Protein Release Systems for Bone Regeneration

Diana Daniel Pérez and Fernando Gomes de Souza Junior*

Institute of Macromolecules, Brazil

*Corresponding author: Fernando Gomes de Souza Junior, Institute of Macromolecules, Professor Eloisa Mano, Brazil

Abstract

Therapeutic proteins have emerged with a significant role in the treatment of a broad spectrum of diseases, including metabolic disorders, autoimmune diseases, and bone regeneration. However, the efficacy of therapeutic proteins is limited by their immunogenicity, instability and short half-life. Nowadays, the use of therapies such as bone morphogenetic proteins (BMP) is limited by the inefficient delivery. The high doses applied are frequently related to adverse and severe effects. Aiming to overcome these limitations, the use of polymers as matrixes provide several strategies for the application of therapeutic proteins in organisms. This work presents the main used polymers besides collects some essential aspects related to therapeutic proteins used in bone regeneration.

Introduction

Proteins are widely used for therapeutic purposes [1]. However, clinical applications of the proteins are restricted by their potential immunogenicity that limits their therapeutic efficacy besides threatens patients with adverse effects. Additional limitations of therapeutic proteins are their degradation through circulation, glomerular filtration, and processing by the immune system, thus leading to a low plasma half-life, poor bioavailability and reduced in vivo activities [2-5]. These problems require frequent injection and the use of large doses to achieve the required therapeutic efficacy, increasing the risk of producing severe allergic responses [6-10]. To overcome these limitations, micro and nanoencapsulation technology using polymers as continuous phase provide several strategies for the application of therapeutic proteins in organisms [11,12].

Polymer science has a salubrious impact on the encapsulation of therapeutic proteins since polymers are the primary materials used to prepare these systems [13-17]. Thus, the search for new properties of these materials based on obtaining new derivatives from the commonly used polymers or new blends of them is a goal of many researchers [18-22]. Biopolymer-based nano and microparticles are being more and more considered as essential carriers of biological agents because of their advantages of biocompatibility, ease of surface modification, localized action and reduced systemic toxicity [23,24]. Microencapsulation of proteins in polymer matrices requires special care due to the fragile nature of these molecules. Each protein family has different characteristics, requiring the adaptation of techniques and materials to their satisfactory encapsulation [25-27]. In this work, an overview of the main therapeutic proteins used in bone regeneration will be presented.

Proteins and Bone Regeneration

Proteins are natural polymers present in all living cells [28,29]. They are the most abundant organic molecules in living systems. These molecules are much more diverse in structure and function than other classes of macromolecules. The use of proteins aiming therapeutic purposes has increased. However, the use of proteins as therapeutic agents presents some limitations, being very sensitive to environmental conditions, e.g., their physicochemical instability in some body fluids (in saliva and gastric juices) which limits the use of specific routes of administration, as the oral one. Likewise, the large size of these biomolecules limits their transdermal use. The most common mode of administration of these drugs is through intravenous injections, which are often not well tolerated by the patient. In addition, most of these proteins have short half-lives in the bloodstream and need to be frequently given in high doses for efficacy, but such systemic administration in high doses can cause side effects [30,31], such as restlessness, hyperhidrosis, lightheadedness, itching and rash, tachycardia and arrhythmias, and so forth [32-34].

Among the numerous proteins that have already been used as therapeutic agents, those used for bone regeneration are a crucial group. The bone morphogenetic proteins (BMPs) are glycoproteins found in bone tissue. BMPs were first described by Marshall Urist in 1960 when the formation of bone after implantation of the demineralized bone matrix at intramuscular points was noticed. BMPs are responsible for the induction and regeneration

of demineralized bone grafts. They are involved in the regulation of the differentiation processes of several cells during skeletal development and fracture as well [35,36]. BMPs are used as a tool for the treatment of degenerative trauma, neoplastic conditions, mandibular reconstruction, oral and maxillofacial surgeries [37].

The Food and Drug Administration (FDA) approved the use of BMPs in July 2002 for the treatment of traumatic, neoplastic, and infectious degenerative diseases. Its application had a rapid increase in the United States despite the high initial cost due to the excellent obtained results [38].
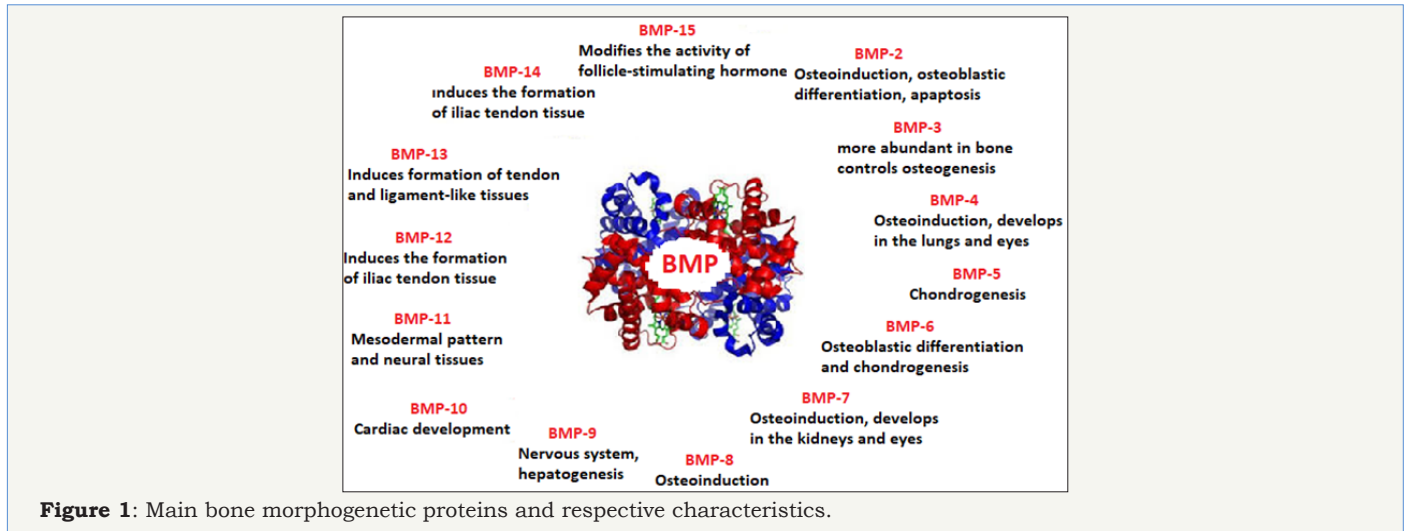
Main bone morphogenetic proteins

Figure 1: Main bone morphogenetic proteins and respective characteristics.

There are several types of BMP with the function of producing bone. Figure 1 shows the main bone morphogenetic proteins and respective characteristics. The types of BMP-2 to BMP-9 belong to the super family transforming growth factor beta. Sequential activation of all BMPs is vital for osteoinduction and bone callus formation. In this specific context, BMP-2, BMP-4, and BMP-7 present the highest chondroinductive and osteoinductive activities. Many processes for cell growth (apoptosis and differentiation) depend on the BMP signaling. These proteins play essential roles in maintaining adult tissue, such as fracture repair initiation, and vascular remodeling [39].

In turn, among BMPs, BMP-2 and BMP-9 are the most active proteins for inducing the activation of alkaline phosphatase, being fundamental for the differentiation of enzymes and progenitor cells into osteoblasts. Besides that, BMP-2 and BMP-9, present potent osteoinductive activity. In turn, BMP-2 plays a crucial role in the processes of chondrogenesis and osteogenesis, as well as revascularization and is considered essential in the repair of fractures. On the other hand, BMP-3 does not induce the formation of specific tissues, being useful to the cartilage formation [40,41].

BMP systems also play a crucial role in folliculogenesis. Specifically, BMP7 is highly expressed in the cell layer of the ovarian follicles. This protein also acts as an endogenous suppressor of new glioblastoma cells (GPC) and thus can become a new cancer treatment [42]. The growth factors BMP4 and BMP7 affect the function of granulosa cells directly. On the other hand, they suppress the apoptosis of these cells [43].

Currently, there are several studies in the literature proving the use of human recombinant morphogenetic protein-2 (rhBMP-2) with good bone neoformation results, especially in critical defects

and in sites with difficult conventional bone grafting [44-55]. Concretely, in the area of dentistry, rhBMP-2 is used to enhance regenerative results in surgeries of significant bone defects in the mandible or maxilla, periodontal surgery, surgical resection associated with tumor lesions and adaptation of dental implants [56].

Protein Release Systems

As already mentioned, the effectiveness of the proteins will depend on their bioavailability at the desired binding site, which depends on the structural and biomechanical properties of the carriers. As those proteins are relatively soluble, if a suitable carrier cannot keep them trapped, they will be eliminated before reaching the desired site. Also, this premature release can cause side effects such as ectopic bone growth, inflammation, and uncontrolled bone formation [57].

Therefore, more in-depth research related to the use of polymer particles as transport systems for these species should be increasingly pursued. In addition to the different techniques of encapsulation since it will offer new functional properties to this asset, as it is controlled release in a specific environment, keeping the asset isolated, increasing its useful life [58]. Figure 2 shows the use of nanoparticles containing BMP for fracture treatments.

Microencapsulation techniques

Microencapsulation is the name of a set of techniques for preserving the quality of delicate substances through a method able to produce materials with remarkable new properties. Aiming this, usually, a polymer shell is prepared on the active substance using a specific technique [59]. A bibliometric research using Google Scholar, performed in March 2018, allowed inferring that

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from more than 203k documents related to master key "Protein release and microparticles", 24.7%, 18.0% and 7.4% of them used the emulsion, spray drying, and coacervation techniques for the preparation of the microparticles. Therefore, these three techniques are responsible for 50.1% of the studies related to the microencapsulation of proteins. Further details about the microencapsulation techniques were already presented in another work of our group [60].
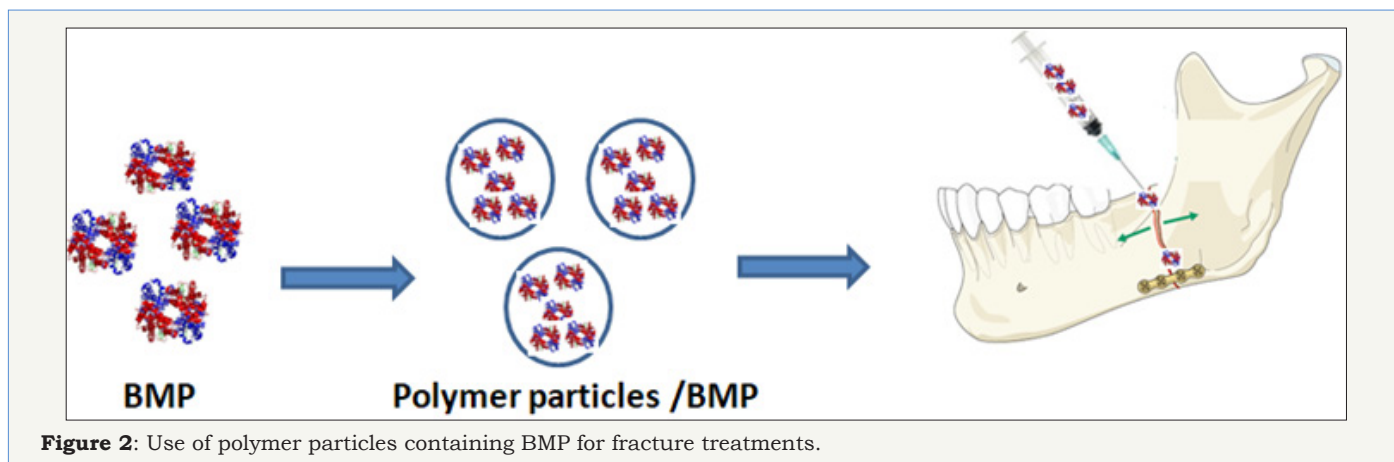

Figure 2: Use of polymer particles containing BMP for fracture treatments.

The release of proteins from polymer particles

Pursuing to preserve the quality of delicate substances, several researchers carried out a myriad of works where they used these different microencapsulation techniques aiming to prepare systems for the controlled release of a protein using polymers as the protective shell [61-68]. The main polymers used for the release of proteins are poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA). More specifically, a second bibliometric research using Google Scholar, also performed in March 2018, allowed inferring that from more than 987k documents related to master key "bone tissue regeneration proteins", 15.4% of them used polymers as the matrix of the delivery system. So, more than 152k documents described the use of several polymers for this purpose. From them, PLA corresponds to 32.1% of the total. In turn, PLGA, polyurethane, and poly(methyl methacrylate) correspond to 23.1%, 13.9%, and 9.1%, respectively. Therefore, these four polymers are responsible for 78.2% of the studies. Some representative examples using polymer materials and microrencapsulation techniques used for the BMPs release are here presented:

Quinlan et al. [69] used the Spray drying technique to encapsulate the BMP-2 protein in polymer matrices. The objective of the work was to evaluate the potential of alginate and PLGA as BMP-2 transporters. They used the double emulsion technique for PLGA particles. PLGA ensured the stabilization of the protein and allowed its controlled release after implantation into a collagen-hydroxyapatite (CHA) framework. The obtained microparticles presented diameter between 1 and 10μm. The morphology of the materials is a function of the preparation procedure used. The alginate microparticles presented an irregular shape with a smooth surface, while the PLGA microparticles had a spherical and porous shape. After the release study, the author inferred that alginate and PLGA microspheres released 46% and 12% of their total contents, respectively. Besides, after incorporation of these microparticles into the frameworks, the BMP-2 protein was sustained release for up to 28 days.

Qiao et al. [70] used poly (lactic-co-glycolic acid) (PLGA) to create a controlled release system of the BMP-2 protein by the double emulsion-solvent evaporation (W/O/W). The authors encapsulated the protein with the calcium phosphate cDNA (CaPi) plasmid complex that was used to promote transfection of the protein. Dynamic light scattering (DLS) showed that the particle size of calcium phosphate was about 350nm and the particle size of BMP-2 / CaPi was about 600nm. The encapsulation efficiency ranged from 30 to 50%. The initial release rate in 24 hours was less than 7.5%. PLGA-BMP2/CaPi microspheres released the BMP-2 cDNA plasmid for up to 30 days. The authors suggested that PLGA-BMP2/CaPi microspheres may promote ectopic osteogenesis, with strong prospects for the promotion of bone regeneration.

Lochmann et al. [71] used block copolymers of polyethylene glycol - poly (lactic-co-glycolic acid) (PEG-PLGA) to produce rhBMP-2 protein controlled release systems. They were prepared by the double emulsion-solvent evaporation technique. The authors investigated the influence of a co-solvent, PEG 300, on the properties of the particles. The results were compared to data from unmodified PLGA microspheres. In this study, the authors were able to encapsulate 85% rhBMP-2 in PLGA microspheres. Thus, the authors concluded that PEG-PLGA microspheres have promising application in sustained release allowing reduction of the required dose of rhBMP-2 to limit adverse effects and costs. Also, the data indicated that the use of PEG as the internal phase co-solvent is not suitable for rhBMP-2.

Conclusion

The use of Bone Morphogenetic Proteins has expanded the treatment options to achieve the regeneration of bone tissue, producing a tremendous impact in human bone reconstruction. Several works about BMPs using release systems based on different polymers as a means of transport presented positive results demonstrating the osteoinductive capacity of the proteins. Most of them were prepared using the combination of PLA

and microencapsulation by emulsion technique. Therefore, this combination must be intensely studied aiming to produce innovative materials, which will improve the human quality of life.

Acknowledgment

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