

FORSTERITE AS AN ALTERNATIVE FOR ORTHOPAEDIC IMPLANTS – SHORT REVIEW

Alexandra AVRAM¹, Aurora MOCANU¹, Gheorghe TOMOAI^{2,3},
Maria TOMOAI-COTISEL^{1,3*}

Abstract. *The research to find an ideal bone substitute material is still ongoing. The majority of research is focused on calcium phosphates and predominantly on hydroxyapatite. However, forsterite, a magnesium silicate (FS, Mg_2SiO_4), has recently received a large attention in regards to biomedical applications due to its high bioactivity. Its superior mechanical properties also recommend it for load-bearing applications. This work focusses on the significance of the properties of FS as a promising candidate for bone substitutions.*

Keywords: forsterite, bioactivity, ceramic scaffolds, hydroxyapatite formation, antibacterial activity

<https://doi.org/10.56082/annalsarsciphyschem.2021.2.32>

1. Introduction. Human bone and implants

A dynamic tissue, bone is different from the rest of human tissues on account of its hardness. It is composed of a limited number of cells in a fibrous collagen matrix that becomes the adhesion surface for hydroxyapatite as well as other inorganic compounds (magnesium hydroxide, fluorides, and sulphates). Although bone cells (osteocytes, osteoblasts, osteoclasts, osteogenic cells) are small in number, they are quite significant for bone function. Osteoclast cells resorb the old bone lining the medullary cavity, while osteoblasts, by intramembranous ossification, produce young bone tissue under the periosteum. The bone goes through a remodeling process, in which the absorption of damaged or old tissue takes place at the same interface where osteoblasts produce new bone to replace the resorbed one. With excessive resorption, the incapability to produce an optimal osseous matter, or an inadequate response to the increased resorption during the bone remodeling process, the skeleton gains the fragility trait of osteoporosis [1].

To aid in healing the bone, or at least support it, several types of materials have been used along the years, such as metals, either pure or in alloy form,

¹Babes-Bolyai University of Cluj-Napoca, Faculty of Chemistry and Chemical Engineering, Research Centre of Physical Chemistry, 11 Arany Janos Str., RO-400028, Cluj-Napoca, Romania

²Department of Orthopedics and Traumatology, Iuliu Hatieganu University of Medicine and Pharmacy, 47 General Traian Mosoiu Street, RO-400132 Cluj-Napoca, Romania

³Academy of Romanian Scientists, 3 Ilfov Street, RO-050044, Bucharest, Romania

* Corresponding author: Maria Tomoaia-Cotisel, mcotisel@gmail.com

polymers, different types of ceramic materials and lastly, composites. This imposed a challenge to create new bone substitutes with a similar composition to that of natural human bone but with the ability to control/improve upon their properties which led to synthetic calcium phosphates. Among these, stoichiometric hydroxyapatite (HAP) has been the favorite material for a large number of studies to its biocompatibility, similarity to natural bone tissue and good osseointegration. Some studies even improved upon the properties of HAP through cationic or anionic substitutions [2-9].

2. Why forsterite?

Developing implants of bioactive materials that can stimulate osseointegration and vascularization has become one of the most important research areas [10]. Forsterite is a promising candidate for such implants due to the ions present in its structure. Magnesium (Mg) and silicon (Si), have roles in a wide variety of metabolic processes, some of which regarding bone health and development.

As the fourth most abundant element in the human body, Mg plays an important part in skeletal growth, being an essential element for osteoblasts and osteoclasts. Approximately 65% of the total Mg amount is mineralized in bone [11]. Of this, about a third can be found in cortical bone, on the hydroxyapatite surface or in the hydration layer surrounding the crystal [12]. A lack of necessary Mg can lead to stiff, brittle bones with low density. The structure of newly formed hydroxyapatite is changed, the crystals becoming larger and much better organized at low Mg levels, the bones being incapable to support large loads [13, 14]. He et al. [15] reported on the role of different concentrations of magnesium on human osteoblasts, where Mg ions increased both cell viability and differentiation.

On the other hand, Si has also been demonstrated to be beneficial to bone health according to clinical trials in humans [16]. It is an essential element in skeletal development and repair, significantly enhancing the proliferation, mineralization, bone matrix proteins and bone gene expression at a 0.625 mM concentration [17]. Particularly concentrated in bone tissue, for the most part in the osteoid, silicate ions stimulate osteoblasts and play a part in bone calcification [18]. Si has been found to impact the function of cells and advance osteogenesis and angiogenesis [19], a lack of it leading to an abnormal growth and possible growth defects.

So, considering the importance of both ions, forsterite is definitely a suitable candidate for bone regeneration. The fact that these elements are already present in normal bone also ensures for a better bone – implant surface interaction giving forsterite a high level of biocompatibility. Regarding this, there are several studies that have demonstrated its ability to generate hydroxyapatite, *in vitro*, on its surface [20-22].

An advantageous durable host-implant attachment has to ensure an effective force transfer between natural bone and the implant material so that the latter does not loosen [23]. However, materials used in orthopedics or dentistry must be able to bear the high level of wear, stresses and fatigue during the course of day-to-day use. Forsterite is a good candidate for load-bearing applications due to its high mechanical properties that have been the focus of a number of studies [24-30].

3. On the synthesis of forsterite

Forsterite nanoparticles can be synthesized through a wide variety of methods such as solid state [31-33], sol-gel [34-38], sol-gel coupled with ball-milling [39], sol-gel-combustion [40-42], sol-gel surfactant approach [43, 44] precipitation [45, 46], mechanical activation [47-52], microwave-assisted [53, 54], alkoxide method [55], geopolymer technique [56], catalyst-free chemical vapor deposition [57] or hydrothermal method [58].

The first synthesis step is followed by a thermal treatment at fairly high temperatures (commonly in the range of 700-1200 °C) to ensure the formation of Mg_2SiO_4 . Regardless of the method, the synthesis parameters (such as amount of solvent, pH, temperature) have to be carefully controlled to obtain a single forsterite phase. However, a common issue is the fact that the final magnesium silicate may contain traces of periclase (MgO) or enstatite ($MgSiO_3$). This problem can be eliminated by using higher temperatures (up to 1600 °C) for the final thermal treatment [59]. This of course is not ideal as the individual particles will not be as small. Usually, the particle size falls in the range of a few nanometers (nm), though some methods do lead to micrometer-type particles (μm) as it is the case for solid state reactions. In regards to this, table 1 presents a correlation of the synthesis method, thermal treatment and final particle size.

Table 1. Comparison of particle size versus some synthesis methods and thermal treatments

Synthesis method	Materials	Thermal treatment	Particle size	Reference
Precipitation	$Mg(NO_3)_2 \cdot 6H_2O$ $C_8H_{20}O_4Si$ sodium hydroxide as pH regulator	900 °C -2h	10 - 42 nm	45
Sol-gel	$Mg(NO_3)_2 \cdot 6H_2O$ $C_8H_{20}O_4Si$ polyvinyl alcohol (PVA), sucrose and nitric acid as binder and pH regulators	800, 900, 1000 °C -2h	10 – 64 nm	39

Sol-gel combustion	Magnesium nitrate $C_8H_{20}O_4Si$ Glycine and Urea (fuels) nitric acid (catalyst)	Combustion at 400 °C -30 min Calcination at 700-100 °C	28 nm – with glycine 1.951 μm – with urea	40
Microwave-assisted	Silica gel $Mg(OH)_2$	500-1200 °C	100 nm	53
Solid-state	$Mg_3Si_4O_{10}(OH)_2$ $MgCO_3$	1000, 1100, 1200 °C-1h	25 nm – 70 μm	33
Mechanical activation	$Mg_3Si_4O_{10}(OH)_2$ MgO	1000, 1200 °C-1h	500 nm	60
Polymer matrix method	$Mg(NO_3)_2 \cdot 6H_2O$ Colloidal silica Sucrose, PVA	500-1000 °C-3h	< 200 nm	61

Along with shape, surface topography and charge, size control and particle size homogeneity are quintessential for biomedical applications. Due to their larger surface area, smaller particles have a higher biological response than larger ones [62].

4. Physical characteristics of forsterite ceramics

Bioactive ceramics have become an emerging field of research related to bone substitutes in orthopedics. Of course, due to its similarity to natural components in human bone, synthetic hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) has been the subject of a wide variety of studies [63-76]. Here, forsterite-based ceramics deserve notice as they are reported to have good mechanical properties [24, 27, 29, 77, 78]. One such comparison can be seen in the data in table 2.

Table 2. Mechanical properties of forsterite (FS) versus hydroxyapatite (HAP) ceramics

Ceramic type	Vickers Hardness [Hv]	Fracture toughness [$MPa m^{1/2}$]	Compressive strength [MPa]	Bending strength [MPa]	Young elastic modulus [MPa]	Ref.
<i>FS</i>	-	-	2.06 (± 0.09) (900 °C)	-	145 (± 9) (900 °C) [MPa]	24
			2.19 (± 0.06) (1000 °C)		165 (± 12) (1000 °C) [MPa]	
			2.31 (± 0.07) (1100 °C)		171 (± 21) (1100 °C) [MPa]	
			2.43 (± 0.11) (1200 °C)		182 (± 19) (1200 °C) [MPa]	

	830-1098	3.2-4.1	-	-	-	27
	450-940	1.5-3.61	-	-	-	29
	-	1.8±0.4 (1350 °C)	-	150±8 (1350 °C)	-	77
		2.3±0.1 (1450 °C)		181±9 (1450 °C)		
		1.6±0.2 (1550 °C)		145±8 (1550 °C)		
	800±55 - 1102±25	1.86±0.21- 4.3±0.19	-	-	-	78
HAP	-	1.87-2.21	0.69-0.84 (1100 °C)	-	4.28-6.20 [GPa] (1100 °C)	79
	-	-	308±46 (1150 °C)	-	42.2±3.8 [GPa] (1150 °C)	80
			415±46 (1200 °C)		74.6±4.1 [GPa] (1200 °C)	
			465±58 (1250 °C)		79.0±4.8 [GPa] (1250 °C)	
			509±57 (1300 °C)		81.4±4.6 [GPa] (1100 °C)	
-	-	-	45.6±4.6 (1150 °C)	-	-	81
			88.6±3.2 (1200 °C)			
			55.5±2.8 (1250 °C)			
			36.4±3.6 (1250 °C)			

Nevertheless, mechanical features resembling those of human bone are particularly desired especially regarding load-bearing applications.

Also, it was reported that a Young elastic modulus, 43.84 ± 3.29 GPa [30] measured by nanoindentation on forsterite ceramics obtained by thermal treatment at 1400 °C, is higher than that found for natural cortical bone [82].

Certainly, the synthesis of a pure phase forsterite is crucial for the mechanical properties of forsterite ceramics, especially when it comes to having enstatite as an impurity. Due to its polymorphism: orthoenstatite is stable at low temperature, and protoenstatite is stable at high temperatures, and clinoenstatite is a metastable form. A change in the structure of enstatite can lead to a volume change and intrinsic stress, thus lowering mechanical values.

For ceramics, compactness is a very important characteristic as it tends to greatly influence a variety of properties such as permeability to liquids, mechanical resistance, thermal stability, deformation under a load at high

temperatures. In order for forsterite-based ceramics to be used as bioceramics, in addition to the fact that they must be biocompatible, they must have a certain porosity, depending on the intended application. The size and distribution of pores assist in degradation rate, implant integration and decrease any chances of rejection [83, 84].

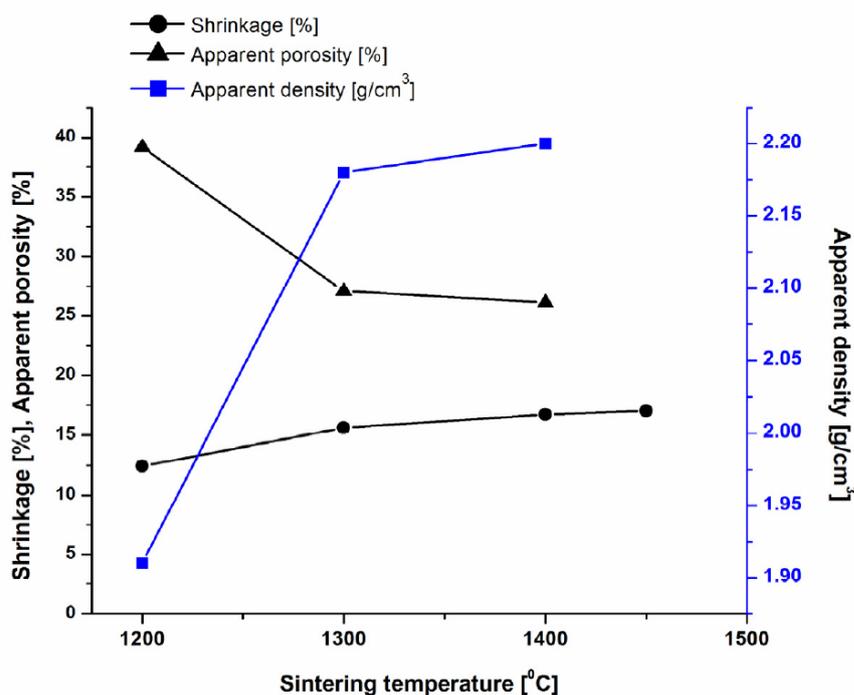


Figure 1. Apparent density, apparent porosity and linear shrinkage determined for forsterite ceramics in function of sintering temperature [30].

This can be better explained by means of Figure 1, looking at the porosity variation for ceramic scaffolds sintered at different temperatures. The porosity for the ceramic sintered at 1200 °C is higher and tends to decrease with the increase in temperature, a normal part of the sintering process. Of course, the decrease in porosity means an increase in compactness and better mechanical properties. The uniformity in size and shape of nanoparticles might also play an important factor in the compactness of forsterite ceramics, with smaller nanoparticles being able to be packed together more tightly leading to more compact ceramics. A heterogeneous powder with differently shaped and sized nanoparticles might cause defects in the ceramic which would lead to a future implant failure.

Given that natural bones have higher porosity on the inside and are more compact on the outside, a possible alternative would be a bioceramic material with bone-like porosity, thus mimicking its structure. By making porous materials

on the inside and more compact on the outside, products with better mechanical properties would be obtained, which would promote a better regeneration of bone tissue. A good porosity would improve the degradation rate and thus reduce the possibility of implant rejection [83, 85].

Additionally, the shrinkage parameter of a scaffold is also important for future processing as a potential orthopedic implant. It is crucial to know how a certain temperature influences the material to better optimize the fabrication of a future implant.

5. Bioactivity studies in SBF

Many studies focus on the biocompatibility and bioactivity of forsterite as a candidate for bone regeneration applications. This is due to Mg and silicate ions in its structure (both essential for bone tissue mineralization) that are easily released in biological environments [86-88]. For a proposed biodegradable ceramic implant to be viable for clinical applications, its degradation rate has to be comparable to the formation rate of new bone. This property is studied first in vitro by immersion in simulated body fluid (SBF) for various amounts of time, followed by an analysis of the amount of hydroxyapatite formed on the surface of the immersed sample. Such studies can be carried out in either a static (the SBF remains unchanged) or dynamic regime (the SBF is periodically changed). Obviously, the dynamic SBF study is better in mimicking the natural process in the human body where bodily fluids are renewed periodically.

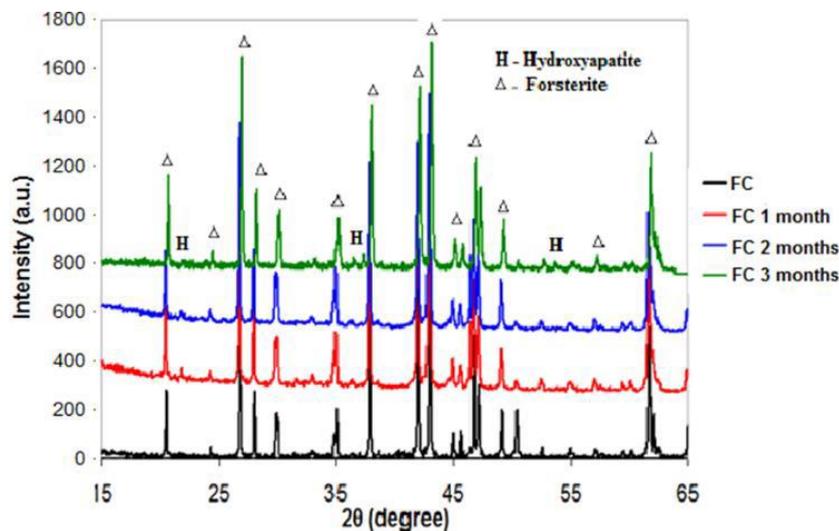


Figure 2. X-ray diffraction pattern for forsterite ceramic, FC-1200, sintered at 1200 °C before and after immersion in SBF, for various time periods [89].

Figure 2 better presents the hydroxyapatite formation on forsterite ceramic scaffolds thermally treated at 1200 °C. In this case, the scaffolds were prepared from forsterite powder synthesized through a sol-gel method. The progression of hydroxyapatite formation on the surface of the Mg_2SiO_4 ceramic is clearly seen from 1 to 3 months of SBF immersion. Once hydroxyapatite starts forming on the scaffold surface, a difference in morphology can be observed between the forsterite ceramic and the newly formed HAP phase. This can be better observed in the SEM image in Figure 3.

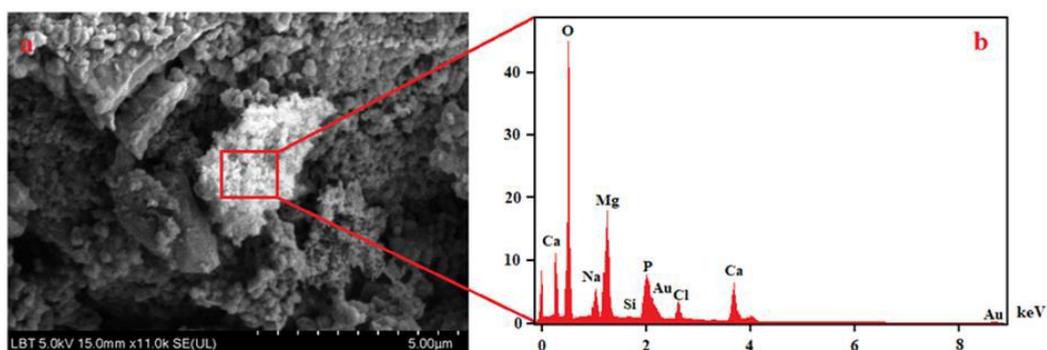


Figure 3. SEM image (a) and EDS spectrum (b) for forsterite ceramic, FC-1400, fired at 1400 °C, after 3 months of immersion in SBF [89].

Another method for analyzing hydroxyapatite formation of forsterite would be Fourier-transform infrared spectroscopy (FTIR). As an example, a solid state forsterite synthesized from talc and magnesium carbonate [33] presents new bands on the FTIR spectra after a 28 day immersion in SBF (OH-bond absorption bands at 1660 cm^{-1} , 3450 cm^{-1} , 3690 cm^{-1} ; and bands specific to the PO_4 group - 496 cm^{-1} , 1074 cm^{-1}). Also, Tavangarian and Emadi [90] reported that after a 14-day period of SBF immersion, small particles of around $7\text{ }\mu\text{m}$, composed of calcium and phosphorous as confirmed by Energy Dispersive X-Ray Analysis (EDX), appeared on the surface of forsterite ceramics. After an additional 14 days more such particles appeared and their size increased to around $10\text{ }\mu\text{m}$. Notably, regardless of the synthesis method all research reporting on the bioactivity of FS have confirmed its ability to lead to hydroxyapatite formation by SBF immersion.

6. Antimicrobial activity

One complication that might arise with orthopedic implants are surgical infections, most of which are caused by *Staphylococcus aureus* (*S. aureus*) strains which are Gram positive. However, it is reported that more than 20% of infections related to orthopedic implants are due to Gram negative bacteria, with *Escherichia coli* (*E. coli*) being the dominant microorganism [91]. This is of particular

importance when using metallic devices, as bacteria has a tendency to form a biofilm on the metallic surface [92] as it can be observed from the simplified diagram in Figure 4 A. Combined with potential antibiotic resistance and tissue contamination; this is making treatment very difficult, leading to chronic inflammation [93].

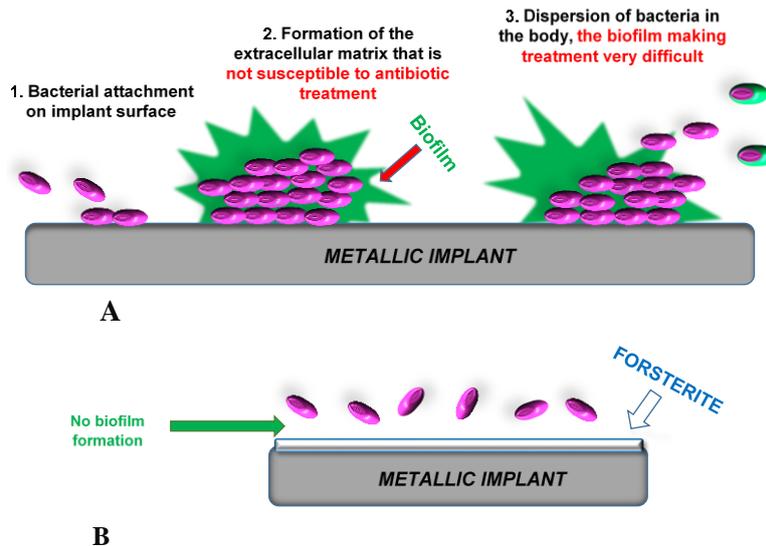


Figure 4. Biofilm formation model (A) and lack thereof (B) in the presence of a forsterite coating on metallic medical implants

To minimize such problems, arrays of inorganic materials that are biocompatible and/or bioactive have been researched as coatings on metallic substrates most of which have added silver nanoparticles (AgNPs). Nonetheless, there are certain materials that can possess a natural intrinsic antibacterial property due to some ions present in their composition. In addition, materials without such a property can be tailored to develop this characteristic through ionic substitution. Substituted hydroxyapatite would fall in the latter category if the ions involved are known to exhibit antibacterial effects such as Sr^{2+} [94], Mg^{2+} [95] or Zn^{2+} [96-98].

In regards to forsterite, there are some studies that examine its potential intrinsic antibacterial properties both as a standalone material [40, 41] and as a composite [42, 99]. However, there is a discrepancy in the amount of forsterite needed to produce an effect for antibacterial purposes, which might be explained by the influence of the synthesis method. For example, an agar diffusion study on a forsterite synthesized through a sol-gel-combustion method using glycine (FG) reveals an effect on *S. aureus* starting at 100 mg while that using urea (FU) shows an effect at 300 mg [40]. A later study with the same materials reveals an inhibitory effect at 0.5 mg/ml broth dilution with the antibacterial effect being slightly higher for FU (58.3 ± 0.1 %) than that for FG (52.8 ± 0.2 %) [41]. On the

other hand, a forsterite synthesized through mechanical activation does not present any effect at all concentrations used in that study (25-200 mg/ml broth) [99]. A 3D-printed porous forsterite scaffold is also reported to not present an effect if not coupled with NIR [100]. However, in this case it is revealed that NIR has no bactericidal effect on *S. aureus* on its own, a synergistic effect being implied.

Certainly, more studies are needed to better understand the mechanism by which forsterite acts like an antibacterial agent. However, an integral part of this mechanism is the small size of the nanoparticles which might cluster on the membrane of bacteria, that is on the micrometer scale, leading to mechanical damage and leakage of proteins, minerals and genetic materials [101]. This clustering around the bacteria was confirmed by Scanning Electron Microscopy (SEM) micrographs on both *E. coli* and *S. aureus*, before and after antibacterial studies with forsterite and diopside composites [41]. Antibacterial studies showed the better effect of forsterite against *S. aureus*. This can be explained by presence of Mg^{2+} ions that have been proven to exhibit a binding affinity to cardiolipin, a major component in the *S. aureus* membrane [102], forming complexes [103-105] causing further disruption in the membrane. The change in the culture pH has also been discussed as a part of any antibacterial study. In the case of forsterite this can be explained by taking into account all of the above. Smaller nanoparticles have a larger specific surface leading to more magnesium ions being released, thus causing a higher pH.

While more work is indeed needed, the few existing literature studies show a promise in using Mg_2SiO_4 as an antibacterial agent. And, taking into account all of the results related to forsterite bioactivity this material would be quite adequate as a coating on metallic orthopedic implants, leading to a better osseointegration and minimizing any potential surgical infections. Forsterite would also be appropriate for dental applications considering the severity of oral cavity infections (e.g. periodontal disease) and the need for tissue regeneration [106-108].

7. Future trends

Research on forsterite has been mainly focused on its further use as a potential bone substitute, taking into account its biocompatibility, bioactivity or antibacterial properties. A future focus would be on a better tailoring of forsterite ceramic scaffolds. This could also mean improving upon the natural properties of forsterite by ionic substitutions following the trend found in hydroxyapatite [109-111]. To our knowledge, there is not much information in regards to this. However, one study synthesizing a Sr-forsterite (0, 0.05, 0.1, 0.2 and 0.4 at% Sr) found it to present an improved bioactivity and a promotion of MG63 proliferation in comparison to simple forsterite [84]. Of course, due to the larger

ionic radius of Sr compared to Mg, the structure is not as stable and other phases were also present in Sr-forsterite. Zampiva et al. [112] reported on an erbium doped (0 to 20% mol) forsterite ($\text{Mg}_2\text{SiO}_4:\text{Er}^{3+}$). Here, the XRD showed a saturation of the host structure through the beginning of MgO formation at maximum erbium addition. However up to 10% erbium, a single phase forsterite is observed. These upconverting nanoparticles (UCNPs) show promise for applications in biomedicine as their tunable properties would allow for both diagnosis and treatment.

Another study niche could be the functionalization of forsterite with different metallic nanoparticles [113-131] and biologically active molecules, [132-163] which improve upon forsterite properties.

Conclusions

Similar in terms of biocompatibility / bioactivity with hydroxyapatite (HAP), forsterite has in its favor the fact that it causes the human body to produce HAP in situ, this HAP being much closer to the bone than the synthetic one. This promotes a better osseointegration of an implant. Also, its higher mechanical properties ensure a better use for load bearing applications. Coupled with its bioactivity, the potential antibacterial properties of forsterite would make it a good candidate for the coating of orthopedic metallic implants minimizing any possible post operative infection.

Acknowledgements

This work was supported by grants of the Ministry of Research, Innovation and Digitization, *CNCS/CCCDI-UEFISCDI*, project number 186 and 481, within *PNCDI III*.

REFERENCES

- [1] L. G. Raisz, Pathogenesis of osteoporosis: concepts, conflicts, and prospects, *J. Clin. Investig.*, **115**(12), 318 (2005).
- [2] A. Mocanu, G. Furtos, S. Rapuntean, O. Horovitz, C. Flore, C. Garbo, A. Danistean, Gh. Rapuntean, C. Prejmerean, M. Tomoaia-Cotisel, Synthesis characterization and antimicrobial effects of composites based on multi-substituted hydroxyapatite and silver nanoparticles, *Appl. Surf. Sci.*, **298**, 225 (2014).
- [3] P.T. Frangopol, A. Mocanu, V. Almasan, C. Garbo, R. Balint, G. Borodi, I. Bratu, O. Horovitz, M. Tomoaia-Cotisel, Synthesis and structural characterization of strontium substituted hydroxyapatites, *Rev. Roum. Chim.*, **61**(4-5), 337 (2016).

- [4] F. Goga, E. Forizs, A. Rotaru, A. Lucian, I. Petean, A. Mocanu, M. Tomoaia-Cotisel, Synthesis and thermal treatment of hydroxyapatite doped with magnesium, zinc and silicon, *Rev. Chim.*, **68**(6), 1193 (2017).
- [5] F. Goga, E. Forizs, G. Borodi, Gh. Tomoaia, A. Avram, R. Balint, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Behavior of doped hydroxyapatites during the heat treatment, *Rev. Chim.*, **68**(12), 2907 (2017).
- [6] C. Garbo, M. Sindilaru, A. Carlea, Gh. Tomoaia, V. Almasan, I. Petean, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Synthesis and structural characterization of novel porous zinc substituted nanohydroxyapatite powders, *Particul. Sci. Technol.* **35**(1), 29 (2017).
- [7] R. Balint, I. Petean, P.T. Frangopol, A. Mocanu, G. Arghir, S. Riga, Gh. Tomoaia, O. Horovitz, M. Tomoaia-Cotisel, Biomimetic nanocomposite structures designed for coating of orthopedic implants: AFM investigation, *Studia Univ. Babeş-Bolyai, Chem.*, **66**(3), 141 (2021).
- [8] S. Rapuntean, P.T. Frangopol, I. Hodisan, Gh. Tomoaia Gh., D. Oltean-Dan, A. Mocanu, C. Prejmerean, O. Soritau, L.Z. Racz, M. Tomoaia-Cotisel, In vitro response of human osteoblasts cultured on strontium substituted hydroxyapatites, *Rev. Chim.*, **69**(12), 3537 (2018).
- [9] C. Garbo, J. Locs, M. D'Este, G. Demazeau, A. Mocanu, C. Roman, O. Horovitz, M. Tomoaia-Cotisel, Si multi-substituted hydroxyapatites for bone regeneration, *Int. J. Nanomed.*, **15**, 1037 (2020).
- [10] M.W. Lascjke, Y. Harder, M. Amon, I. Martin, J. Farhadi, A. Ring, N. Torio-Padron, R. Schramm, M. Rucker, D. Junker, J.M. Haufel, C. Carvalho, M. Heberer, G. Germann, B. Vollmar, M.D. Menger, Angiogenesis in tissue engineering: breathing life into constructed tissue substitutes, *Tissue Eng.*, **12**(8), 2093 (2006).
- [11] F.I. Wolfe, A. Cittadini, Chemistry and biochemistry of magnesium, *Mol. Aspects Med.*, **24**, 3 (2003).
- [12] S. Castiglioni, A. Cazzaniga, W. Albisetti, J.A.M. Maier, Magnesium and osteoporosis: current state of knowledge and future research directions, *Nutrients*, **5**, 3022 (2013).
- [13] L. Cohen, R. Kitzes, Infrared spectroscopy and magnesium content of bone mineral in osteoporotic women, *Isr. J. Med. Sci.*, **17**, 1123 (1981).
- [14] R.K. Rude, H.E. Gruber, Magnesium deficiency and osteoporosis: Animal and human observations. *J. Nutr. Biochem.*, **15**, 710 (2004).
- [15] L.Y. He, X.M. Zhang, B. Liu, Y. Tian, W.H. Ma, Effect of magnesium ion on human osteoblast activity, *Braz. J. Med. Biol. Res.*, **49**(7), e5257 (2016).
- [16] W. Gotz, E. Tobiasch, S. Witzleben, M. Schulze, Effects of silicon compounds on biomineralization, osteogenesis, and hard tissue formation, *Pharmaceutics*, **11**, 117 (2019).
- [17] P. Han, C. Wu, Y. Xiao, The effect of silicate ions on proliferation, osteogenic differentiation and cell signalling pathways (WNT and SHH) of bone marrow stromal cells, *Biomater. Sci.*, **1**, 379 (2013).
- [18] Z.-Y. Qiu, I.-S. Noh, S.-M. Zhang, Silicate-doped hydroxyapatite and its promotive effect on bone mineralization, *Front. Mater. Sci.* **7**(1), 40 (2013).
- [19] K. Dashnyam, A. El-Fiqi, J.O. Buitrago, R.A. Perez, J.C. Knowles, H.-W. Kim, A mini review focused on the proangiogenic role of silicate ions release from silicon-containing biomaterials, *J. Tissue Eng.*, **8**, 1 (2017).

- [20] S. Ni, J. Chang, In vitro degradation, bioactivity and cytocompatibility of calcium silicate, dimagnesium silicate, and tricalcium phosphate bioceramics, *J. Biomater. Appl.*, **24**(2), 139 (2009).
- [21] F. Tavangarian, R. Emadi, Improving degradation rate and apatite formation ability of nanostructure forsterite, *Ceram. Int.*, **37**, 2275 (2011).
- [22] M.A. Naghiu, M. Gorea, E. Mutch, F. Kristaly, M. Tomoaia-Cotisel, Forsterite nanopowder: structural characterization and biocompatibility evaluation, *J. Mater. Sci. Technol.*, **29**(7), 628 (2013).
- [23] R.M. Pilliar, J.E. Davies, D.C. Smith, The bone-biomaterial interface for load-bearing applications, *MRS Bulletin*, **16**, 55(1991).
- [24] H. Ghomi, M. Jaberzadeh, M.H. Fathi, Novel fabrication of forsterite scaffold with improved mechanical properties, *J. Alloys Compd.*, **509**, L63 (2011).
- [25] S. Ramesh, A. Yaghoubi, K.Y.S. Lee, K.M.C. Chin, J. Purbolaksono, M. Hamdi, M.A. Hassan, Nanocrystalline forsterite for biomedical applications: Synthesis, microstructure and mechanical properties, *J. Mech. Behav. Biomed. Mater.*, **25**, 63 (2013).
- [26] F.S. Sayyed, M.H. Fathi, H. Edris, A. Doostmohammadi, V. Mortazavi, A. Hanifi, Effect of forsterite nanoparticles on mechanical properties of glass ionomer cements, *Ceram. Int.*, **40**, 10743 (2014).
- [27] S.A. Hassanzadeh-Tabrizi, Spark plasma sintering of forsterite nanopowder and mechanical properties of sintered materials, *Ceram. Int.*, **43**, 15714 (2017).
- [28] S. Pratapa, W.D. Handoko, U. Nurbaiti, M. Mashuri, Synthesis and characterization of high-density B₂O₃-added forsterite ceramics, *Ceram. Int.*, **43**, 7172 (2017).
- [29] M.H. Fathi, M. Kharaziha, Two-step sintering of dense, nanostructural forsterite, *Mater. Lett.*, **63**, 1455 (2009).
- [30] M. Gorea, M.-A. Naghiu, A. Avram, I. Petean, M. Tomoaia-Cotisel, Sintering and characterization of new forsterite ceramics, *Studia Univ. Babeş-Bolyai, Chem.*, **64**(2(2)), 383 (2019).
- [31] L. Chen, G. Ye, Q. Wang, B. Blanpain, A. Malfliet, M. Guo, Low temperature synthesis of forsterite from hydromagnesite and fumed silica mixture, *Ceram. Int.*, **41**, 2234 (2015).
- [32] L. Mathur, S.K.S. Hossain, M.R. Majdi, P.K. Roy, Synthesis of nano-crystalline forsterite (Mg₂SiO₄) powder from biomass rice husk silica by solid-state route, *Bol. Soc. Esp. Ceram. V.*, **57**, 112 (2018).
- [33] M. Gorea, M.A. Naghiu, M. Tomoaia-Cotisel, G. Borodi, Nano and microstructure effects on the bioactivity of forsterite powders, *Ceram.-Silik.*, **57**(2), 87 (2013).
- [34] N.T. Adrianov, S.S. Strelnikova, S.M. Dyagilets, S.Y. Fedorova, The effect of the initial components on the synthesis of forsterite produced by the sol-gel method, *Glass Ceram.*, **59**(5-6), 199 (2002).
- [35] G.A. Afonina, V.G. Leonov, O.N. Popova, Production of forsterite powder using sol-gel technology, *Glass Ceram.*, **62**(7-8), 248 (2005).
- [36] F. Ghariani, R. fezei, A. Hichem Hamzaoui, Synthesis, characterization, and application of sol gel derived Mg₂SiO₄ powder, *J. Solgel Sci. Technol.*, **88**, 100 (2018).
- [37] M. Kharaziha, M.H. Fathi, Synthesis and characterization of bioactive forsterite nanopowder, *Ceram. Int.*, **35**, 2449 (2009).
- [38] K.P. Sanosh, A. Balakrishnan, L. Francis, T. N. Kim, Sol-gel synthesis of forsterite nanopowders with narrow particle size distribution, *J. Alloy Compd.*, **495**, 113 (2010).

- [39] S.M. Mirhadi, A. Forghani, F. Tavangarian, A modifies method to synthesize single-phase forsterite nanoparticles at low temperature, *Ceram. Int.*, **42**, 7974 (2016).
- [40] R. Choudhary, P. Manohar, J. Vecstaudza, M.J. Yanez-Gascon, H. Perez Sanchez, R. Nachimuthu, J. Locs, S. Swamiappan, Preparation of nanocrystalline forsterite by combustion of different fuels and their comparative in-vitro bioactivity, dissolution behaviour and antibacterial studies, *Mater. Sci. Eng. C*, **77**, 811 (2017).
- [41] R. Choudhary, A. Chatterjee, S.K. Venkatraman, S. Koppala, J. Abraham, S. Swamiappan, Antibacterial forsterite (Mg_2SiO_4) scaffold: A promising bioceramic for load bearing applications, *Bioact. Mater.*, **3**(3), 218 (2018).
- [42] R. Choudhary, S.K. Venkatraman, I. Bulygina, A. Chatterjee, J. Abraham, F. Senatov, S. Kaloshkin, A. Ilyasov, M. Abakumov, M. Knyazeva, D. Kukui, F. Walther, S. Swamiappan, Impact of forsterite addition on mechanical and biological properties of composites, *J. Asian Ceram. Soc.*, **8**(4), 1051 (2020).
- [43] L.M. Anovitz, A.J. Rondinone, L. Sochalski-Kolbus, J. Rosenqvist, Nano-scale synthesis of the complex silicate minerals forsterite and enstatite, *J. Colloid. Interf. Sci.*, **495**, 94 (2017).
- [44] S.A. Hassanzadeh-Tabrizi, A. Bigham, M. Rafienia, Surfactant-assisted sol-gel synthesis of forsterite nanoparticles as a novel drug delivery system, *Mater. Sci. Eng. C*, **58**, 737 (2016).
- [45] M.A. Naghiu, M. Gorea, F. Kristaly, M. Tomoaia-Cotisel, A new method for synthesis of forsterite nanomaterials for bioimplants, *Ceram.-Silik.*, **58**(4), 303 (2014).
- [46] R.Y.S. Zampiva, L.H. Acauan, L. Moreira dos Santos, R. Hauch Ribeiro de Castro, A.K. Alves, C.P. Bergman, Nanoscale synthesis of single-phase forsterite by reverse strike coprecipitation and its high optical and mechanical properties, *Ceram. Int.*, **43**, 16225 (2017)
- [47] L. Chen, G. Ye, W. Zhou, J. Dijkmans, B. Sels, A. Malfliet, M. Guo, Influence of MgO precursors on mechanically activated forsterite synthesis, *Ceram. Int.*, **41**, 12651 (2015).
- [48] M.H. Fathi, M. Kharaziha, Mechanically activated crystallization of phase pure nanocrystalline forsterite powders, *Mater. Lett.*, **62**, 4306 (2008).
- [49] M.H. Fathi, M. Kharaziha, The effect of fluorine ion on fabrication of nanostructure forsterite during mechanochemical synthesis, *J. Alloys Compd.*, **472**, 540 (2009).
- [50] C. Kosanovic, N. Stubicar, N. Tomasic, V. Bermanec, M. Stubicar, Synthesis of a forsterite powder by combined ball milling and thermal treatment, *J. Alloys Compd.*, **389**, 306 (2005).
- [51] U. Nurbaiti, D. Darminto, T. Triwikantoro, M. Zainuri, S. Partapa, Synthesis and characterization of silica sand-derived nano-forsterite ceramics, *Ceram. Int.*, **44**, 5543 (2018).
- [52] F. Tavangarian, R. Emadi, Mechanical activation assisted synthesis of pure nanocrystalline forsterite powder, *J. Alloys Compd.*, **485**, 648 (2009).
- [53] H. Barzegar Bafrooei, T. Ebadzadeh, H. Majidian, Microwave synthesis and sintering of forsterite nanopowder produced by high energy ball milling, *Ceram. Int.*, **40**, 2869 (2014).
- [54] M. Kheradmandfard, S.F. Kashani-Bozorg, A.H. Noori-Alfesharaki, A.Z. Kharazi, M. Kheradmandfard, N. Abutalebi, Ultra-fast, highly efficient and green synthesis of bioactive forsterite nanopowder via microwave irradiation, *Mater. Sci. Eng. C*, **92**, 236 (2018).
- [55] M.B.D. Mitchell, D. Jackson, P.F. James, Low-density forsterite (Mg_2SiO_4) powders prepared from modified alkoxides, *J. Solgel Sci. Technol.*, **26**, 777 (2003).

- [56] R. Vallepu, Y. Nakamura, R. Komatsu, K. Ikeda, Preparation of forsterite by the geopolymer technique—gel compositions as a function of pH and crystalline phases, *J. Solgel Sci. Technol.*, **35**, 107 (2005).
- [57] R.Y.S. Zampiva, L. Acauan, A.K. Alves, C.P. Bergman, Novel forsterite nanostructures with high aspect ratio via catalyst-free route, *Mater. Res. Bull.*, **60**, 507 (2014).
- [58] Y. Liu, P. Liu, C. Hu, Hydrothermally assisted synthesis of pure-phase and well-dispersed forsterite nanopowders, *Ceram. Int.*, **44**, 23339 (2018).
- [59] A. Douy, Aqueous syntheses of forsterite (Mg_2SiO_4) and enstatite ($MgSiO_3$), *J. Solgel Sci. Technol.*, **24**, 221 (2002).
- [60] F. Tavangarian, R. Emadi, Synthesis of nanocrystalline forsterite (Mg_2SiO_4) powder by combined by mechanical activation and thermal treatment, *Mater. Res. Bull.*, **45**(4), 388 (2010).
- [61] A. Saberi, B. Alinejad, Z. Negahdari, F. Kazemi, A. Almasi, A novel method to low temperature synthesis of nanocrystalline forsterite, *Mater. Res. Bull.*, **42**(4), 666 (2007).
- [62] P.E. Schwarze, J. Ovrevik, R.B. Hetland, R. Becher, F.R. Cassee, M. Lag, M. Lovik, E. Dybing, M. Refnes, Importance of size and composition of particles for effects on cells in vitro, *Inhal. Toxicol.*, **19**(Suppl. 1), 17 (2007).
- [63] G. Furtos, M. Tomoaia-Cotisel, C. Garbo, M. Senila, N. Jumate, I. Vida-Simiti, C. Prejmerean, New composite bone cement based on hydroxyapatite and nanosilver, *Particul. Sci. Technol.*, **31**(4), 392 (2013).
- [64] G. A. Fielding, M. Roy, A. Bandyopadhyay, S. Bose, Antibacterial and biological characteristics of silver containing and strontium doped plasma sprayed hydroxyapatite coatings, *Acta Biomater.*, **8**(8), 3144 (2012).
- [65] Gh. Tomoaia, O. Soritau, M. Tomoaia-Cotisel, L.B. Pop, A. Pop, A. Mocanu, O. Horovitz, L. D. Bobos, Scaffolds made of nanostructured phosphates, collagen and chitosan for cell culture, *Powder Technol.*, **238**, 99 (2013).
- [66] A. Mocanu, R. Balint, C. Garbo, L. Timis, I. Petean, O. Horovitz, M. Tomoaia-Cotisel, Low crystallinity nanohydroxyapatite prepared at room temperature, *Studia Univ. Babeş-Bolyai Chem.*, **62**(2), 95 (2017).
- [67] Gh. Tomoaia, A. Mocanu, I. Vida-Simiti, N. Jumate, L. D. Bobos, O. Soritau, M. Tomoaia-Cotisel, Silicon effect on the composition and structure of the composition and structure of nanocalcium phosphates in vitro biocompatibility to human osteoblasts, *Mater. Sci. Eng. C*, **37**, 37 (2014).
- [68] A. Danistean, M. Gorea, A. Avram, S. Rapuntean, Gh. Tomoaia, A. Mocanu, C. Garbo, O. Horovitz, M. Tomoaia-Cotisel, Antimicrobial activity of ceramic disks loaded with silver ions and nitroxoline, *Studia Univ. Babeş-Bolyai Chem.*, **61**(3), Tom I, 275 (2016).
- [69] C. J. Harrison, P. V. Hatton, P. Gentile, C. A. Miller, Nanoscale Strontium-Substituted hydroxyapatite pastes and gels for bone tissue regeneration, *Nanomaterials*, **11**(6), 1611 (2021). <https://doi.org/10.3390/nano11061611>
- [70] C. Prejmerean, M. Tomoaia-Cotisel, E. Vasile, G. Furtos, L. B. Pop, M. Moldovan, C. Sarosi, I. Petean, Characterisation of surface organisation and morphology of some new experimental dental resin-based composites, *Int. J. Nano and Biomater.*, **3**(4), 344 (2011).
- [71] Gh. Tomoaia, M. Tomoaia-Cotisel, L. B. Pop, A. Pop, O. Horovitz, A. Mocanu, N. Jumate, L. D. Bobos, Synthesis and characterization of some composites based on nanostructured phosphates, collagen and chitosan, *Rev. Roum. Chim.*, **56**(10-11), 1039 (2011).

- [72] D. Oltean-Dan, G. B. Dogaru, M. Tomoaia-Cotisel, D. Apostu, A. Mester, H. R. C. Benea, M. G. Paiusan, E. M. Jianu, A. Mocanu, R. Balint, C. O. Popa, C. Berce, G. I. Bodizs, A. M. Toader, Gh. Tomoaia, Enhancement of bone consolidation using high-frequency pulsed electromagnetic short-waves and titanium implants coated with biomimetic composite embedded into PLA matrix: in vivo evaluation, *Int. J. Nanomed.*, **14**, 5799 (2019).
- [73] C. Capuccini, P. Torricelli, E. Boanini, M. Gazzano, R. Giardino, A. Bigi, Interaction of Sr-doped hydroxyapatite nanocrystals with osteoclast and osteoblast-like cells, *J. Biomed. Mater. Res. A*, **89**(3), 594 (2009).
- [74] A. Avram, M. Gorea, R. Balint, L. Timis, S. Jitaru, A. Mocanu, M. Tomoaia-Cotisel, Portland cement enriched with hydroxyapatite for endodontic applications, *Studia Univ. Babeş-Bolyai Chem.*, **62**(4), 81 (2017).
- [75] A. Avram, T. Frentiu, O. Horovitz, A. Mocanu, F. Goga, M. Tomoaia-Cotisel, Hydroxyapatite for removal of heavy metals from wastewater, *Studia Univ. Babeş-Bolyai Chem.*, **62**(4), 93 (2017).
- [76] E. Forizs, F. Goga, A. Avram, A. Mocanu, I. Petean, O. Horovitz, M. Tomoaia-Cotisel, Thermal analysis of pure and multisubstituted hydroxyapatite pastes, *Studia-Univ. Babeş-Bolyai Chem.*, **62**(4), 173 (2017).
- [77] S. Ni, C. Lee, J. Chang, Preparation and characterization of forsterite (Mg_2SiO_4) bioceramic, *Ceram. Int.*, **33**, 83 (2007).
- [78] M. Kharaziha, M.H. Fathi, Improvement of mechanical properties and biocompatibility of forsterite bioceramic addressed to bone tissue engineering materials, *J. Mech. Behav. Biomed. Mater.*, **3**, 530 (2010).
- [79] D.O. Obada, E.T. Dauda, J.K. Abifarin, D. Dodoo-Arhin, N.D. Bansod, Mechanical properties of natural hydroxyapatite using low cold compaction pressure: effect of sintering temperature, *Mater. Chem. Phys.*, **239**, 122099 (2020).
- [80] M. Akao, H. Aoki, K. Kato, Mechanical properties of sintered hydroxyapatite for prosthetic applications, *J. Mater. Sci.*, **16**, 809 (1981).
- [81] A. Raksujarit, K. Pengpat, G. Rujjanagul, T. Tunkasiri, Processing and properties of nanoporous hydroxyapatite ceramics, *Mater. Des.*, **31**, 1658 (2010).
- [82] J.Y. Rho, R.B. Ashman, C.H. Turner, Young's modulus of trabecular and cortical bone material: ultrasonic and microtensile measurements, *J. Biomech.*, **26**(2), 111 (1993).
- [83] M. Bohner, Y. Loosli, G. Barud, D. Lacroix, Commentary: deciphering the link between architecture and biological response of a bone graft substitute, *Acta Biomater.*, **7**(2), 478 (2011).
- [84] K.B. Devi, S.K. Nandi, M. Roy, Magnesium silicate bioceramics for bone regeneration: a review, *J. Indian Inst. Sci.*, **99**(3), 261 (2019).
- [85] R.Z. Legeros, Calcium phosphate-based osteoinductive materials, *Chem. Rev.*, **108**(11), 4742 (2008).
- [86] M. Saqaei, M.H. Fathi, H. Edris, V. Mortazavi, Preparation and biocompatibility evaluation of bioactive glass–forsterite nanocomposite powder for oral bone defects treatment applications, *Mater. Sci. Eng. C*, **56**, 409 (2015).
- [87] R. Gheitanchi, M. Kharaziha, R. Emadi, Sr-doped forsterite nanopowder: Synthesis and biological properties, *Ceram. Int.*, **43**(15), 12018 (2017).

- [88] R. Torkaman, S. Darvishi, M. Jokar, M. Kharaziha, M. Karbasi, Electrochemical and in vitro bioactivity of nanocomposite gelatin-forsterite coatings on AISI 316 L stainless steel, *Progr. Org. Coat.*, **103**, 40 (2017).
- [89] M. Gorea, M.-A. Naghiu, A. Avram, I. Petean, A. Mocanu, M. Tomoaia-Cotisel, Novel porous forsterite ceramics biocompatibility and bioactivity evaluation, *Rev. Chim.*, **71**(2), 343 (2020).
- [90] F. Tavangarian, R. Emadi, Nanostructure effects on the bioactivity of forsterite bioceramic, *Mater. Lett.*, **65**, 740 (2011).
- [91] L. Cremet, A. Broquet, B. Brulin, C. Jaquelina, S. Dauvergne, R. Brion, K. Asehnoune, S. Corvec, D. Heymann, N. Caroff, Pathogenic potential of Escherichia coli clinical strains from orthopedic implant infections towards human osteoblastic cells, *FEMS Pathog. Dis.*, **73**, ftv065 (2015).
- [92] S. Kumar, M. Sengupta, V. Hada, S. Sarkar, R. Bhatta, M. Sengupta, Early post-operative wound infection in patients undergoing orthopaedic surgery with implant, *Int. J. Sci. Study*, **5**(8), 44 (2017).
- [93] W. Ahmed, Z. Zhai, C. Gao, Adaptive antibacterial biomaterial surfaces and their applications, *Mater. Today Bio*, **2**, 100017 (2019).
- [94] A.D. Anastasiou, M. Nerantzaki, E. Gounari, M.S. Duggal, P.V. Giannoudis, A. Jha, D. Bikiaris, Antibacterial properties and regenerative potential of Sr²⁺ and Ce³⁺ doped fluorapatites; a potential solution for periimplantitis, *Sci. Rep.*, **9**, 14469 (2019).
- [95] D. Predoi, S.L. Iconaru, G.E. Stan, Synthesis, characterization, and antimicrobial activity of magnesium-doped hydroxyapatite suspensions, *Nanomaterials*, **9**, 1295 (2019).
- [96] R.-J. Chung, M.-F. Hsieh, C.-W. Huang, L.-H. Perng, H.-W. Wen, T.-S. Chin, Antimicrobial effects and human gingival biocompatibility of hydroxyapatite sol-gel coatings, *Clin. J. Biomed. Mater. Res. B. Appl. Biomater.*, **76**, 169 (2006).
- [97] E.S. Thian, T. Konishi, Y. Kawanobe, P.N. Lim, C. Choong, B. Ho, N. Aizawa, Zinc-substituted hydroxyapatite: a biomaterial with enhanced bioactivity and antibacterial properties, *J. Mater. Sci.: Mater. Med.*, **24**, 437 (2013).
- [98] A. Anwar, S. Akbar, A. Sadiqa, M. Kazmi, Novel continuous flow synthesis, characterization and antibacterial studies of nanoscale zinc substituted hydroxyapatite bioceramics, *Inorganica Chim. Acta*, **453**, 16 (2016).
- [99] M. Saqaei, M.H. Fathi, H. Edris, V. Mortazavi, N. Hosseini, Effects of adding forsterite bioceramic on in vitro activity and antibacterial properties of bioactive glass-forsterite nanocomposite powders, *Adv. Powder Technol.*, **27**, 1922 (2016).
- [100] T. Zhu, M. Zhu, Y. Zhu, Fabrication of forsterite scaffolds with photothermal-induced antibacterial activity by 3D printing and polymer-derived ceramics strategy, *Ceram. Int.*, **46**, 13607 (2020).
- [101] Q. Li, S. Mahendra, D.Y. Lyon, L. Brunet, M.V. Liga, D. Li, P.J.J. Alvarez, Antimicrobial nanomaterials for water disinfection and microbial control: potential applications and implications, *Water. Res.*, **42**, 4591 (2008).
- [102] A. Som, L. Yang, G.C.L. Wong, G.N. Tew, Divalent metal ion triggered activity of a synthetic antimicrobial in cardiolipin membranes, *J. Am. Chem. Soc.*, **131**(42), 15102 (2009).
- [103] Y. Xie, L. Yang, Calcium and magnesium ions are membrane-active against stationary-phase Staphylococcus aureus with high specificity, *Sci. Rep.*, **6**, 20628 (2016).

-
- [104] M. Tsai, R.L. Ohniwa, Y. Kato, S.L. Takeshita, T. Ohta, S. Saito, H. Hayashi, K. Morikawa, *Staphylococcus aureus* requires cardiolipin for survival under conditions of high salinity, *Microbiol.*, **11**, 13 (1011).
- [105] S.A. Short, D.C. White, Metabolism of phosphatidylglycerol, lysylphosphatidylglycerol, and cardiolipin of *Staphylococcus aureus*, *J. Bacteriol.*, **108**(1), 219 (1971).
- [106] D. Acatrinei, N. Forna, B. S. Acatrinei, N. Rosoiu, The action of treatments with micronutrients and bioactive compounds in stopping the evolution of the periodontal disease, *Romanian Journal of Oral Rehabilitation*, **13**(1), 68 (2021).
- [107] D. Acatrinei, R. Vinteanu, N. Rosoiu, Biochemical and histological researches regarding the use of new therapeutic methods in some oral and facial pathologies, *Academy of Romanian Scientists, Annals Series on Biological Sciences*, **8**(2), 35 (2019).
- [108] D. Acatrinei, N. Forna, I. Diaconu, N. Rosoiu, Interaction of *Porphyromonas gingivalis* bacterium with other bacteria in determining periodontal disease and valid treatments, *Romanian Journal of Oral Rehabilitation*, **12**(2), 37-51 (2020).
- [109] D. Oltean-Dan, G.-B. Dogaru, E.-M. Jianu, S. Riga, M. Tomoaia-Cotisel, A. Mocanu, L. Barbu-Tudoran, Gh. Tomoaia, Biomimetic composite coatings for activation of titanium implant surfaces: methodological approach and in vivo enhanced osseointegration, *Micromachines*, **12**(11), 1325 (2021).
- [110] A. Mocanu, O. Cadar, P.T. Frangopol, I. Petean, Gh. Tomoaia, G.-A. Paltinean, C.P. Racz, O. Horovitz, M. Tomoaia-Cotisel, Ion release from hydroxyapatite and substituted hydroxyapatites in different immersion liquids: in vitro experiments and theoretical modelling study, *R. Soc. Open. Sci.*, **8**(1), 201785 (2021).
- [111] A. Mocanu, P.T. Frangopol, R. Balint, O. Cadar, I.M. Vancea, R. Mantiu, O. Horovitz, M. Tomoaia-Cotisel, Higuchi model applied to ions release from hydroxyapatites, *Studia Univ. Babeş-Bolyai, Chem.*, **66**(3), 195 (2021).
- [112] R.Y.S. Zampiva, L.H. Acauan, J. Venturini, J.A. Martins Garcia, D.S. da Silva, Z. Han, L. Reyes Pires Kassab, N.U. Wetter, A. Agarwal, A. Kopp Alves, C. Perez Bergmann, Tunable green/red luminescence by infrared upconversion in biocompatible forsterite nanoparticles with high erbium doping uptake, *Opt. Mater.*, **76**, 407 (2018).
- [113] A. Avram, Gh. Tomoaia, A. Mocanu, M. Tomoaia-Cotisel, Gold nanoparticles and chemotherapeutic agents, *Academy of Romanian Scientists, Annals Series on Biological Sciences*, **5**(2), 23 (2020).
- [114] M. A. Ujica, G.A. Paltinean, A. Mocanu, M. Tomoaia-Cotisel, Silver and gold nanoparticles: challenges and perspectives, *Academy of Romanian Scientists, Annals Series on Biological Sciences*, **9**(1), 97 (2020).
- [115] M. Tomoaia-Cotisel, A. Mocanu, O. Horovitz, E. Indrea, Gh. Tomoaia, I. Bratu, Self-assembly of gold nanoparticles functionalized with amino acids and aleurone globular protein, in *Book series (Proceedings of SPIE): Advanced Topics in Optoelectronics, Microelectronics, and Nanotechnologies IV*, edited by P. Schiopu, C. Panait, G. Caruntu, A. Manea, (Constanta, Romania, 2009), Vol. 7297, Article No: UNSP 729708. doi: 10.1117/12.823616.
- [116] L. Barbu-Tudoran, Gh. Tomoaia, O. Horovitz, A. Mocanu, M. Tomoaia-Cotisel, Self-assembly characteristics of gold nanoparticles in the presence of arginine, *J. Optoelectron. Adv. M.*, **10**(9), 2293 (2008).

- [117] Gh. Tomoaia, P.T. Frangopol, O. Horovitz, L.D. Bobos, A. Mocanu, M. Tomoaia-Cotisel, The effect of arginine on gold nanoparticles in colloidal solutions and in thin films, *J. Nanosci. Nanotechnol.*, **11**(9), 7762 (2011).
- [118] O. Horovitz, Gh. Tomoaia, A. Mocanu, T. Yupsanis, M. Tomoaia-Cotisel, Protein binding to gold colloids, *Gold Bull.*, **40**(3), 213 (2007).
- [119] M. Tomoaia-Cotisel, Gh. Tomoaia, E. Indrea, L. D. Bobos, O. Horovitz, A. Mocanu, Interfacial nanomaterials based on gold nanoparticles, protein and chitosan, *J. Optoelectron. Adv. M., Symposia*, **2**(1), 125 (2010).
- [120] O. Horovitz, A. Mocanu, Gh. Tomoaia, L. Olenic, Gh. Mihailescu, O. Borostean, A. Popoviciu, C. Craciun, T. Yupsanis, M. Tomoaia-Cotisel, Synthesis, characterization and properties of gold nanoparticles in colloidal aqueous solutions in the absence and in the presence of globular proteins. Auto-assembled gold nanostructures in thin films, in *Convergence of Micro-Nano-Biotechnologies*, edited by M. Zaharescu, E. Burzo, L. Dumitru, I. Kleps and D. Dascalu (Romanian Academy Press, Bucharest, Romania, 2006), Vol. 9, pp. 132-146.
- [121] A. Mocanu, I. Cernica, Gh. Tomoaia, L.D. Bobos, O. Horovitz, M. Tomoaia-Cotisel, Self-assembly characteristics of gold nanoparticles in the presence of cysteine, *Colloid. Surf. A*, **338**(1-3), 93 (2009).
- [122] Gh. Tomoaia, O. Horovitz, A. Mocanu, A. Nita, A. Avram, C.P. Racz, O. Soritau, M. Cenariu, M. Tomoaia-Cotisel, Effects of doxorubicin mediated by gold nanoparticles and resveratrol in two human cervical tumour cell line, *Colloid. Surf. B*, **135**, 726 (2015).
- [123] I. Petean, Gh. Tomoaia, O. Horovitz, A. Mocanu, M. Tomoaia-Cotisel, Cysteine mediated assembly of gold nanoparticles, *J. Optoelectron. Adv. Mater.*, **10**(9), 2289 (2008).
- [124] A. Mocanu, R.D. Pasca, Gh. Tomoaia, A. Avranas, O. Horovitz, M. Tomoaia-Cotisel, Selective effect of procaine tetracaine and dibucaine on gold nanoparticles, *J. Nanosci. Nanotechnol.*, **12**(12), 8935 (2012).
- [125] M. Tomoaia-Cotisel, Multifunctional nanostructures formed of gold or silver nanoparticle and different biomolecules with medical applications, (e-Book, Cluj University Press, Cluj-Napoca, Romania, 2016) pp. 1-322.
- [126] E. Indrea, S. Dreve, I. Bratu, Gh. Mihailescu, L. Olenic, Gh. Tomoaia, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Multifunctional materials based on chitosan, globular protein and gold nanoparticles, *Technical Proceedings of the 2007 NSTI-Nanotech*, (Santa Clara, California, USA, 2007) Vol. 4, Chapter 3, pp. 461-464.
- [127] O. Horovitz, Gh. Tomoaia, A. Mocanu, T. Yupsanis, M. Tomoaia-Cotisel, Protein binding to gold auto assembled films, *Gold Bull.*, **40**(4), 295 (2007).
- [128] O. Horovitz, A. Mocanu, Gh. Tomoaia, M. Crisan, L. D. Bobos, C. Racz, M. Tomoaia-Cotisel, Amino acids binding to gold nanoparticles, *Studia. Univ. Babes-Bolyai Chem.*, **52**(3), 53 (2007).
- [129] O. Horovitz, A. Mocanu, Gh. Tomoaia, L. D. Bobos, D. Dubert, I. Daian, T. Yupsanis, M. Tomoaia-Cotisel, Lysine mediated assembly of gold nanoparticles, *Studia. Univ. Babes-Bolyai Chem.*, **52**(1), 97 (2007).
- [130] R.D. Pasca, A. Mocanu, S.C. Cobzac, I. Petean, O. Horovitz, M. Tomoaia-Cotisel, Biogenic syntheses of gold nanoparticles using plant extracts, *Particul. Sci. Technol.*, **32**(2), 131 (2014).

- [131] A. Avram, M. Gorea, S. Rapuntean, A. Mocanu, G. A. Paltinean, C. Varhelyi Jr., O. Horrovitz, M. Tomoaia-Cotisel, The in-vitro antibacterial activity of novel nanostructured composites based on forsterite and silver nanoparticles, *Rev. Chim.*, **71**(1), 13 (2020).
- [132] R. Katz, M. Tomoaia-Cotisel, Site-specific biomolecular complexes, World Intellectual Property Organization (WIPO), WO 96/04001 (1996).
- [133] R. Katz, M. Tomoaia-Cotisel, Carrier compositions for anti-neoplastic drugs, United States Patent Number 5,925,669, Jul. 20 (1999).
- [134] R. Katz, M. Tomoaia-Cotisel, Method for delivering active agents to mammalian brains in a complex with eicosapentaenoic acid or docosahexaenoic acid-conjugated polycationic carrier, United States Patent Number 5,716,614, Feb. 10 (1998).
- [135] R. Katz, M. Tomoaia-Cotisel, M. C. Rattazzi, P. Fishman, Docosahexaenoic acid/poly-L-lysine conjugates bind to the cerebrovascular endothelium, *J. Mol. Neurosci.*, **33**, 133 (2007).
- [136] Gh. Tomoaia, M. Tomoaia-Cotisel, A. Mocanu, O. Horovitz, L.-D. Bobos, M. Crisan, I. Petean, Supramolecular organization of collagen and anti-cancer drugs, *J. Optoelectron. Adv. Mater.*, **10**(4), 961 (2008).
- [137] Gh. Tomoaia, V.-D. Pop-Toader, A. Mocanu, O. Horovitz, L.-D. Bobos, M. Tomoaia-Cotisel, Supramolecular organization and nano structuration of collagen and anti-cancer drugs, *Studia Univ. Babeş-Bolyai, Chem.*, **52**(4), 137 (2007).
- [138] L.D. Bobos, Gh. Tomoaia, Cs. Racz, A. Mocanu, O. Horovitz, I. Petean, M. Tomoaia-Cotisel, Morphology of collagen and anti-cancer drugs assemblies on mica, *Studia Univ. Babeş-Bolyai, Chem.*, **53**(4), 99 (2008).
- [139] Gh. Tomoaia, C. Borzan, M. Crisan, A. Mocanu, O. Horovitz, L.-D. Bobos, M. Tomoaia-Cotisel, Nanostructure formation of collagen and anti-cancer drugs investigated by atomic force microscopy, *Rev. Roum. Chim.*, **54**(5), 363 (2009).
- [140] E. Chifu, M. Tomoaia, A. Ioanette, Behaviour of canthaxanthin at the benzene/water and air/water interfaces, *Gazz. Chim. Ital.*, **105**(11-12), 1225 (1975).
- [141] M. Tomoaia-Cotisel, D.V. Pop-Toader, U. V. Zdrenghia, Gh. Tomoaia, O. Horovitz, A. Mocanu, Desferal effect on human erythrocyte membrane. An atomic force microscopy analysis, *Studia Univ. Babeş-Bolyai, Chem.*, **54**(4 (2)), 285 (2009).
- [142] E. Chifu, M. Tomoaia-Cotisel, Z. Andrei, Mixed monolayers of canthaxanthin with lipids, *Studia Univ. Babeş-Bolyai, Chem.*, **24**(2), 63 (1979).
- [143] E. Chifu, M. Tomoaia-Cotisel, Insoluble monolayers of lecithin and carotenoid pigments, *Rev. Roum. Chim.*, **24**(7), 979 (1979).
- [144] L.-C. Pop, N. Katir, A. Castel, L. Silaghi-Dumitrescu, H. Gomoitzka, D. MacLeod-Carey, N. Saffon, N, N' and N, O chelated phosphoniumcations containing aminotroponimate or aminotroponate units, *J. Organomet. Chem.*, **694**(9-10), 1562 (2009).
- [145] L.-C. Pop, D. MacLeod-Carey, A. Munoz-Castro, L. Silaghi-Dumitrescu, A. Castel, R. Arratia-Perez, Relativistic calculations of aminotroponimate complexes containing group 15 (P, As, Sb, Bi) elements, *Polyhedron*, **30**, 841 (2011).
- [146] L.-C. Pop, A. Castel, L. Silaghi-Dumitrescu, N. Saffon, Aminotroponimate and aminotroponate complexes of group 15 (P, As) elements: syntheses, X-ray diffraction analyses and reactivity, *Eur. J. Inorg. Chem.*, **22**, 3357 (2011).
- [147] M. Tomoaia-Cotisel, J. Zsako, E. Chifu, Dipalmitoyl lecithin and egg lecithin monolayers at an air/water interface, *Ann. Chim. (Rome)*, **71**(3-4), 189 (1981).

- [148] E. Chifu, J. Zsako, M. Tomoaia-Cotisel, Xanthophyll films. I. Single-component monolayers at the air/water interface, *J. Colloid Interface Sci.*, **95**(2), 346 (1983).
- [149] M. Tomoaia-Cotisel, E. Chifu, Xanthophyll films. II. Two-component monolayers of some xanthophylls and egg lecithin at the air/water interface, *J. Colloid Interface Sci.*, **95**(2), 355 (1983).
- [150] M. Tomoaia-Cotisel, E. Chifu, J. Zsako, Mixed monolayers of egg lecithin and carotenoids, *Colloids Surf.*, **14**, 239 (1985).
- [151] M. Tomoaia-Cotisel, J. Zsako, M. Sălăjan, E. Chifu, Interaction of unimolecular films of some carotenoids with electrolytes at the air/water interface, in *Water and Ions in Biological Systems*, Edited by A. Pullman, V. Vasilescu, and L. Packer, (Union of Societies for Medical Sciences, Bucharest, 1985), pp. 371-381.
- [152] M. Tomoaia-Cotisel, J. Zsako, A. Mocanu, M. Lupea, E. Chifu, Insoluble mixed monolayers. III. The ionization characteristics of some fatty acids at the air/water interface, *J. Colloid Interface Sci.*, **117** (2), 464 (1987).
- [153] M. Tomoaia-Cotisel, J. Zsako, E. Chifu, Ejection curves and miscibility of egg lecithin with some carotenoid derivatives, *Rev. Roum. Chim.*, **32**(7), 663 (1987).
- [154] E. Chifu, A. Chifu, M. Tomoaia-Cotisel, J. Zsako, Specific interactions in monomolecular membranes of biological interest, *Rev. Roum. Chim.*, **32**(7), 627 (1987).
- [155] J. Zsako, M. Tomoaia-Cotisel, E. Chifu, A. Mocanu, P. T. Frangopol, Influence of stearic acid monolayers upon the procaine adsorption from underlying alkaline aqueous solutions, *Biochim. Biophys. Acta*, **1024**, 227 (1990).
- [156] M. Tomoaia-Cotisel, On the mechanism of procaine penetration into stearic acid monolayers spread at the air/water interface, *Progr. Colloid. Polym. Sci.*, **83**, 155 (1990).
- [157] J. Zsako, M. Tomoaia-Cotisel, E. Chifu, A. Mocanu, P. T. Frangopol, Procaine interactions with phospholipid monolayers at the air/water interface, *Gazz. Chim. Ital.*, **124**, 5 (1994).
- [158] A. Mocanu, Gh. Tomoaia, M. Tomoaia-Cotisel, Cs. Racz, C. Ispas, J. Zsako, Simulations of some biomembrane interfacial phenomena. I. Specific molecular interactions between bovine serum albumin and melatonin, *Studia, Univ. Babes-Bolyai, Chem.*, **49**(1), 29 (2004).
- [159] M. Tomoaia-Cotisel, A. Tomoaia-Cotisel, T. Yupsanis, Gh. Tomoaia, I. Balea, A. Mocanu, Cs. Racz, Coating layers of major storage protein from aleurone cells of barley studied by atomic force microscopy, *Rev. Roum. Chim.*, **51**(12), 1181 (2006).
- [160] U. V. Zdrengea, Gh. Tomoaia, D.-V. Pop-Toader, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Procaine effect on human erythrocyte membrane explored by atomic force microscopy, *Comb. Chem. High Throughput Screen.*, **14**(4), 237 (2011).
- [161] Cs. P. Racz, R.-D. Pasca, S. Santa, I. Kacso, Gh. Tomoaia, A. Mocanu, O. Horovitz, M. Tomoaia-Cotisel, Inclusion complex of β -cyclodextrin and quercetin. Thermodynamic approach, *Rev. Chim.*, **62**(10), 992 (2011).
- [162] P.T. Frangopol, D. A. Cadenhead, Gh. Tomoaia, A. Mocanu, M. Tomoaia-Cotisel, The effect of procaine on lipid domains investigated by contact mode atomic force microscopy, *Rev. Roum.Chim.*, **60**(2-3), 265 (2015).
- [163] Cs. P. Racz, G. Borodi, M.M. Pop, I. Kacso, S. Santa, M. Tomoaia-Cotisel, Structure of the inclusion complex of β -cyclodextrin with lipoic acid from laboratory powder diffraction data, *Acta Cryst. B*, **68**, 164 (2012).