer et al., 2012; Herrero et al., 2012; Mora-Huertas et al., 2010). In fact, carriers may, compared to drug solutions, provide better membrane absorption and targeting of the drug to the tissue where the pharmacotherapeutic action takes place. Reproducible and long-term release of the drug at the target site is then provided (Cintra e Silva et al., 2012; Levchenko et al., 2012; Poletto et al., 2012; Wang et al., 2012a; Cenni et al., 2008; Sahoo et al., 2007).

4. Methods used for the preparation of carriers

Various methods were used for the preparation of carriers depending on their nature: particulate carriers (with vesicular or spherical form) or lipid carriers like liposomes which are vesicles composed of concentric lipid bilayers (Beija et al., 2012). Used techniques for the formulation of particulate carrier systems are classified in two categories: techniques based on the use of preformed polymers and methods relying on polymerization of monomers. Techniques based on the use of preformed polymers comprise solvent evaporation, nanoprecipitation, salting out, dialysis, spray drying, emulsion solvent diffusion and emulsion coacervation.

On the other hand, methods relying on the use of the polymerization of monomers include emulsion polymerization and interfacial polymerization. Liposomes are obtained by other methods such as lipid film hydration, reverse phase evaporation, solvent injection, freeze–thaw and the microfluidization technique (Meure et al., 2008). The adsorption of drug molecules to preformed carriers' surface is also an alternative. In this study, we will focus on methods used for preparation of carriers intended to the treatment of osteoporosis. For further data about all the above-cited preparation methods, interested reader may refer to reviews of Rao and Geckeler (2011) and Mora-Huertas et al. (2010).

Eight of the methods cited above were used to prepare carriers designed for osteoporosis treatment: emulsion solvent