Maastricht University

Bioceramic nanoparticles for bone regeneration

Citation for published version (APA):

Sutthavas, P. (2023). *Bioceramic nanoparticles for bone regeneration*. [Doctoral Thesis, Maastricht University]. Maastricht University. https://doi.org/10.26481/dis.20231011ps

Document status and date:
Published: 01/01/2023

DOI:
10.26481/dis.20231011ps

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
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Chapter 8

Statement of impact

There is an urgent need for new solutions to treat large bone defects in our ever-increasing aging western population. However, current gold standard treatment is based on using patients own bone (i.e., autograft) which has limitations in availability and is associated with complications such as donor site morbidity. Therefore, researchers have explored different types of synthetic materials, which are off the shelf available in large quantities and have similarities to native bone. Calcium phosphate ceramics and silica-based biomaterials such as bioactive glass have been heavily researched for bone regeneration applications because they display good biocompatibility and possess some ability to induce bone regeneration. However, although calcium phosphate ceramics and bioglass materials can promote bone repair processes such as differentiation of primary bone cells (osteogenesis),[1] their biological performance remains inferior to natural bone. Additives such as drugs and growth factors can be incorporated into the materials to improve their bioactivity, but increases the cost and reduces the shelf life of the materials. To circumvent this issue, bioinorganic ions such as strontium, zinc, and copper have been added to the materials to improve their bioactivity, as they play important roles in bone regeneration [2, 3]. Incorporation of these synthetic bioinorganic ions in ceramic biomaterials is usually based on ion substitution; however, this can alter both the physical and chemical properties of the materials. Furthermore, ion release is hard to control as it often relies on material degradation rates. This is important, as the ability of ions to promote bone regenerative processes is highly concentration dependent.

Nanoparticles can be used as reservoirs for ion or growth factor delivery, where ion release rates can be decoupled from biomaterial

degradation rates. For bone regeneration, especially nanoparticles created from calcium phosphate and bioactive glass biomaterials are of interest, due to their inherent bioactivity and chemical similarity to inorganic component of bone. In fact, several papers have shown that nano-sized calcium phosphate and bioactive glass biomaterials have superior bioactivity compared to their micro-sized counterparts. Finally, nanoparticles can be easily (surface) modified to allow tissue targeting, stimuli responsive drug release, and can be easily incorporated into other biomaterials to improve their mechanical and biological properties [4].

Despite their extraordinary potential, how nanoparticles physical properties such as their shape, composition and morphology influences their bioactivity is not well understood. Moreover, what parameters play important roles in optimizing ion delivery from nanoparticles is not known. This thesis concerns the investigation of several silica and calcium phosphate based nanoparticles, and their structural optimization towards application in the bone regeneration field.

To identify potential knowledge gaps in the field, first a literature research of bioceramic nanoparticle synthesis methods, ion-incorporating methods and their application in the bone regeneration field was conducted. While several studies investigated the effect of nanoparticle size and crystallinity on their ability to promote bone regenerative processes, not much is known about the importance of nanoparticle shape. In **chapter 3** we showed that nanoparticles shape is an important factor determining their ability to induce cell adhesion and hMSCs osteogenic differentiation. Specifically, we showed that homogeneously synthesized needle-shaped hydroxyapapatite nanoparticles can promote hMSCs osteogenesis more

efficiently compared to spherical or rice shaped nanoparticles both when applied as coatings and as nanoparticle suspensions. As such, needle shaped HA particles can be used as a promising strategy to improve the clinical performance of biomedical implants, such as the frequently used metallic implants in orthopedics and maxillofacial surgery. Moreover, our research contributed to an improved understanding of how nanoparticle shape influences their ability to promote early, middle, and late osteogenic markers, which can help scientist in the field design better performing biomaterials.

Mesoporous bioglass and silica nanoparticles have been heavily explored in the drug delivery field. Their use for the delivery of ions has expanded over the past decade. However, much is still unknown on how to optimally use them in the bone regeneration field. This is partly due to difficulties in their preparation: ion doping can negatively affect nanoparticle formation and homogeneity. This thesis attempted to bridge this knowledge gap by investigating nanoparticle design parameters that allow multiple ion incorporation and controlled ion release mechanisms.

In **chapter 4,** we demonstrated that mesoporous silica nanoparticles can be modified to deliver single or multiple ions. We demonstrated that a calcium phosphate surface layer on mesoporous nanoparticles (MSN) could be used to allow pH responsive ion release and that this significantly improved their efficacy to promote osteogenesis in hMSCs. Our developed MSN could efficiently induce the expression of early, middle and late osteogenic markers in the absence of other stimulators of osteogenic differentiation where MSN containing CaZnP surface coating were most osteogenic. Our study was the first to demonstrate that a single nanoparticle

construct delivering multiple ions (i.e. Sr, Ca, Zn, P) can efficiently promote osteogenic marker expression in hMSCs at a much lower dose compared to adding the same ions but directly dissolved in the cell culture media. Thus, our MSN can be used as to effectively induce hMSCs osteogenesis at relatively low ion doses. Considering these advantages, the MSN developed here represent promising constructs for use in bone regeneration applications, for example as coatings or as components in biomaterials. Our study also contributes to a better understanding of how ion dosing and possible ion synergy influences hMSCs osteogenesis processes.

In **chapter 5**, we built on this knowledge by investigating different Zn incorporation modes in degradable MSN and mesoporous bioactive glass nanoparticles (MBG). Zn was incorporated in the CaP surface layer, inside the mesopores or inside the silica matrix of MSN or MBG particles. We demonstrated that CaP surface coating led to stable MSN and MBG at neutral conditions but stimulated ion release at acidic conditions. Moreover, degradable MSN with Zn incorporated in the mesopores were most effective in promoting ALP production in hMSCs. We demonstrated that Zn incorporation amount and release profile in association with Si ion release, were important factors in determining their bioactivity. As such, these factors should be considered in the design of therapeutically active ion doped ceramic nanoparticles.

In **Chapter 6**, we investigated an alternative synthesis method to incorporate multiple bioinorganic ions into solid bioactive glass nanoparticles (nBGs) using a laser-doping technology. We showed that laser doping can be used to incorporate multiple ions in nBGs without negatively

affecting their morphology or structure, however, ion concentrations were low and their biological activity only slightly improved.

While the social impact of in- vitro studies such as those done in this thesis, are difficult to estimate, the understanding and knowledge gained in this thesis could lead to the development of synthetic nanobiomaterials that are more bioactive than current synthetic biomaterials. As such, the knowledge and developed materials may lead to new products that are more cost-effective and represent a less invasive alternative to existing autograft treatments. Better performing synthetic biomaterials could make bone defect treatments more accessible and improve patients overall quality of life. The proposed nanomaterials can also be improved in the future by incorporating other ions and biologics to fulfil additional functions such as reducing inflammation and improve angiogenesis, further optimizing their tissue healing capabilities. Furthermore, the efficient and low cost of inorganic additives delivered by these nanoparticles can reduce the cost of medical treatments and help improve overall healthcare outcomes for patients suffering from large bone defects.

In summary, this thesis contributes to an increased understanding on how bioceramic nanoparticles can be designed and optimized for bone regeneration purposes, which could lead to more affordable, effective and accessible bone regeneration treatments in the future.

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