MINISTRY OF EDUCATION AND RESEARCH
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Ph.D. THESIS
SUMMARY

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MULTIFUNCTIONAL COATINGS BASED ON 45S5 BIOACTIVE GLASS DOPED WITH SAMARIUM AND FUNCTIONALIZED WITH BIOACTIVE COMPOUNDS FOR BIOMEDICAL APPLICATIONS

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1 Introduction

The progressive development of knowledge in the field of materials has led to the emergence of different types of biomaterials, classified as bioinert, bioactive, and bioresorbable [1].

In 1969, Larry Hench and colleagues developed the first glass capable of bonding directly to bone, which later became known as bioactive glass [2-3]. This material promotes the formation of a hydroxyapatite layer, thereby stimulating osseointegration. Bioactive materials are distinguished by their ability to interact with the host tissue and to induce the formation of a layer with a composition similar to that of the bone mineral phase [1, 4].

Although bioactive glasses exhibit good compressive strength, they suffer from high brittleness and low tensile strength. To overcome these limitations, bioactive composites have been proposed, combining the bioactivity of glass with the mechanical strength of metallic substrates [5-10].

In recent decades, the deposition of bioactive glass on metallic implant surfaces has become an intensively studied research area, with interest increasing significantly over the last 15 years. Such coatings can exhibit behavior similar to hydroxyapatite or calcium phosphates, thereby facilitating osseointegration [10-17]. However, technological challenges remain, including the preservation of chemical composition, the prevention of reactions with the substrate, and the mismatch of thermal expansion coefficients [18].

More than 50 years after their discovery, bioactive glasses remain a benchmark in regenerative medicine, being capable not only of being tolerated by the body but also of stimulating tissue regeneration [19]. This thesis focuses on the development of bioactive glass–based coatings modified with antimicrobial and bioactive agents, aimed at improving the integration of metallic implants and reducing the risk of postoperative infections.

1.1 Research Topic and Significance

Maintaining the functionality of the osteoarticular system remains a major challenge despite technological progress. Bone injuries and degenerative disorders require effective solutions for tissue regeneration and integration.

The 45S5 bioactive glass has been extensively studied for its ability to stimulate bone tissue formation; however, its brittleness and lack of antimicrobial effect limit its clinical use. Bioactive glass–based coatings applied on metallic implants can promote osseointegration and reduce postoperative infections. In order to overcome these limitations, doping with metallic ions and functionalization with bioactive/antimicrobial compounds have been investigated as strategies to develop multifunctional coatings capable of ensuring bone regeneration, infection protection, and rapid implant integration.

This work investigates the synthesis and characterization of 45S5 coatings doped with samarium and functionalized with benfotiamine or Miramistin, deposited on stainless steel. The thesis is aligned with current trends in the field of advanced biomaterials, proposing an original approach with potential clinical impact.

1.2 Objectives of the Thesis

The main objective of this thesis is to develop bioactive coatings with osteoinductive and antimicrobial properties, based on 45S5 glass doped with samarium and functionalized with bioactive compounds, deposited on metallic substrates. The relevance of the research derives from the high demand for bone grafts, exceeded only by that of blood,—and from the need for solutions that enhance osseointegration and reduce implant-associated infections.

To achieve this goal, the research was structured in stages: (i) preparation of undoped 45S5 glass and its functionalization with Miramistin, an antimicrobial agent, both to enhance the antibacterial properties of the bioactive glass coatings and to gain a deeper understanding of the deposition and functionalization processes; (ii) synthesis of samarium-doped compositions to assess the influence on bioactivity and antimicrobial properties; (iii) functionalization with benfotiamine to stimulate bone regeneration; (iv) deposition of layers by spin coating on stainless steel for homogeneous coatings; (v) physicochemical characterization by modern techniques (XRD, SEM-EDS, FTIR, TGA); (vi) bioactivity testing in SBF, monitoring hydroxyapatite formation; (vii) evaluation of cytocompatibility and antimicrobial activity.

These objectives aim to obtain advanced multifunctional materials able to address, at the same time, the challenges of osseointegration, postoperative infections, and coating stability on metallic implants.

1.3 General Methodology

The experimental activity was structured in stages, in line with the research objectives. In the first phase, undoped 45S5 bioactive glass was obtained by the sol–gel method, deposited on stainless steel, and functionalized with Miramistin to validate the method and establish a biological reference. Subsequently, samarium-doped compositions were synthesized, assessing their influence on bioactivity, antimicrobial activity, and cytocompatibility. It was found that 1.0% Sm ensured an optimal balance between antibacterial effect and reduced cytotoxicity.

Based on this result, the doped glass was functionalized with benfotiamine, for which a dedicated synthesis and application method was developed. Deposition on metallic substrates was carried out by spin coating, yielding homogeneous and adherent coatings. Characterization included morphological, structural, and chemical analyses (SEM, EDS, FTIR, XRD, TGA), while biological evaluation focused on bioactivity tests in SBF and cytocompatibility. The study aimed to correlate Sm doping and benfotiamine functionalization with the performance of the coatings, in order to identify the most promising solutions for implantology.

1.4 Structure of the Thesis

The thesis is organized into six chapters, grouped into two major parts:

Theoretical part:

Chapter 1 introduces the context, objectives, and general methodology, while Chapter 2 synthesizes the literature regarding biomaterials, bioactive glass, ion doping, and functionalization with bioactive compounds, with emphasis on osteoinductive and antimicrobial properties.

Experimental part:

Chapter 3 describes the materials used, synthesis, deposition and characterization techniques, while Chapter 4 presents the obtained results, structured by stages: synthesis of simple and Sm-doped 45S5 bioactive glass, functionalization with benfotiamine and Miramistin, deposition on metallic substrates, and physicochemical and biological evaluation. Chapter 5 summarizes the general conclusions and original contributions, and Chapter 6 contains the bibliography. A significant part of the results has been published in scientific journals.

2 Critical Review of the Literature

Recent advances in biomaterials have enabled the development of increasingly effective solutions for the treatment of bone defects, particularly through metallic implants. Although these provide adequate mechanical support, they exhibit low bioactivity and are perceived as passive structures. Coating them with bioactive materials represents a key strategy for stimulating osseointegration and improving biological performance.

Bioactive glass has become a material of major interest due to its ability to form a hydroxyapatite layer similar to bone and its versatility: the composition can be adjusted, it can be doped with active ions, and functionalized with osteoinductive or antimicrobial compounds. The main application areas are illustrated in Figure 2.1.

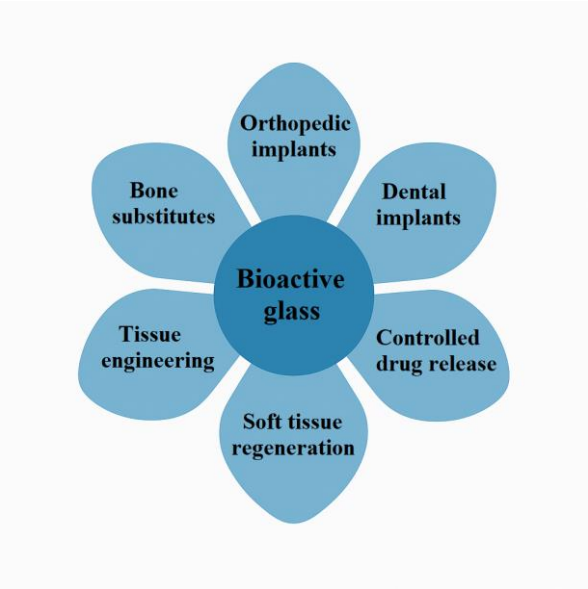

Figure 2.1 Application areas of bioactive glass.

The specialized literature includes numerous studies dedicated to glass compositions, deposition techniques, improvement strategies and biological testing. This chapter synthesizes these theoretical and experimental data, forming the foundation of the research presented in the thesis.

2.1 Bioactive Glass – Composition, Properties, and Applications

Bioactive glasses represent a class of reactive glass–ceramic biomaterials, characterized by biocompatibility and the ability to actively interact with living tissues. They gradually degrade in the physiological environment, releasing ions that stimulate regeneration processes and favor the formation of a hydroxyapatite layer similar to the mineral phase of bone [3].

In vivo experiments have demonstrated the excellent integration of 45S5 glass, highlighting the rapid formation of a strong bond with bone. Its ability to interact with soft tissues was later confirmed, explaining its broad applicability [20-24]. Based on these results, bioactive glass has been clinically applied in commercial products such as PerioGlas® and BioGran®, designed for the treatment of periodontal defects and bone regeneration, as well as in implantology, where it contributes to initial implant stability and subsequent integration. Its derivatives (e.g., NovaMin®) are incorporated into toothpastes for enamel remineralization and dentin hypersensitivity reduction [25].

Due to their osteoconductive character and stimulatory effect on osteoblasts, bioactive glasses are widely used in bone regeneration (maxillary, post-traumatic, or post-oncological), but also in the form of granules, thin layers, or inserts in customized implants [26]. Moreover, they have proven useful in dermatology, accelerating the healing of chronic wounds or burns by stimulating angiogenesis, reducing inflammation, and absorbing exudate. When combined with polymers such as chitosan or alginate, these materials form part of modern bioactive dressings [26-27]. Therefore, bioactive glasses represent highly versatile materials with promising applications for the regeneration of both bone and soft tissues, remaining a priority direction in current biomedical research.

2.2 Methods for Obtaining Bioactive Glass

Bioactive glasses can be used in the form of powders or coatings, and the synthesis method influences their structure, porosity, and bioactivity. The most widely used approaches are conventional melting and the sol–gel method, each with specific advantages and limitations.

The conventional melting method involves mixing and melting inorganic precursors at high temperatures (1300–1450 °C), followed by rapid cooling to obtain the amorphous structure. It is a well-established technology that allows precise control of composition and the production of large amounts of material. However, it requires expensive equipment (platinum crucibles) and is not suitable for incorporating thermosensitive substances.

The sol–gel method uses chemical reactions, at low temperatures, to transform organic and inorganic precursors into a porous oxide network. Major advantages include porosity

control, high specific surface area, the possibility of ion doping or encapsulating bioactive molecules, and the direct application of the sol by deposition techniques such as spin coating or dip coating. The main limitations are process complexity and the high cost of precursors.

Therefore, the melting method is preferred for large-scale production, while the sol–gel method is more suitable for obtaining nanostructured powders or thin coatings used in tissue engineering and controlled drug delivery systems.

2.3 Methods for Depositing Bioactive Glass

The application of bioactive glass on metallic substrates is an essential step in obtaining functional coatings with biomedical applications. The choice of deposition method influences the thickness, morphology, adhesion, and homogeneity of the layer. Numerous techniques have been reported in the literature, but the most widely used are presented below.

Pulsed Laser Deposition (PLD) is based on the ablation of a target material using a high-energy laser, followed by condensation of the particles on the substrate. The method enables accurate reproduction of the composition, precise thickness control and the production of high-purity thin films. However, the process is mainly suitable for small substrates, as film uniformity decreases with increasing surface area; in addition, the deposition rate is relatively low, and requires expensive equipment[28-30].

Radio Frequency Magnetron Sputtering (RF-MS) involves bombarding the target with ions, which leads to the emission of particles that are deposited on the substrate. This method produces uniform and adherent films with controlled thickness, applicable at low temperatures. Its limitations include the complexity of the equipment and the relatively low deposition rate [31-32].

Plasma Spraying employs very high temperatures to melt bioactive glass powder and project it onto the substrate, resulting in thick and adherent layers. The technique is already used clinically for implant coatings, but it may affect thermosensitive compounds [33-35].

Spin Coating involves spreading a liquid sol onto the substrate by rapid rotation. This method produces uniform films of nanometric or micrometric thickness, with good parameter control. Its disadvantage is that it can only be applied to flat and relatively small substrates [36-38].

Dip Coating is a simple and versatile technique in which the substrate is immersed in a sol and withdrawn at a controlled rate. It allows the coating of complex geometries, but thickness and uniformity depend on solution stability and process conditions [39].

Electrophoretic Deposition (EPD) is based on the migration of electrically charged particles under an applied field and their accumulation on the substrate. It is a simple and cost-

effective method that allows the formation of uniform coatings even on complex geometries. However, it requires stable suspensions and subsequent heat treatments to consolidate the layer [40-42].

In conclusion, physical methods (PLD, RF-MS, plasma spraying) produce dense and high-performance coatings but are expensive, whereas chemical (spin coating, dip coating) and electrophoretic methods offer more accessible and versatile solutions with broader applicability, though with limitations regarding the thickness and uniformity of the films.

2.4 Strategies for Improving the Properties of Bioactive Glass

Although bioactive glasses combine bioactivity and biocompatibility, their performance can be further optimized through compositional or structural modifications. The main directions aim at enhancing mechanical strength, controlling degradability, increasing bioactivity and imparting antibacterial or osteoinductive properties. Figure 2.2 illustrates the correlation between dopant ions and their associated biological effects [43].

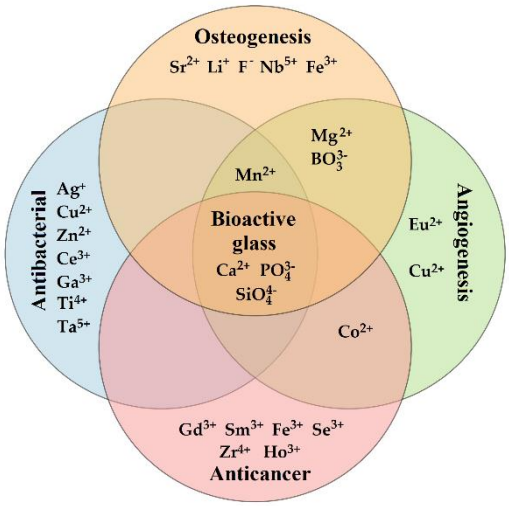

Figure 2.2 Correlation between dopant ions and the biological effects of bioactive glasses.

Doping with metallic ions (Zn^{2+}, Cu^{2+}, Ag^{+}, Sr^{2+}, Ce^{3+}, etc.) is one of the most widely studied strategies [54]. It allows the adjustment of physicochemical properties while simultaneously adding biological effects such as antibacterial, osteogenic, or angiogenic activity. Recent studies have shown, for example, that Sr doping provides significant antioxidant and antimicrobial effects [44-45], Zn and Cu confer antimicrobial and anti-inflammatory properties [46-49], and the addition of Ag ensures effective antibacterial resistance against pathogenic strains. In contrast, other ions (Fe, F, B) may reduce cell

proliferation, which highlights the importance of rigorous selection depending on the application [50].

Functionalization with bioactive molecules (vitamins, antibiotics, peptides or natural polymers) represents another important strategy, enabling the controlled release of active substances and the extension of material functionality. The porous structure typical of sol–gel–derived glasses facilitates this type of functionalization, while the use of nanoparticles accelerates hydroxyapatite formation [15]. Examples include bioactive glass combined with chitosan, which promotes osseointegration and reduces oxidative stress, and combinations with PMMA, which improve adhesion to metallic substrates and provide anticorrosive protection [51-54].

In conclusion, doping and functionalization of bioactive glass provide versatile solutions for the development of multifunctional materials tailored to current biomedical requirements.

2.5 Other Bioactive Materials Used in Coatings

In addition to bioactive glass, research in the field of biomaterials has focused on a wide range of bioactive materials with specific properties and applications. These include calcium phosphates, oxide bioceramics, biocompatible metals, natural or synthetic polymers, and composite materials. Each class has its advantages and limitations, and the choice depends on the clinical context and the type of regeneration desired. A comparative synthesis of these materials, including examples, applications and key properties, is presented in Table 2.1.

Table 2.1 Examples of bioactive materials used in implantology.

Class of materials	Examples	Applications	Key properties	References
Calcium phosphates	Hydroxyapatite (HAp), tricalcium phosphate (TCP)	Implant coatings, bone substitutes, granules for bone defects	Bioactive, osteoconductive, resorbable (depending on crystallinity); structure similar to bone	[55-60]
Oxide bioceramics	Al_2O_3, ZrO_2 (Y-TZP)	Hip prosthesis heads, structural implants	High mechanical and chemical resistance, excellent biocompatibility, but bioinert	[61-69]
Biocompatible metals	Ti and alloys (Ti-6Al-4V), Mg, Ta, stainless steel	Orthopedic and dental implants, resorbable stents	Superior mechanical properties, corrosion resistance; Mg is resorbable, Ta shows high osseointegration	[70-84]
Natural polymers	Collagen, chitosan, alginate, hyaluronic acid	Coatings, scaffolds for tissue regeneration, drug delivery systems	Biocompatible, biodegradable, promote osseointegration and cellular interaction	[85-87]

Bioactive composites	HAp–polymer, bioactive glass–polymer, PCL/HAp, PEEK composite	Dental implants, bone substitutes, 3D scaffolds	Combine ceramic stiffness with polymer flexibility; osteoconductive, customizable	[88-92]

In conclusion, these classes of materials complement the role of bioactive glass in implantology and regenerative medicine. They provide complementary solutions, ranging from bioactive coatings and structural supports to advanced systems for tissue regeneration and controlled drug delivery.

2.6 Theoretical Conclusions

The critical review of the literature highlights the diversity of bioactive materials developed in recent decades, each with specific advantages and limitations. This thesis focuses on 45S5 bioactive glass due to its biocompatibility, its ability to be doped with functional ions, and its ease of functionalization with biologically active compounds. This composition, already validated in clinical applications for bone and dental regeneration, provides a reliable starting point for the development of functional coatings.

The sol–gel method was used to obtain the glass, valued for its simplicity and efficiency, avoiding the need for costly equipment associated with conventional melting. For deposition, the spin coating method was selected due to its reproducibility and easy applicability on flat substrates.

Optimization strategies included doping with samarium, an element with antimicrobial potential that has been insufficiently explored, as well as functionalization with benfotiamine, a vitamin B1 analogue with osteoinductive effects. The samarium–benfotiamine combination represents an original approach not previously investigated. In parallel, functionalization with Miramistin, a broad-spectrum antiseptic, was also explored to evaluate its impact on the properties of the coatings.

This research direction is based on the critical analysis of the existing literature, including a review published by the author, and aims at developing innovative multifunctional coatings [93]. The results obtained are presented in the following chapters.

3 Materials and Methods

This chapter summarizes the materials used and the experimental procedures through which 45S5 bioactive glass–based coatings, in both undoped and samarium-doped variants, were obtained, deposited, functionalized, and evaluated. The section highlights the essential elements of the experimental design in a coherent and concise presentation.

Materials and substrates. The classical 45S5 composition (45 % SiO_2, 24.5 % Na_2O, 24.5 % CaO, 6 % P_2O_5; wt.%) was obtained by the sol–gel method, using common precursors for silicon (TEOS) and phosphorus (TEP), as well as soluble salts for calcium and sodium (calcium and sodium nitrates). For samarium doping, additional samarium nitrate was introduced during the synthesis stage, without altering the proportions of the other components. For bioactivity testing, bioactive glass samples, both as powders and coatings, were immersed in SBF prepared according to the Kokubo–Takadama protocol [94]. Functionalization of the coatings was carried out with two classes of agents: Miramistin, as a broad-spectrum antiseptic, and benfotiamine, a liposoluble analogue of vitamin B1, synthesized in the laboratory based on a previously published method [95]. Stainless steel AISI 304L discs were used as deposition supports, selected for their chemical stability, mechanical robustness, clinical relevance, and low cost. Surface preparation (controlled polishing, degreasing, and acid activation) ensured adhesion and uniformity of the films.

Preparation of 45S5 and 45S5–Sm powders. Bioactive glass was obtained by the sol–gel route, following the steps of precursor hydrolysis and condensation, formation of a homogeneous sol, gelation, drying, and calcination. The final product consisted of amorphous bioactive powders, with high yields and reproducible composition. Sm^{3+} ions were introduced at the sol stage, in concentrations of 0.1, 1.0, and 3.0 wt.%, to evaluate the influence of doping level on physicochemical and biological properties.

Deposition on metallic substrates. Thin coatings were obtained by the spin coating method, which allows the preparation of uniform films on flat surfaces. The main parameters (speed, time, number of layers) were adjusted to avoid non-uniform deposition at low speeds and crack formation at excessively high rotation rates. Optimal conditions were 2500 rpm for 45 s, with two successive layers deposited, resulting in a continuous coating. Subsequent heat

treatment densified the glass structure and removed organic residues, without affecting substrate integrity.

Coating functionalization. In the initial stage of research, glassy surfaces were functionalized with Miramistin by controlled immersion in its solution, followed by drying. This treatment did not alter the glass structure and conferred antimicrobial properties. Later, attention shifted to multifunctional coatings by combining the antimicrobial effect of samarium with the osteoinductive potential of benfotiamine. For this, thin-layer spraying of a concentrated benfotiamine solution onto 45S5–Sm (1.0%) films was performed, with successive drying and gravimetric monitoring of loading. The procedure ensured a uniform distribution of the active compound without compromising adhesion of the base film.

Physicochemical characterization. Complementary methods were used for material characterization. X-ray diffraction (XRD) was applied to verify whether the powders and coatings were amorphous or contained crystalline phases. FTIR spectroscopy, performed on both powders and surfaces, allowed identification of chemical groups and monitoring of hydroxyapatite formation during bioactivity tests. Scanning electron microscopy (SEM), coupled with EDS analysis, provided information on surface morphology and elemental distribution. Thermal analyses (TGA/DSC) highlighted solvent removal and decomposition of compounds (particularly nitrates), data useful for establishing heat treatment protocols. BET measurements provided specific surface area and porosity data, while density and contact angle measurements complemented the evaluation by assessing compactness and surface hydrophilicity.

Bioactivity testing in SBF. Both powders and coatings were immersed in SBF for periods ranging from several days to several weeks, to evaluate the formation and evolution of hydroxyapatite or other calcium phosphate layers. FTIR and SEM observations were correlated with pH, conductivity, and mass loss measurements to describe the interaction between glass and the physiological medium. This procedure enabled direct comparison between undoped and doped compositions, as well as between functionalized and non-functionalized samples.

In vitro biological evaluation. Cytocompatibility was tested on MC3T3-E1 preosteoblast cells, using media obtained by contact with powders containing different Sm concentrations and by direct seeding on 45S5–Sm (1.0%) coatings, with or without benfotiamine. Live/Dead assays were employed for qualitative evaluation, while MTT and LDH tests were performed for quantitative assessment, all conducted in triplicate and statistically analyzed (ANOVA, $p < 0.05$).

Antimicrobial activity was investigated on Gram-positive and Gram-negative bacteria and on yeasts, using agar diffusion tests and determination of the minimum inhibitory concentration (MIC). Anti-adhesion tests and analyses of microbial virulence factors were

also performed. Results allowed comparison between undoped and Sm-doped glass, as well as evaluation of the additional effect brought by benfotiamine.

Aim of the experiments. The experiments aimed at obtaining thin, uniform coatings with strong adhesion to the substrate, preserving the bioactivity of 45S5 glass while introducing additional properties such as antimicrobial effect and stimulation of bone cells. Evaluation by physicochemical methods and biological tests enabled the correlation of structure and composition with functional performance. In this way, several variants were compared and the most promising ones for biomedical applications were identified.

4 Results and Discussion

This chapter presents the main stages of the doctoral research, focused on the development of multifunctional bioactive coatings for medical applications. In the first stage, 45S5 glass coatings were obtained on stainless steel substrates by the spin coating method, followed by functionalization with Miramistin to achieve an antimicrobial effect.

The research then continued with the doping of 45S5 bioactive glass with samarium (0.1–3.0%) and its evaluation from both physicochemical and biological perspectives. It was found that the addition of 1.0% Sm provided the best compromise between antimicrobial activity and cytocompatibility, reducing the need for external adjuvants.

Based on this composition, coatings were prepared on metallic substrates and subsequently functionalized with benfotiamine, a compound with potential antioxidant, osteoinductive, and antiresorptive roles. The complex coatings (45S5 + 1.0% Sm + benfotiamine) were analyzed structurally and biologically, highlighting the influence of functionalization on morphology, bioactivity, and cytocompatibility.

The results are presented and discussed in separate sections, each stage contributing to the development of the final material.

4.1 Preparation and Characterization of 45S5 Bioactive Glass Coatings on Stainless Steel Functionalized with Miramistin

In this stage of the study, 45S5 bioactive glass coatings were deposited on stainless steel substrates by the spin coating technique. The method enabled the formation of thin, uniform, and continuous films without visible cracks. To provide an additional functionality, the coatings were treated by controlled immersion in a Miramistin solution, a broad-spectrum antimicrobial agent. This procedure ensured uniform surface coverage without compromising the integrity and bioactivity of the glass layer. The functionalization scheme is shown in Figure 4.1.

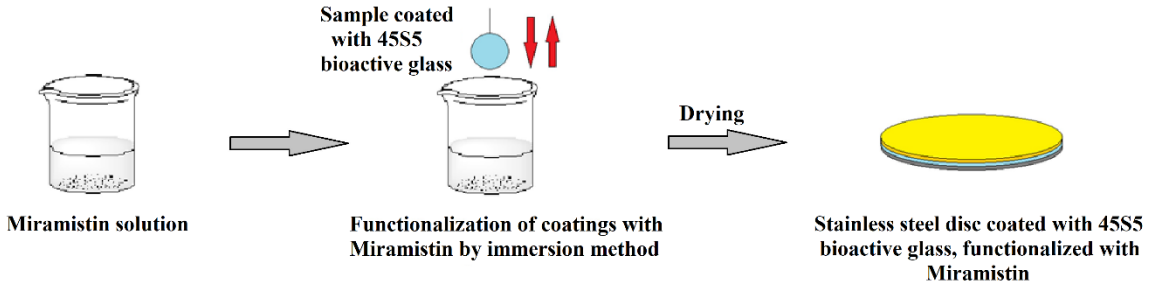

Figure 4.1 Schematic representation of the functionalization of coatings with Miramistin.

FTIR analyses confirmed the deposition of the glass by revealing the characteristic bands of the silicate network. After functionalization, specific signals of Miramistin appeared uniformly distributed on the surface. SEM observations showed a rough and porous morphology, typical of bioactive glass, onto which Miramistin formed an additional uniform layer covering the base structure. EDS investigations confirmed the characteristic composition of 45S5 glass (Si, Ca, Na, P, O), as well as the presence of elements from Miramistin (C, N, Cl), demonstrating the successful integration of the antimicrobial agent.

In vitro bioactivity tests, performed by immersion in SBF for up to 14 days, revealed moderate increases in pH and conductivity, indicating ionic release and the initiation of hydroxyapatite formation. SEM analysis revealed calcium phosphate crystalline aggregates on the sample surfaces, confirmed by FTIR and EDS. At the same time, Miramistin signals decreased rapidly and disappeared after the first few days, indicating complete release of the compound from the superficial layer. This early release is considered clinically beneficial, reducing the risk of bacterial colonization immediately after implantation, a critical period for the prevention of postoperative infections.

In conclusion, the applied method enabled the preparation of uniform and adherent coatings that combine the bioactivity of 45S5 glass with the immediate antimicrobial effect of Miramistin. The results validate the strategy of combining osteointegrative properties and antibacterial protection in a single layer, providing a solid basis for the subsequent stages of the research.

4.2 Preparation and Characterization of 45S5 Bioactive Glass Doped with Samarium

In the intermediate stage of the research, the aim was to obtain and characterize 45S5 bioactive glass doped with different amounts of samarium, in order to evaluate whether this element could provide antimicrobial properties without compromising the characteristic bioactivity. Interest in lanthanides derives from studies indicating possible antimicrobial

effects and from the use of the isotope ^{153}Sm in oncological treatments. In this context, the objective was to develop compositions with intrinsic antimicrobial properties.

Three variants were prepared with additions of 0.1%, 1.0%, and 3.0% Sm (wt.%), using the same synthesis procedure as for undoped 45S5 glass.

Thermogravimetric analyses performed on the dried gels obtained from synthesis (before the final heat treatment) highlighted several decomposition stages: removal of water and solvents, followed by the decomposition of sodium, calcium, and samarium nitrates. Based on these data, the optimal heat treatment interval was set between 700–800 °C, sufficient for complete elimination of nitrates and prevention of excessive crystallization.

SEM analysis showed that the resulting powders consisted of agglomerates of smaller particles; as the samarium content increased, particle sizes decreased, reaching the nanometric scale for 3.0% Sm. EDS analysis confirmed the characteristic composition of 45S5 glass and the presence of samarium.

FTIR spectroscopy revealed the specific silicate and phosphate bands typical of 45S5 glass. The introduction of samarium produced slight band shifts and intensity variations, but the matrix remained predominantly amorphous, with reduced crystallization tendency at low and medium doping levels. X-ray diffraction confirmed the presence of a glassy matrix with moderate fractions of combeite and devitrite. At low doping (0.1–1.0%), the proportion of devitrite decreased, which favors bioactivity; at 3% Sm, it increased, indicating more pronounced phase separation.

Density increased progressively with samarium addition, as an effect of its higher atomic mass. BET analyses showed compact powders with reduced specific surface area but confirmed bioactivity, as demonstrated by subsequent tests. After immersion in SBF, FTIR spectra revealed the rapid appearance of bands characteristic of hydroxyapatite, while silicate bands decreased. The solution pH increased during the first days, especially for 1.0% and 3.0% Sm compositions; the same trend was observed for conductivity. Mass loss reached ~13% after 21 days, with a rapid initial decrease followed by stabilization, indicating a balance between dissolution and precipitation. X-ray diffraction confirmed hydroxyapatite formation, showing that doping did not compromise bioactivity.

Biological tests showed good cytocompatibility for all compositions. MC3T3-E1 cells maintained viability at 24 and 48 hours, with only a modest decrease at 3.0% Sm. LDH tests indicated low cytotoxicity, while Live/Dead assays confirmed normal cell distribution. Among the three compositions, the 1.0% Sm variant exhibited the most balanced biological behavior.

Antimicrobial activity was selective. The doped compositions were effective against Gram-positive bacteria (*S. aureus*, *S. epidermidis*) and certain fungi (*C. parapsilosis*), with lower MIC values for 1% and 3% Sm. Bacterial adhesion decreased significantly for

staphylococci, especially *S. aureus*. For Gram-negative bacteria, the effect was weak or absent.

In conclusion, doping 45S5 glass with samarium by the sol–gel method was successfully achieved, yielding compact, bioactive, cytocompatible powders with selective antimicrobial activity. Among the studied variants, the 1.0% Sm composition represents a compromise between physicochemical properties, bioactivity, and biological profile, being recommended for biomedical applications, particularly for orthopedic implants where staphylococcal infections are frequent.

4.3 Deposition of 45S5 + 1.0% Sm Bioactive Glass on Stainless Steel Substrates and Functionalization with Benfotiamine

In the final stage of the research, multifunctional coatings based on 45S5 bioactive glass doped with 1.0% Sm were obtained, deposited on stainless steel by spin coating, and subsequently functionalized with benfotiamine. The choice of 1.0% Sm was based on previous results, which indicated a balance between bioactivity, cytocompatibility and antimicrobial effect. Functionalization with benfotiamine was intended as an osteoinductive addition, by reducing oxidative stress and stimulating osteoblast proliferation, without diminishing the intrinsic bioactivity of the glass. The preparation steps are summarized in Figure 4.2, which illustrates the spraying of the benfotiamine solution onto bioactive glass–coated substrates.

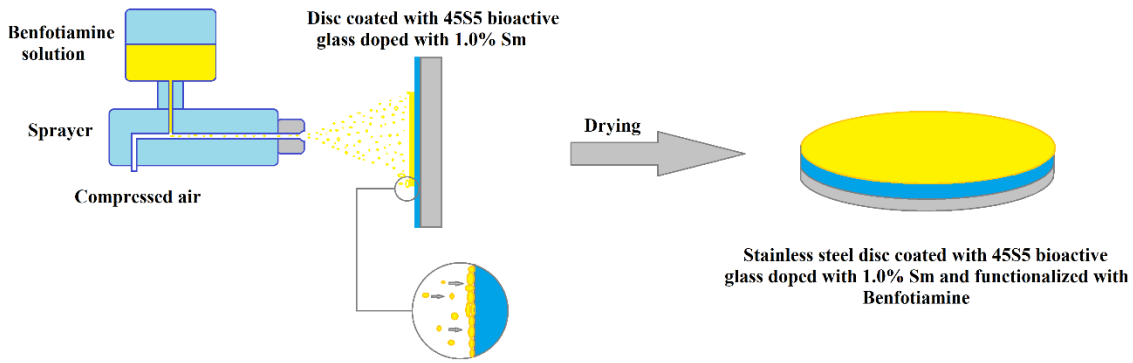

Figure 4.2 Schematic representation of the functionalization process of 45S5 + 1.0% Sm coatings with benfotiamine by successive spraying.

SEM analysis showed that the 45S5–Sm films deposited on steel were continuous and uniform, without macroscopic cracks, with a fine granular morphology. At higher magnifications, well-defined crystals embedded in a denser matrix were observed, indicative of a partially crystalline state due to the applied heat treatment. After functionalization with

benfotiamine, needle-like organic crystals were visible on the surface, relatively uniformly distributed, characteristic of the deposited organic compound. These structures did not affect the cohesion of the layer but acted as micro-reservoirs of active substance, favorable for rapid release immediately after implantation.

EDS analysis confirmed the elemental composition characteristic of 45S5 glass (O, Na, Si, P, Ca), together with signals of samarium incorporated in the network. Additional Fe, Cr, and Ni signals originated from the metallic substrate. The light elements typical of benfotiamine (C, N, S) could not be directly detected by EDS, but the presence of the compound was confirmed by the needle-like morphology observed by SEM and more clearly by specific FTIR signatures.

FTIR microscopy performed at 1010 cm^{-1} on the unfunctionalized bioactive glass coating confirmed the uniform deposition, with the obtained maps showing nearly constant composition across the analyzed surface; small transmittance variations (~5%) were associated with film thickness differences. The IR spectrum of unfunctionalized samples displayed the characteristic silicate bands (~1010, 950, 880 cm^{-1}). After functionalization, in addition to these signals, bands characteristic of benfotiamine appeared, confirming the presence of the organic compound. Transmittance maps at 1665 cm^{-1} showed a relatively uniform distribution of benfotiamine on the substrate surface.

Immersion in SBF was carried out for 7 days, monitoring pH, mass loss, and FTIR spectra. The pH increased slightly from 7.42 to ~7.76 during the first 3 days, then stabilized, reflecting an initial ionic exchange ($Na^+/Ca^{2+} \leftrightarrow H_3O^+$) followed by equilibrium between dissolution and precipitation. Mass loss followed the same trend: a more rapid decrease in the first days due to benfotiamine release and sodium ion leaching, followed by stabilization, typical for bioactive glasses in physiological environments. Samples with and without benfotiamine showed similar trends, with very small differences.

FTIR microscopy of the sample surfaces after immersion revealed the appearance of phosphate bands at 1060 cm^{-1} from the first day, their intensity progressively increasing at 3 and 7 days. In parallel, the intensity of silicate bands decreased, indicating mineralization. For functionalized samples, organic bands in the 1650–1670 cm^{-1} region almost completely disappeared after 7 days, indicating benfotiamine release. At the same time, the appearance of a band at ~794 cm^{-1} from the first day of immersion suggested rearrangements of the silicate network associated with mineral layer nucleation. Overall, the data showed that the layer gradually transformed, while immersed in SBF, through calcium phosphate formation, concomitant with the release of the organic component. The EDS analysis showed an increase in phosphorus concentration at the surface, thus confirming the previous statement.

The hydrophilicity of the surfaces before and after functionalization was evaluated by contact angle measurements. The 45S5 + 1.0% Sm films exhibited a value of ~68°, characteristic of moderately hydrophilic surfaces. After functionalization, the angle decreased

significantly to ~30°, indicating a pronounced increase in hydrophilicity. This change is favorable for protein adsorption, initial cell attachment, and efficient osseointegration.

Biological tests performed on the MC3T3-E1 cell line confirmed good cytocompatibility for both types of coatings. The LDH assay showed low cytotoxicity at 2 and 7 days, with no significant differences between groups. The MTT assay showed comparable values at 2 days; however, at 7 days, cell viability was higher on benfotiamine-functionalized films, with statistically significant differences ($p < 0.05$). Live/Dead analysis showed good cell density on both surfaces, with greater coverage and a tendency to form small aggregates on benfotiamine-containing samples, in agreement with MTT results.

The results confirm the successful preparation of multifunctional, homogeneous, and adherent coatings that preserve the bioactivity of 45S5 glass. Functionalization with benfotiamine increased surface hydrophilicity and supported more intense cell proliferation. By combining these effects, the coatings are suitable for biomedical applications requiring a stable bioactive layer capable of promoting early calcium phosphate nucleation and providing an adequate initial support for bone cells.

5 General Conclusions

This thesis focused on obtaining thin, bioactive and multifunctional coatings based on 45S5 glass for implantology applications. In the first stage, uniform films were deposited on stainless steel by spin coating, confirmed by SEM (continuous, crack-free surfaces) and FTIR (characteristic silicate bands). Functionalization with Miramistin, performed by controlled immersion, was uniform. Bioactivity tests in SBF showed the rapid release of Miramistin and the formation of a calcium phosphate layer shortly after immersion.

In the intermediate stage, 45S5 glasses doped with different amounts of samarium (0.1–3.0 wt.%) were obtained. All compositions were cytocompatible; antimicrobial activity was selective, more evident against *S. aureus* and *S. epidermidis*, suggesting relevance for orthopedic implants. Bioactivity was confirmed by SBF immersion and the formation of a hydroxyapatite-like layer. Based on the balance between bioactivity, cytocompatibility, and antimicrobial effect, 1.0% Sm was selected for the final stage.

In the final stage, 45S5 + 1.0% Sm bioactive glass coatings were deposited on stainless steel substrates and subsequently functionalized with benfotiamine. SEM and FTIR analyses confirmed a continuous inorganic layer and a superficial organic layer. SBF tests indicated rapid release of benfotiamine followed by calcium phosphate layer formation; moreover, benfotiamine significantly increased hydrophilicity. Cellular tests (MC3T3-E1) performed on functionalized and non-functionalized surfaces showed low cytotoxicity and enhanced proliferation at 7 days for benfotiamine-containing samples.

The originality of the thesis lies in: (i) the use of Miramistin for the functionalization of bioactive glass coatings as an antimicrobial agent, (ii) the exploration of Sm doping to obtain bioactive glass with intrinsic antimicrobial properties, and (iii) the unique combination of 45S5 + 1.0% Sm + benfotiamine in thin coatings, simultaneously demonstrating bioactivity, cytocompatibility, and selective antibacterial effects with clinical relevance.

Conclusion: the developed coatings are promising for orthopedic implants, where the risk of staphylococcal infection is dominant, providing initial protection, sustained bioactivity, and good cellular compatibility. **Future directions:** in vivo validation, optimization of release kinetics and development of stratified architectures tailored to specific clinical indications.

5.1 Scientific Activity Carried Out During the Doctoral Studies

5.1.1 Published Papers

During the doctoral studies, I published the following scientific articles, which reflect the results obtained within the research topic:

1. Maximov, M.; Maximov, O.-C.; Craciun, L.; Ficai, D.; Ficai, A.; Andronescu, E., Bioactive Glass—An Extensive Study of the Preparation and Coating Methods. *Coatings* **2021,** *11*(11), 1386. (Impact factor 2,881; ranked Q2 (Materials Science, Coatings & Films – Web of Science, JCR)).

   https://doi.org/10.3390/coatings11111386

2. Hanganu, A.; Maximov, M.; Maximov, O.-C.; Popescu, C. C.; Sandu, N.; Florea, M.; Mirea, A. G.; Gârbea, C.; Matache, M.; Funeriu, D. P., Insights into Large-Scale Synthesis of Benfotiamine. *Organic Process Research & Development* **2024,** *28*(11), 4069–4078. (Impact factor 3,5; ranked Q1 (Chemical Engineering – Scopus/SJR)).

   https://doi.org/10.1021/acs.oprd.4c00351

3. Maximov, M. V.; Maximov, O. C.; Motelica, L.; Ficai, D.; Oprea, O. C.; Truscă, R. D.; (Stămat), L.-R. B.; Pericleanu, R.; Dumbravă, A.; Corbu, V. M.; Surdu, V.-A.; Vasilievici, G.; Ficai, A.; Dinescu, S.; Gheorghe-Barbu, I., Comprehensive Evaluation of 45S5 Bioactive Glass Doped with Samarium: From Synthesis and Physical Properties to Biocompatibility and Antimicrobial Activity. *Coatings* **2025,** *15*(4), 404. (Impact factor 2,9; ranked Q2 (Materials Science, Coatings & Films – Web of Science, JCR)). https://doi.org/10.3390/coatings15040404

4. Maximov, M.V.; Maximov, O.-C.; Trușcă R. D.; Ficai D.; Ficai A., Bioactive Coating with Antimicrobial Effect for Stainless Steel: Preparation and Characterization. *U.P.B Sci. Bull.*, Series B, **2025**, 87(3), 267-278.

5. Maximov, M. V.; Sleiman, L.; Maximov, O. C.; Trușcă, R. D.; Motelica, L.; Spoială, A.; Ficai, D.; Ficai A.; Dinescu S., Synthesis and characterization of bioactive coatings with bone regeneration potential and anti-resorptive effect. *Coatings* **2025,** *15*(10), 1120. (Impact factor 2,9; ranked Q2 (Materials Science, Coatings & Films – Web of Science, JCR)). https://doi.org/10.3390/coatings15101120

5.1.2 Participation in Conferences and Scientific Sessions

During the doctoral studies, the intermediate research results were presented at the following scientific events:

1. **National Autumn Conference of AOSR, 2020** – online oral presentation (Romanian language); Maximov, M.; Ficai, A. *Biocompatible Coatings for Implants*
2. **International Conference NanoBioMat – Summer Edition, 2022** – online oral presentation (English language); Maximov, M.; Trușcă, R.; Ficai, A. *Biocompatible Coatings with Antimicrobial Properties on Stainless Steel Supports*
3. **Scientific Communications Session – Chemistry Day, University of Bucharest, October 16, 2024** – live oral presentation; Maximov, M. *Application of Modern Analytical Techniques in the Study of Benfotiamine Synthesis at Industrial Scale*

5.2 Limitations and Future Research Directions

The study was carried out mainly through in vitro tests, which do not allow a complete evaluation of the coatings' behavior under complex biological conditions. Antimicrobial activity was investigated on a limited number of bacterial and fungal strains (though representative), and the results indicated selective efficiency—while for some microorganisms the coatings showed inhibitory effects, for others no significant reduction was observed, and in some cases proliferation even occurred. This limitation suggests the need for further optimization of the composition, for example by adding a dopant with a strong antimicrobial effect, such as silver ions (Ag^{+}), or by investigating other elements from the lanthanide series.

In future research, we intend to extend in vitro biological tests by including more clinically relevant cell types and microorganisms, to perform in vivo tests for validating osseointegration and biocompatibility under real conditions, and to assess the mechanical behavior of the coatings under stresses similar to those in the physiological environment. In addition, the release kinetics of benfotiamine and its influence on osteogenesis processes will be analyzed.

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