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*Review*

# Hybrid Organic–Inorganic Materials Prepared by Sol–Gel and Sol–Gel-Coating Method for Biomedical Use: Study and Synthetic Review of Synthesis and Properties

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**Abstract:** The need to improve the expectancy and quality of life of subjects affected by disabling pathologies that require the replacement or regeneration of tissues or parts of the body has fueled the development of innovative, better-performing materials that are capable of integrating into and being tolerated by body tissues. Materials with these characteristics, i.e., bio-functionality, biosafety, and biocompatibility, are defined as biomaterials. One of the many methods for producing such materials is the sol–gel technique. This process is mainly used for the preparation of ceramic oxides at low temperatures, through hydrolysis and polycondensation reactions of organometallic compounds within a hydroalcoholic solution. This study is based on a specific type of biomaterial: organic–inorganic hybrids. The aim of this study is to provide an overview of the advantages and disadvantages of the sol–gel technique, as well as describe the preparation and chemical and biological characterization, uses, and future prospects of these biomaterials. In particular, the use of plant drugs as organic components of the hybrid material is the innovation of this manuscript. The biological properties of plant extracts are numerous, and for this reason, they deserve great attention from the scientific community.

**Keywords:** biomaterials; sol–gel method; sol–gel-coatings technique; organic–inorganic hybrids



**Citation:** Barrino, F. Hybrid Organic–Inorganic Materials Prepared by Sol–Gel and Sol–Gel-Coating Method for Biomedical Use: Study and Synthetic Review of Synthesis and Properties. *Coatings* **2024**, *14*, 425. https://doi.org/10.3390/coatings14040425

Academic Editor: Olga A. Shilova

Received: 11 March 2024
Revised: 26 March 2024
Accepted: 30 March 2024
Published: 1 April 2024



## 1. Introduction

In recent years, demographic growth, technological progress, and the lengthening of life expectancy and quality have led to an exponential increase in the number of requests from individuals suffering from disabling pathologies for the replacement of tissues or body parts with prosthetic systems. In fact, the current clinical need for innovative surgical implants has given rise to an advanced biomedical technological sector that synergistically involves academic researchers and industries, with results of enormous relevance in the medical, economic, and social arenas [1,2].

In this field, specific materials called biomaterials are used, which, when placed in intimate contact with living tissue, do not cause adverse reactions or rejection by the body [3]. Therefore, a biomaterial is defined as a material designed to interface with biological systems to evaluate, support, or replace any tissue, organ, or function of the body [4].

Over 1.5 million joint replacements are performed annually in Europe alone; in the US, this number rises to 7 million [5].

Due to overwhelming demand, surgeons worldwide are now able to perform relatively simple operations to replace body parts. Additionally, by limiting the use of localized anesthesia to the area where the tissue or bone has to be replaced, the adverse effects of invasive surgery are significantly reduced. Even with this significant progress in technology, the longevity of the implanted biomaterial is still uncertain for many years to come. Reactions such as biomaterial wear or rejection are common. This is mainly due to the

adverse reactions of the immune system or chemical and/or mechanical issues within the production of the biomaterial [6,7].

Precisely for this reason, materials, to be defined as biomaterials, must possess adequate mechanical properties capable of ensuring biofunctionality and biosafety [8]. Furthermore, biomaterials must be biocompatible, i.e., cause a living system to react favorably to their presence [9].

Sol–gel is a suitable process for creating biocompatible materials [10–12]. Through the hydrolysis and polycondensation processes of organometallic compounds inside a hydroalcoholic solution, this procedure is often used to produce ceramic oxides at low temperatures [13].

Because of its remarkable adaptability, which allows molecular manipulation of the material for the produced and proper synthetic design, the adoption of the sol–gel technology has experienced a significant uptick. Additionally, by incorporating thermolabile organic molecules (polymers, anti-inflammatory, antibiotic, anticancer, and biomolecules, among others) into the inorganic matrix, the low process temperature enables the creation of organic–inorganic hybrids, which can be used to create drug delivery systems [14] capable of reducing inflammatory processes or diseases that may result from their implantation [15].

The focus of this study is the synthesis and characterization of a particular type of biomaterial: the organic–inorganic hybrid. These are biphasic materials whose specific characteristics derive from the synergy between the properties of the individual components [16]. Their synthesis has the aim of removing the limits connected to the use of the individual parts and enhancing their merits. For example, silica is a material that has been used for many years for its chemical and physical characteristics, but above all for its biocompatibility. With the introduction of a drug or a plant extract, we try to reduce the fragility of the glassy inorganic phase and improve biocompatibility [17–19].

It is known that plant extracts have high chemical/biological activities. The aim of using herbal medicines is to replace traditional medicines, synthesized with chemical reactions. The use of herbal medicines has numerous advantages: very high biological activities at very low doses (antioxidant, antibacterial properties, biocompatibility, etc.). Furthermore, low doses also decrease the risk of toxicity (hepatic and/or renal).

Examples of these materials with their advantages and disadvantages have been reported by Catauro et al. [10,14]. Herbal drugs in different weight percentages have been incorporated into the glassy $SiO_2$ matrices to obtain materials used in the biomedical field as prostheses. The organic matrix, in addition to performing the biologically active function, also reduces the fragility of the glass matrix, thus also improving the mechanical properties of the final hybrid material.

In summary, organic–inorganic hybrids offer an interesting combination of properties, but it is important to balance the advantages with the disadvantages specific to the desired applications, considering aspects such as manufacturing complexity, environmental safety, and associated costs.

Numerous compounds, including polyphenols, flavonoids, terpenes, alkaloids, and other molecules with biological activities, may be found in these extracts [20]. Here, we list a few typical biological characteristics linked to plant extracts:

1. Antioxidants: Rich in antioxidants, plant extracts aid in the body's defense against free radicals [21]. These substances have the ability to lower oxidative stress and shield cells from harm.
2. Anti-inflammatory: A few plant extracts have been shown to have anti-inflammatory abilities, which may aid in lowering bodily inflammation. Treating inflammatory diseases and enhancing general health may benefit from this [22].
3. Antimicrobial: Certain plant extracts may be able to combat bacteria, fungi, and other diseases thanks to antimicrobial qualities. These qualities can be used for sanitary and medical purposes [23].
4. Anticancer: Research has been conducted on some plant extracts that may have the ability to stop the development of cancer cells or reduce their expansion [24].

5. Antivirals: Certain plant extracts may include antiviral properties that aid in the defense against viral infections and bolster the immune system [25].
6. Cardioprotective: By controlling blood pressure, lowering cholesterol, and exhibiting other cardioprotective properties, plant extracts may be beneficial to the heart and lower the risk of heart disease [26].
7. Antidiabetics: A few plant extracts have the ability to control blood sugar levels, which may be advantageous for diabetic diseases [27].
8. Neuroprotective: Certain plant extracts may have the ability to protect nerve cells and maintain brain health [28].

It is significant to remember that the effects might change based on the particular plant, the component utilized, and the extraction technique. The goal of current research in herbal medicine is to gain a deeper understanding of the biological characteristics of plant extracts and their potential use in a range of therapeutic settings.

Because of these factors, the process of characterizing biomaterials is essential and entails a thorough examination of the mechanical, chemical, biological, and physical characteristics of materials intended for use in human interaction [29–32]. To ensure the safety, efficacy, and usefulness of biomaterials in medical applications, this procedure is critical. Some key aspects of biomaterial characterization are:

The identification and quantification of the chemical components of the biomaterial with infrared spectroscopy (FTIR), Raman spectroscopy, thermogravimetric analysis (TGA), mass spectrometry, etc. [33].

The study and analysis of the molecular structure of the biomaterial with nuclear magnetic resonance (NMR) spectroscopy can be used to obtain detailed information on the chemical structure [34].

Analysis of the surface morphology and internal structure of the biomaterial using imaging techniques such as scanning electron microscopy (SEM) and atomic force microscopy (AFM) can be used to obtain high-resolution images [35].

Another fundamental aspect of a biomaterial, in particular for organic–inorganic hybrids, is the evaluation of mechanical properties, such as strength, hardness, and elasticity with tensile tests, compression tests, and microindentation [36].

For biomedical use, the evaluation of the biomaterial's ability to interact with biological tissues without causing adverse responses is essential. Cytotoxicity, cell adhesion, and biodegradability studies are examples of biological tests [37].

In this case, the study of the biomaterial's ability to absorb and release substances, such as drugs or biomolecules, is also fundamental [38].

To be applied or installed, both in the medical and non-medical fields, the biomaterial must possess chemical and thermal stability. Techniques such as TGA and differential scanning calorimetry (DSC) can provide information on thermal stability [39].

Finally, the electrical and magnetic properties can be determined depending on the characteristics of the biomaterial.

For the biomaterial to be successful in biomedical applications, these analyses must be integrated to offer a comprehensive understanding of the material's properties. Precise characterization makes it easier to create and optimize biomaterials for particular therapeutic applications.

## 2. Biomaterials

### *2.1. Characteristics and Properties*

Biomaterials are substances created specifically to work safely and effectively with the human body to replace, repair, or enhance biological tissues. These materials are essential to the development of systems, implants, and gadgets that enhance healing and quality of life in a wide range of biological and medical applications. Biomaterials have many characteristics such as:

- Biocompatibility: These materials need to work with the biological system without posing a risk of negative responses. To prevent the body from rejecting something or reacting in an inflammatory manner, biocompatibility is crucial. In fact, certain biomaterials have the ability to precisely control the biological response, affecting things like cell adhesion, cell division, and blood vessel creation [40].
- The capacity to disintegrate naturally over time, which might be favorable in some situations and allow for a progressive replacement of the biomaterial with the surrounding biological tissue. This is particularly crucial in situations when the material must permanently integrate with the body, such as in temporary applications [41].
- Mechanical characteristics: biomaterials need suitable mechanical characteristics to carry out their intended purpose. Orthopedic implants, for instance, need to be robust enough to endure the mechanical strain of the surrounding bone tissue [42].
- A wide range of materials, including composites, metals, polymers, and ceramics, may be used to create many kinds of biomaterials. Every type of material has distinct qualities that make it appropriate for particular uses. In fact, biomaterials are used in a wide range of applications, such as prosthetics, dental implants, medical devices, scaffolds for tissue regeneration, drug delivery systems, and much more [43,44].
- Continuous work is in progress because research on biomaterials is constantly evolving to improve the performance, safety, and durability of materials used in medicine and biology.

In-depth knowledge of the interactions between materials and organisms is necessary for the design and development of biomaterials, as is the careful consideration of the particular requirements of the application. Biotechnological solutions and medical therapies are improved by ongoing innovation in this area.

### *2.2. Different Classes*

Biomaterials can be classified into different categories based on their characteristics, compositions, and applications [45] (Figure 1). Some of the main classes of biomaterials are:

- Polymeric materials are separated into two categories: synthetic materials and natural materials. The former are taken out of biological materials including alginate, cellulose, and collagen [46,47]. Synthetic materials such as polyethylene, polyurethane, and polytetrafluoroethylene (PTFE) are illegal in laboratories.
- Metallic materials such as biocompatible alloys (titanium alloys and cobalt–chromium-based alloys) or noble metals such as gold and platinum are often used in dental applications [48,49].
- Ceramic materials such as hydroceramics; bone materials that interact well with water, such as hydroxyapatite; or zirconium dioxide, silicon, titanium, etc., which are used in prosthetics and dental implants [50,51].
- Composite materials, like glass or carbon, which are blended into fibers and polymers, or mixes of polymers and ceramics that allow us to obtain the required qualities through the combined action of the separate components [52,53].
- Hydrogels, which are highly water-containing gelatinous solids with a consistency akin to biological tissues [54,55].
- Organic–inorganic hybrid materials, which combine organic and inorganic elements to provide features that work well together, such as the organic material's flexibility and the inorganic material's mechanical resistance [56,57].
- Bioactive substances, such as hydroxyapatite found in bone biomaterials, that elicit certain physiological reactions [58,59].
- Bioinert materials, like Teflon, which do not significantly alter bodily processes [60].

The particular application and the qualities needed to interact with the biological system in a safe and efficient manner determine the use of one biomaterial class over another. The goal of ongoing biomaterials research is to create ever-more-advanced materials that will perform better and be more biocompatible in a range of biotechnological and medical applications.

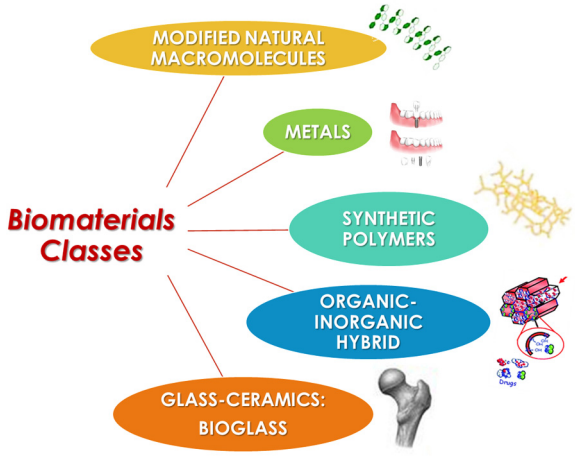


**Figure 1.** Classification of different categories of biomaterials.

### *2.3. Organic–Inorganic Hybrids*

Materials that combine organic and inorganic elements into a single structure are known as organic–inorganic hybrids [61]. These materials strive to produce a synergistic set of features by utilizing the special qualities of both types of materials. Actually, the goal of organic–inorganic hybrids is to blend the characteristics of inorganic and organic constituents. For instance, the mechanical strength and thermal stability of inorganic materials can be coupled with the flexibility and light weight of organic polymers [62,63].

Numerous sectors, including electronics, sensors, tissue engineering materials, catalysis, and controlled medication release systems, take advantage of these materials.

Many processes, including the sol–gel method, in situ polymerization, chemical vapor deposition (CVD), and other techniques that permit the production of organic–inorganic networks, can be used to synthesize organic–inorganic hybrid materials [64].

FTIR (Fourier Transform Infrared Spectroscopy) is an analytical method that is commonly employed in the analysis of biomaterials, including hybrids of organic and inorganic materials [65–67]. In actuality, this approach may be utilized to verify the existence of certain linkages and, thus, the emergence of a novel organic–inorganic network (Figure 2). By analyzing the absorption bands of molecular vibrations in the infrared portion of the electromagnetic spectrum, this technique offers information on the molecular structure of materials.

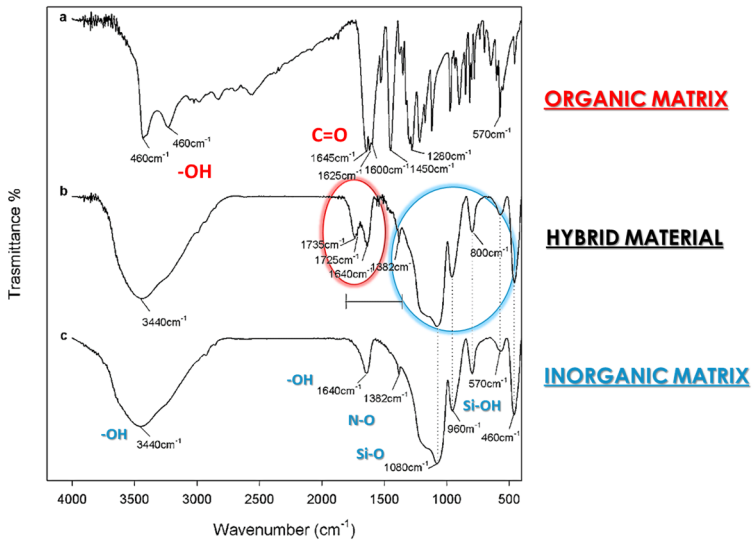


**Figure 2.** FTIR spectra of (**a**) organic matrix, caffeic acid, (**c**) inorganic matrix, $SiO_2$, and (**b**) hybrid material $SiO_2$ + caffeic acid x%wt [10].

The purpose of these hybrids is to outperform individual components. One may attain enhanced mechanical strength, better chemical stability, or enhanced biocompatibility, for instance. Because of this, the design of hybrid materials enables exact control over the structure at the nanometric level, enabling the production of materials with particular characteristics that are suitable for certain uses [68].

Hybrid organic–inorganic biomaterials are often utilized in the medical field to create tissue engineering structures, medication delivery systems, and implants [69–73].

The use of hybrid organic–inorganic materials is indicative of a multidisciplinary approach to materials design, which aims to integrate the best aspects of both organic and inorganic materials to provide innovative and cutting-edge solutions across a range of materials science domains.

## 3. Sol–Gel Technique: An Innovative Process

### *3.1. From Concept to Application*

The sol–gel technique is a chemical process that forms a gel from a liquid solution to create inorganic materials including coatings, glasses, and ceramics [74]. This method is renowned for its adaptability and exact control over the final product's structure and chemical makeup [75,76].

The 1920s and 1930s saw the beginning of research on gel formation in colloidal liquids. Science began to take an interest in the idea of a gelatinous solution ("sol") that had the ability to change into a gelatinous condition ("gel") [77].

In the 1940s, the phrase "sol–gel" was first used in scientific contexts by American scientist Edward Teller. Teller and his associates investigated the polymerization process that forms silica gel from the sol phase [78]. The 1970s saw a rise in interest in and the advancement of the sol–gel process, especially with the introduction of material chemistry research.

The ability to regulate the inorganic-material creation process from liquid solutions has created new opportunities in the field of materials engineering. During those years, the synthesis of glasses, ceramics, and coatings was accomplished using the sol–gel technique, which led to even further advancements in the industry [79–81].

The sol–gel process is still being developed today, and it is used in many different industries to produce sophisticated materials, biomaterials, sensors, smart coatings, and optical devices, among other things.

### *3.2. Sol–Gel Process*

The synthesis of inorganic materials could be achieved by the flexible sol–gel approach, which consists of starting from liquid solutions (sol) and turning them into gels, which are solid three-dimensional structures [82–86]. This process offers precise control over the chemical composition and properties of the resulting material. In particular for organic–inorganic hybrids obtained with the sol–gel method, the reaction parameters, precursors, and plant components used are fundamental. It is known that by varying the reaction conditions (time, temperature, concentrations) starting from the same precursors, materials with different morphologies and properties can be obtained. The structure of the biomaterial can be designed, obtained, and controlled depending on the intended biomedical application (gels, powders, films, glasses, or ceramics).

The main phases of the sol–gel technique are (Figure 3) [87,88]:

1. Solution preparation (Sol): the first step consists of the preparation of a solution containing inorganic precursors, such as metallic or alkylated salts. These precursors are soluble in an organic or aqueous solvent.
2. Hydrolysis and condensation: the process of hydrolysis involves hydrogen atoms in water reacting with the oxides of inorganic precursors to break chemical bonds and generate hydrolyzed oxides. This occurs when the oxides or precursors are in the solution. The hydrolyzed oxides then proceed through condensation, where they join

forces to create stronger connections. During this phase, an inorganic particle network forms in three dimensions, giving the gel its structure.

3. Gelation: in the process of gelation, the liquid solution turns into a three-dimensional gel with the particles dispersed across a continuous matrix.
4. Drying: the resultant gel can be dried in order to release any trapped water, creating xerogel, a porous solid substance.
5. Subsequent treatments: the material can go through additional heat or chemical treatments to develop the structure and gain certain qualities like crystallinity, mechanical resistance, or porosity reduction, depending on the intended uses.

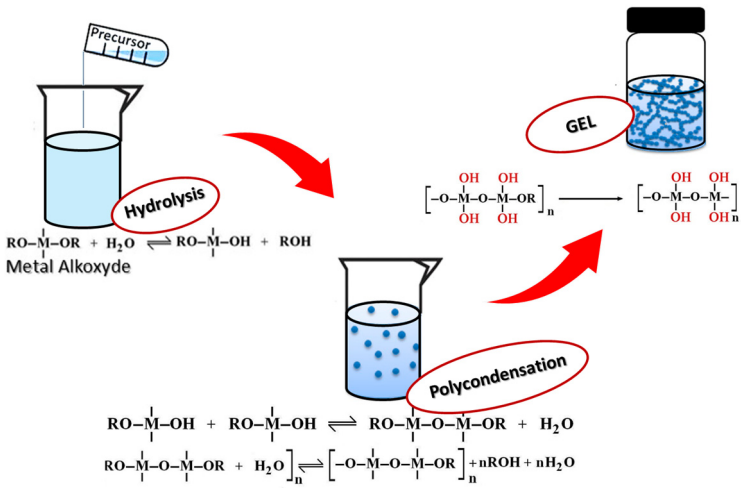


**Figure 3.** Flowchart of the sol–gel technique.

A wide range of materials, such as glass, ceramics, coatings, catalysts, and biomaterials, are produced using the sol–gel process [89–91] (Figure 4). Adjusting process variables including pH, temperature, drying time, and solution composition will change the finished material's characteristics. Because of its adaptability, the sol–gel technique is a useful process for creating sophisticated materials that may be used in a variety of areas [92,93].

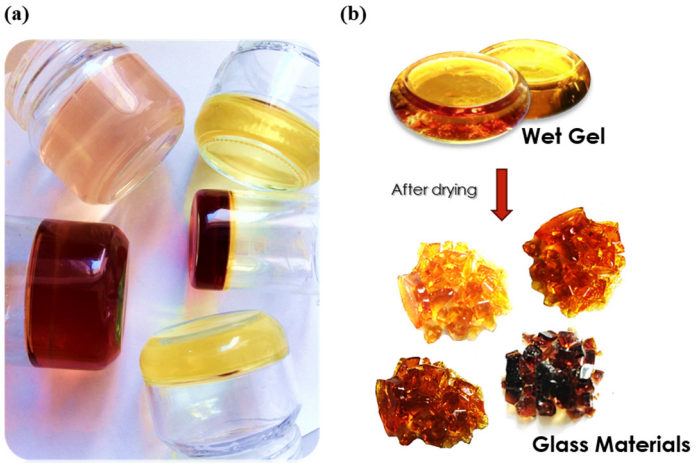


**Figure 4.** Classic organic–inorganic networks (gel) obtained after hydrolysis and polycondensation reactions (**a**) and glass materials obtained by drying gels (**b**).

### *3.3. Advantages and Disadvantages of the Sol–Gel Method*

The sol–gel technique has several advantages and disadvantages, depending on the specific applications and material requirements [94–97]. The main advantages are:

- Materials with particular qualities may be synthesized thanks to the exact control over the chemical composition of the final product provided by the sol–gel process.
- Many of the reactions involved in the sol–gel technique take place at relatively low temperatures, allowing for the production of materials in a more energetic and economical way than other synthesis methods. In particular, it is possible to incorporate vegetal drugs and thermolabile drugs into the inorganic matrix of interest [98].
- The versatility of the technique allows for the production of a wide range of materials, including glasses, ceramics, coatings, catalysts, and biomaterials.
- The material's consistent particle distribution brought about by the gel's production aids in the creation of a homogenous structure.
- The options for material design are increased by the integration of organic components into the inorganic matrix made possible by the sol–gel process.
- Lastly, by adjusting the process parameters, the porosity of the material may be regulated, producing porous materials like aerogels or xerogels [99].

While the disadvantages of this technique are:

- Production time and productivity may be impacted by the lengthy curing periods needed for some sol–gel techniques.
- Applying the sol–gel technology to large-scale industrial manufacturing can be difficult, and issues with the repeatability and consistency of the process may occur [100].
- Impurities in the surroundings or the solution may have a detrimental effect on the final product's quality.
- When using exceptionally rare or pure materials, the cost of inorganic precursors might be high.
- Trying to create complicated objects or big structures might be limited by gel formation.

In conclusion, the sol–gel approach is a strong and adaptable technology with many benefits; nevertheless, before using it to produce materials, it is crucial to thoroughly assess the particular requirements of the application and take into account any potential drawbacks [101].

### *3.4. Combination of the Sol–Gel Method with Other Modern Techniques*

The sol–gel technique is a chemical method for preparing solid materials from liquid solutions. The dip-coating technique, on the other hand, involves immersing an object in a liquid solution, followed by drying until a thin layer forms on the surface of the object [102,103]. Using sol–gel solutions as coatings during the dipping process is the application of sol–gel technology to the dip-coating technique [104–107].

Figure 5 shows the basic steps of the sol–gel-coatings technique.

Depending on the required characteristics of the finished film, these precursors might be either organic or inorganic. Different immersion rates and periods of residence inside the sol–gel solution are offered for the submerged item to be covered. these characteristics may have an impact on the coating's thickness. After being submerged, the item is taken out of the mixture so that the gel may stick to its exterior. The coating must next be dried, which can be accomplished either by air drying or by utilizing an oven with a temperature control. In this procedure, the gel solidifies into a layer.

Applying the sol–gel method to the dip-coating method yields thin coatings with a variety of characteristics, such as chemical and heat resistance, transparency, and resistance to chemicals [108] (Figure 6). A variety of industries, including the semiconductor industry, the production of special glass, corrosion protection, and other fields requiring certain coating properties, like the biomedical field, where materials are coated with sol–gel solutions to acquire antibacterial, antioxidant, and anti-inflammatory properties, can use this combination [109].

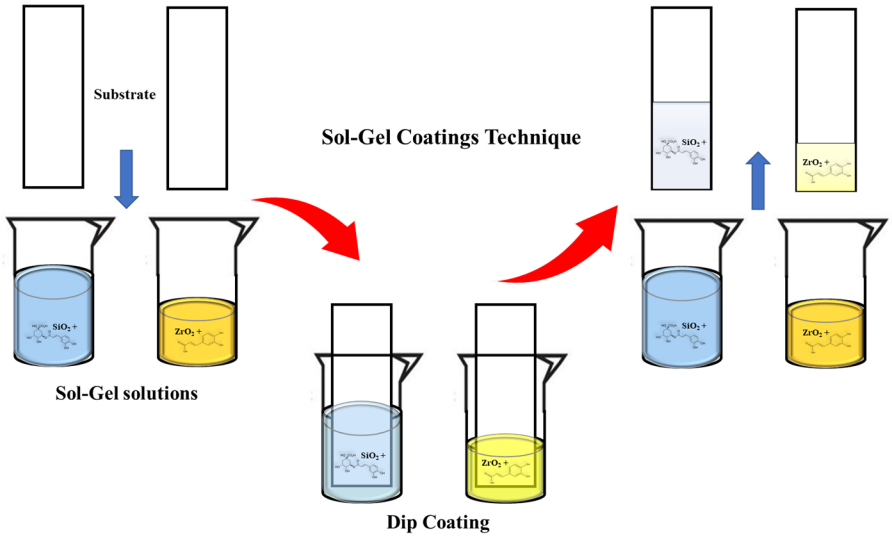


**Figure 5.** Flowchart of the sol–gel-coatings technique.

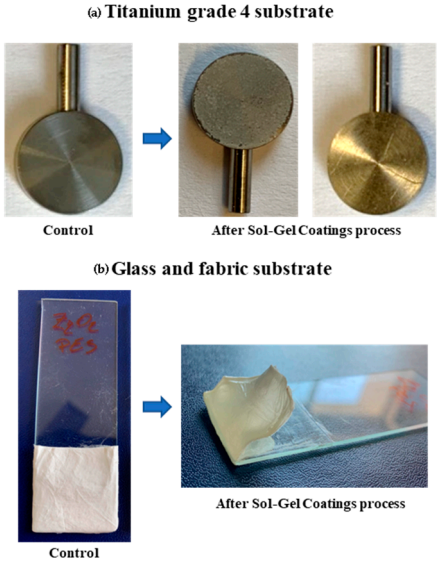


**Figure 6.** Different types of substrates coated with materials obtained with the sol–gel technique: (**a**) Titanium grade 4 substrate + $SiO_2$ and $ZrO_2$ x%wt [51]; (**b**) glass and fabric substrate PES + $ZrO_2$.

Very similar to the dip-coating method, "spin-coating" and "spray-coating" techniques also exist.

Spin-coating is a process that involves pouring a liquid solution containing the required material onto a flat surface, usually a substrate, and then spinning it quickly. The liquid is forced outward by the rotation's centrifugal force, covering the substrate in a thin, homogeneous layer [110]. This technique is frequently applied in the production of electronic devices and nanotechnology—for example, in the deposition of thin polymer, semiconductor, or protective coating layers [111,112].

Spray-coating is a technique that uses a misting system or compressed air application to spray a liquid solution or fine particle dispersion onto a target surface. The material is vaporized or dispersed into small droplets that settle on the surface, forming a uniform layer as the solvent evaporates [113]. In the manufacturing sector, this technique is frequently employed for tasks including painting, protecting surfaces from corrosion, and creating coatings for glass, metal, plastic, and other substrates [114,115].

In terms of manufacturing speed, layer uniformity, thickness control, and material compatibility, both techniques have benefits and drawbacks. The particular requirements

of the application and the desired qualities of the deposited layer will determine whether to use spray-coating or spin-coating.

It is also possible to produce materials for 3D printing using the sol–gel process. By combining the benefits of 3D printing with the special qualities of sol–gel materials, this method allows for the production of three-dimensional objects with desired characteristics [116,117]. Special additives, such as binding agents, rheological agents, or other compounds that enhance the material's printability, can be added to the sol–gel solution to modify it for 3D printing.

The 3D printer is filled with the sol–gel solution. Layer by layer, the material is deposited during the printing process, adhering to the preprogrammed path to construct the three-dimensional item. The object might need to be dried after printing in order to eliminate any moisture and start the curing process.

The application of the sol–gel technique to 3D printing allows for obtaining objects with specific chemical and physical properties—for example, high resistance, thermal conduction, or particular optical characteristics [118]. This combination has applications in materials engineering, electronic device production, biomedicine, and other fields where customized material qualities are essential for the intended use [119].

### *3.5. Uses, Properties, and Comparisons between Sol–Gel Biomaterials*

Organic–inorganic hybrid materials made using the sol–gel process are known as sol–gel biomaterials. The special qualities of these materials, such as biocompatibility, design flexibility, and the ability to integrate bioactive substances, have led to their widespread use in the biomedical and healthcare sectors [120–122]. Several potential uses and applications for sol–gel biomaterials include:

- Creating biocompatible coatings on medical devices, implants, or prostheses. By enhancing the material's contact with the surrounding biological tissues, these coatings lower the possibility of negative reactions and hasten the healing process [123].
- The sol–gel matrix can be created to include medicines or other bioactive compounds. This makes it possible for medicinal compounds to be released gradually and under control, increasing treatment efficacy and minimizing negative effects [124].
- Three-dimensional scaffolds can be built for tissue engineering using sol–gel biomaterials. These scaffolds aid in the repair of missing or injured tissue by offering short-term structural support for the proliferation and differentiation of cells [125].
- The development of biomimetic sensors, which are able to identify particular chemical or biological substances, is made possible by the adaptability of the sol–gel process. In the medical field, these sensors can be applied for monitoring or diagnostic purposes [126].
- The potential of sol–gel biomaterials for bone and dental tissue regeneration has been investigated. They can be made to resemble the properties of the extracellular matrix, which will promote the development of tooth or bone cells [127].

Research on sol–gel biomaterials is always changing, and there are many exciting potential uses in medicine and health. They are especially intriguing for the difficulties and requirements in the biomedical industry because of their capacity to be customized for certain uses [128].

Some examples of sol–gel biomaterials that differ in advantages and disadvantages depending on the end use include:

- One of the most popular sol–gel biomaterials is silica-based sol–gel bio-glass [129]. It is utilized in coatings for dental and orthopedic implants and has strong biocompatibility.
- Antibacterial coatings and dental prostheses are two uses for sol–gel titanium dioxide [130].
- The sol–gel process can be used to create hydroxyapatite, a key element of the bone matrix that is used in bone regeneration [131].
- Hydrogels made using the sol–gel method might act as scaffolds for tissue engineering or utilized as drug delivery systems [132].

The particular requirements of the application will determine how these sol–gel biomaterials compare. The requirement for biocompatibility, mechanical strength, bioactivity, or other unique qualities necessary for a certain biomedical application may influence the choice of biomaterial.

## 4. Properties of Sol–Gel Materials

### *4.1. Bioactive Materials*

The Kokubo test, also known as the "Kokubo Bioactivity Test" [133,134], is a methodology used to assess the bioactivity of organic and inorganic materials made by the sol–gel process. Examples of these materials are ceramic biomaterials, which are meant to be utilized in the human body, specifically for applications involving bone replacement. The term "bioactivity" describes a substance's capacity to elicit a certain biological reaction when it comes into touch with bodily fluids [135].

The purpose of the test is to assess hydroxyapatite production on the test material's surface, a mineral that makes up bone. The presence of hydroxyapatite is indicative of the substance's bioactivity and capacity to favorably interact with bone tissue.

The Kokubo test process can vary, but in general, it involves immersing the material sample in a solution similar to body fluids (SBFs) for a specified period of time [136,137]. This solution is often prepared with a composition similar to the extracellular fluid present in human tissues.

After immersion, the sample is analyzed for the formation of hydroxyapatite on its surface using the same characterization techniques, such as infrared spectroscopy, X-ray diffraction, or scanning electron microscopy (Figure 7).

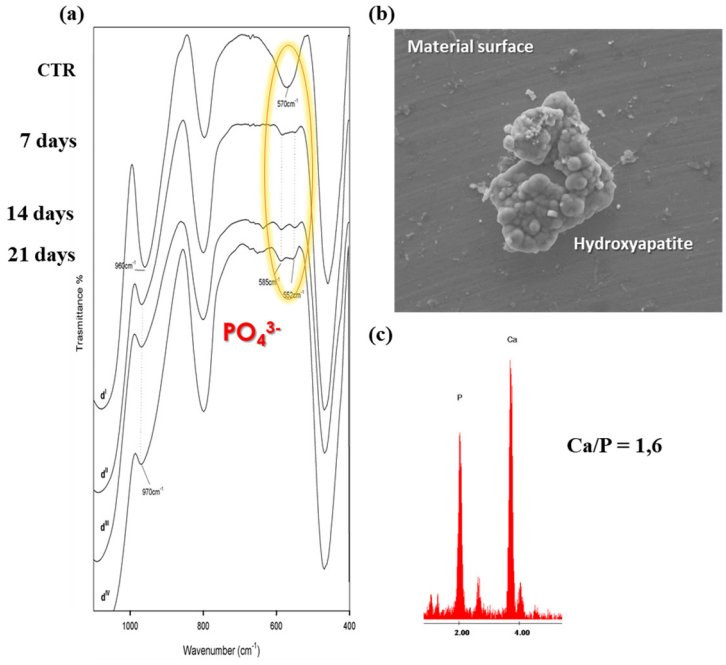


**Figure 7.** FTIR spectra of $SiO_2$ + caffeic acid x%wt material [10], after 7, 14 and 21 days soaking in SBF (**a**), SEM micrograph of the formation of hydroxyapatite on the surface of a sol–gel material after 21 days immersed in SBF (**b**) and EDX analysis carried out on a hydroxyapatite globule formed after 21 days (**c**).

The primary goal of the Kokubo test is to assess the material's capacity to form a bioactive surface that encourages mineralization, cell adhesion, and development, hence making it easier for the material to integrate with the surrounding bone tissue. For biomaterials to be effective and have long-term clinical success in orthopedic and bone replacement applications, bioactivity is an essential feature.

### *4.2. Antioxidant Activity*

Antioxidant-active sol–gel material design is becoming more and more popular, particularly in the biomedical industry [138–140]. In a variety of contexts, including biomedicine and tissue engineering, the antioxidant activity of these materials can be used to shield biological tissues from oxidative damage, lowering inflammation and accelerating recovery.

Because of this, designing materials with inherent antioxidant qualities or those that can create an environment in which antioxidants may be released or integrated is a common step in investigations into the antioxidant activity of sol–gel materials. It is possible to build organic–inorganic hybrids with the direct incorporation of antioxidant molecules, including vitamins, polyphenols, or antioxidant enzymes obtained from plant extracts (for example, chlorogenic acid, quercetin, caffeic acid, etc.) [141,142].

The evaluation of the antioxidant activity of these materials can be conducted through various methods such as the DPPH$^{\bullet}$ (2,2-diphenyl-1-picrylhydrazyl) and/or ABTS$^{\bullet+}$ (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonate)) test [143,144]. Both are colorimetric tests based on measuring a sample's ability to neutralize free radicals, thus providing information on antioxidant efficacy.

### *4.3. Antibacterial Activities*

Antibacterial sol–gel materials are drawing more and more attention from researchers, particularly in the biomedical setting where preventing bacterial infections is crucial. One of the many benefits of using the sol–gel process to provide materials with antibacterial qualities is the ability to create surfaces or devices that inhibit the development of bacteria [145,146].

In fact, antibacterial agents may be added straight into the material matrix during the sol–gel process, including substances like organic molecules, such as herbal medicines or metal ions (like silver, copper, and zinc) [147–149]. Antibacterial sol–gel materials are useful for coatings, implants, prostheses, and medical devices that need to be resistant to bacterial attack in order to avoid infection and the body rejecting them. They may be engineered to release antibacterial chemicals in a controlled manner over time [150,151].

In vitro studies employing certain bacteria (Gram$^{-}$ and Gram$^{+}$) are frequently used to assess the antibacterial activity of sol–gel materials in order to determine their capacity to inhibit bacterial development (Figure 8).


**Figure 8.** Inhibition halo of different bacterial strains (Gram$^{-}$ and Gram$^{+}$) inoculated in the presence of sol–gel hybrid materials: $SiO_2$ + caffeic acid x%wt [10].

### *4.4. Biocompatibility*

Sol–gel materials' biocompatibility is contingent upon multiple elements, such as the material's surface, structure, and chemical makeup, as well as the application context. Sol–gel materials are renowned for their adaptability, and their composition and properties can be changed to make them biocompatible [152,153].

Certain sol–gel materials, such as titanium dioxide ($TiO_2$) and silicon dioxide ($SiO_2$), have been studied and applied extensively in the biomedical field and are regarded as biocompatible [154]. These substances are frequently employed in the creation of biocompatible coatings for use on orthopedic prostheses, tissue engineering tools, biosensors, and controlled drug delivery systems, among other medical devices.

In order to better understand the interactions between the materials and biological tissues, studies on the biocompatibility of sol–gel materials are being conducted. These studies involve both in vitro and in vivo evaluations. Furthermore, novel strategies are constantly being developed to increase the biocompatibility of sol–gel materials. Two such strategies include surface functionalization with biomolecules and hybrid material design, which combines the advantageous aspects of several materials.

To assess the safety and effectiveness of sol–gel materials in biological applications, biocompatibility testing is essential. To assess how well sol–gel materials interact with biological tissues, a variety of in vitro (cytotoxicity, cell adhesion, release tests, etc.) and in vivo (inflammation and immune response testing) studies may be used [155–158]. It is significant to remember that the requirements for biomedical regulations and particular applications may change the nature of biocompatibility testing.

International standards and guidelines, such as those established by the International Organization for Standardization (ISO) and the Food and Drug Administration (FDA) in the United States, provide guidance for evaluating the biocompatibility of medical materials, including sol–gel materials.

## 5. Conclusions

In conclusion, biomaterials constitute an essential area of study and application in the fields of medical science, biomedical engineering, and materials science. The discipline's ongoing progress has resulted in the creation of cutting-edge materials with safe and efficient interactions with the human body.

They may be made to serve as prostheses, implants, scaffolds for tissue engineering, medication delivery systems, and much more to fulfill specialized functions inside the body.

The sol–gel approach has shown to be very useful in the field of biomaterials, as it facilitates the development of structures that exhibit biological compatibility and specific interaction capabilities with target substances. Antibacterial agents, biocompatible surfaces, and scaffolds for tissue engineering can all be included in the design of biomaterials made using sol–gel technology.

The development of sol–gel technology is still ongoing, with efforts concentrated on finding novel materials and comprehending the mechanics behind sol–gel processes.

Even with significant advancements, problems still exist, including the need to enhance biocompatibility even more, lower inflammatory responses, and deal with problems pertaining to the interface between the biomaterial and the surrounding tissue. For these reasons, new avenues for the development and manufacturing of innovative materials are expected to be opened up by the integration of cutting-edge techniques like 3D printing and nanotechnology.

Ultimately, the sol–gel method continues to be a vital tool for the synthesis of novel materials, influencing the direction of materials science and its useful applications across a range of industries. Its ongoing development presents bright possibilities for the future, encouraging scholarly inquiry and technological advancement.

**Funding:** This research was funded by European Union's Euratom Research and Training Programme (EURATOM) Horizon Europe, grant number 101061694.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data are contained within the article.

**Conflicts of Interest:** The author declares no conflict of interest.

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