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Functionalized nanoporous architectures derived from sol–gel processes for advanced biomedical applications

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The sol–gel method is a highly versatile and precise technique, making it a powerful tool for the synthesis and functionalization of nanoporous materials that play a critical role in advancing biomedical applications. Nanoporous structures, due to their unique pore architectures and high surface areas, offer significant advantages in drug delivery systems, tissue engineering, biosensing, and diagnostic technologies. These materials can efficiently encapsulate and release bioactive compounds, such as proteins, nucleic acids, and chemotherapeutic agents, making them ideal candidates for targeted therapies. The sol–gel process enables the tailored design of nanoporous materials with adjustable pore sizes, surface chemistry, and electrostatic properties, enhancing their compatibility with biological systems. Functionalization techniques, including PEGylation and surface modification with targeting ligands or bioactive molecules, further enhance their therapeutic and diagnostic potential by allowing precise targeting, reducing immune responses, and prolonging circulation times. Nanoporous materials also hold great promise in tissue engineering, where they can serve as scaffolds that mimic the extracellular matrix, supporting cell adhesion, differentiation, and tissue regeneration. Additionally, their large surface areas facilitate biomolecule immobilization, enabling the development of sensitive biosensors and offering advancements in disease detection. This paper provides a comprehensive review of the sol–gel method for synthesizing and functionalizing nanoporous structures, underscoring their significant biomedical applications. It also delves into their promising future potential in revolutionizing drug delivery, advancing tissue engineering, and enhancing diagnostic systems.

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1. Introduction

The sol–gel method, renowned for its versatility and precision, has become a transformative technique in the synthesis and functionalization of nanoporous structures, unlocking new possibilities in advanced biomedical applications poised to revolutionize healthcare technologies.[1] Nanoporous materials are essential to modern biomedical research due to their unique structural characteristics, which include nanometer-scale pores ranging from 1 to 100 nm.[2] These materials are invaluable in a range of biomedical applications, offering adjustable features, flexible functionalities, and large surface areas that make them ideal for drug delivery systems, tissue engineering, biosensing technologies, and diagnostic advancements.[3,4] The distinct pore architecture of nanoporous materials allows for an extensive surface area distribution within a single-volume unit, which significantly enhances their ability to retain therapeutic agents, such as proteins, nucleic acids, and imaging agents. The remarkable surface area-to-volume ratio of mesoporous silica nanoparticles, which exceeds 1000 $m^2\ g^{-1}$, facilitates their use as bioactive compound reservoirs, enabling controlled release and sustained therapeutic efficacy.[5,6]

Furthermore, nanoporous materials gain additional functionality through their ability to alter pore dimensionality, electrostatic properties, and surface chemistry, which supports the binding of a wide range of biological molecules.[7] This versatility is particularly beneficial in the development of drug delivery systems, which can be tailored for disease-targeting applications by incorporating surface-bound peptides or antibodies, thus enhancing diagnostic capabilities.[8] The combination of silica and titanium dioxide with carbon-based nanomaterials has led to the creation of three types of nanoporous materials with low cytotoxic potential and strong biological activity. In particular, the PEGylation technique, which involves the addition of polyethylene glycol chains, has been extensively studied for its ability to reduce immune response and prolong the circulation time of nanoparticles in the bloodstream.[9,10] The adjustable mechanical properties of

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nanoporous scaffolds further make them suitable for tissue engineering, where they can mimic the mechanical properties of native tissues, thus enabling effective regeneration of bone, cartilage, and vascular structures.[11]

The rising importance of nanoporous materials in targeted biomedical applications, especially in drug delivery, is evident in their ability to encapsulate both hydrophilic and hydrophobic therapeutic agents.[12] Mesoporous silica nanoparticles have attracted significant attention for their capacity to deliver a broad range of chemotherapeutic drugs, including doxorubicin, with improved pharmacokinetics. Research has demonstrated the successful use of folic acid-modified MSNs to target cancer cells, leveraging their elevated folate receptor expression levels to enhance therapeutic efficacy. In tissue engineering, nanoporous materials serve as structural scaffolds that mimic the extracellular matrix, facilitating cell adhesion, replication, and differentiation processes.[13,14] Hydroxyapatite-based nanoporous scaffolds, for example, have shown promising results in bone tissue engineering, supporting osteoconductivity and bone cell integration, particularly when combined with biodegradable polymers and growth factors to enhance reparative processes.[15]

Beyond drug delivery and tissue engineering, nanoporous materials hold great promise in diagnostic applications. Their high surface area and customizable surface chemistry make them ideal candidates for biomolecule immobilization, enabling sensitive detection of biomarkers.[16] Nanoporous gold, for instance, has been employed in electrochemical biosensors for the early detection of cancer biomarkers, significantly improving diagnostic sensitivity.[17] Moreover, the incorporation of nanoporous materials into point-of-care devices has facilitated rapid diagnosis of diseases such as cancer, diabetes, and infectious diseases, offering a valuable tool for precision medicine.[18]

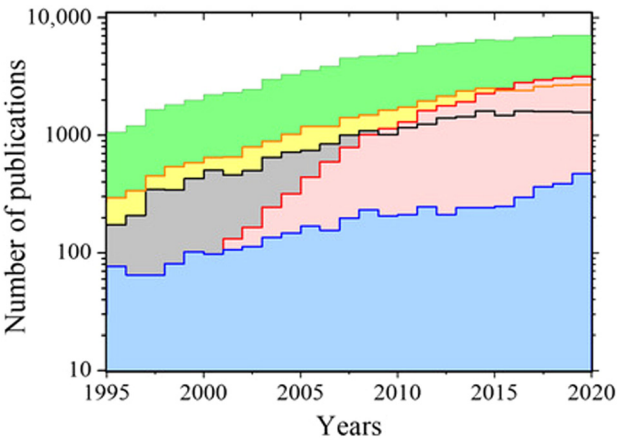
The functionalization of nanoporous materials plays a pivotal role in their biomedical applications, as surface modifications can significantly enhance their biological properties and performance. Through functionalization, nanoparticles can be tailored to bind with specific biomolecules, improving their interaction with biological systems.[19] Techniques such as the integration of amine, thiol, or carboxyl groups onto nanoparticle surfaces enable the binding of proteins, peptides, or antibodies, which is crucial for gene delivery, sustained drug release, and targeted therapies.[20] Additionally, surface charge modifications influence nanoparticle interactions with cells, affecting their internalization, retention, and elimination in the body. The use of PEGylation, for example, has been shown to reduce the immune detection of nanoparticles, extending their circulation time and improving therapeutic outcomes.[21,22]

Surface functionalization also facilitates the selective targeting of nanoparticles to specific tissues or cells, enabling precision in drug delivery and enhancing therapeutic efficacy. Modifications with targeting ligands, such as antibodies, peptides, and aptamers, allow nanoparticles to selectively bind to antigens expressed on the surfaces of cancer cells, improving drug delivery to the target site while minimizing toxicity.[23,24] Furthermore, the incorporation of peptide sequences, such as RGD (arginine–glycine–aspartic acid), enhances nanoparticle adhesion to tissues, making them valuable tools in tissue engineering and regenerative medicine.[25,26]

With all these advancements in the synthesis, functionalization, and application of nanoporous materials, this paper aims to provide a comprehensive review of the sol–gel method for the synthesis and functionalization of nanoporous structures, exploring their potential and future directions for use in advanced biomedical applications.

2. The sol–gel method: a primer

Sol–gel methods enable affordable economic production of controlled nanoporous materials that belong to the advanced biomedical materials category. The dissolution transition from sol to gel occurs because hydrolysis chemical reactions combine with condensation reactions inside precursor-based colloidal systems. The production method leads scientific researchers to create ceramics and metal oxides and hybrid nanostructures through combining organic and inorganic elements to obtain functional materials with tunable pore features and increased surface areas.[27,28] Fig. 1 shows the number of publications in the last 25 years including the keywords "sol–gel", "sol–gel" + "oxide",



Years \ Topic	"Sol Gel"	+ "Oxide"	+ "Coating"	+ "Nano"	+ "Perovskite"
2020	6740	2522	1380	3201	429
2019	7075	2692	1571	3166	469
2018	7083	2664	1597	3061	387
2017	6832	2605	1592	2957	364
2016	6765	2413	1606	2809	295
2015	6404	2403	1479	2500	248
2014	6521	2515	1605	2271	243
2013	6126	2387	1442	1932	243
2012	6016	2156	1403	1784	212
2011	5757	1960	1248	1630	247
2010	5021	1735	1157	1296	212

Fig. 1 Top: Number of publications in the last 25 years including the keywords "sol–gel" (green), "sol–gel" + "oxide" (yellow), "sol–gel" + "coating" (grey), "sol–gel" + "nano" (red) and "sol–gel" + "perovskite" (blue). Bottom: Table of the number of publications in the with the number of publications in 2020–2010 period. All the data was extracted from Web of science.[29]

"sol–gel" + "coating", "sol–gel" + "nano", and "sol–gel" + "perovskite".[29]

Several specific features enhance biomedical nanomaterials when scientists utilize the sol–gel method for their implementation. Researchers can manipulate material compositions and perform molecular-level structural arrangements through sol–gel method applications. The equipment fabrication process becomes more effective because scientists adjust precursor content or heat level, together with solvent property adjustments, to boost the delivery and development of pharmaceutical solutions and tissue engineering applications.[30] The sol–gel method processing delivers preservation of bioactive molecules and proteins by conducting operations at low temperatures, which prevent destructive heat effects. Synthetic biomedical materials under ideal conditions require this method because they depend heavily on biocompatibility requirements.[31] Moreover, the sol–gel system operates at peak efficiency for biomedical applications because it accepts diverse synthesis methods, which produce either thin films or coatings as well as powders because of its adjustable and versatile nature. The production process shows high scalability because it makes it possible to easily transform research-level operations into industrial-scale manufacturing.[32]

2.1 Synthesis routes and functionalization strategies

The main drug delivery system utilizes sol–gel-derived mesoporous silica nanoparticles (MSNs) because they enable dual drug encapsulation along with adjustable pore structures and large surface areas. Researchers use the sol–gel method to add precursor substances of silica and titanium alkoxides together with organic compounds for controlling drug release from the system. The chemotherapy capacities of MSN nanoparticles increase through a process of folic acid and antibody functionalization that enables receptor-targeted integration with cancer cells while enhancing diagnostic accuracy.[33,34]

Patient-specific porous bone regeneration scaffolds require hydroxyapatite (HA) materials as they are developed from sol–gel processes. The scaffolds serve as structural equivalents to the extracellular matrix by creating optimal cell connection spaces for typical cell development. Scientific management of pore dimensions using the sol–gel method becomes essential because it enables tissue-level exchange of nutrients and waste during developmental processes.[35] Selectivity and bioactivity properties of sol–gel materials become improved by adding functionalization methods. The addition of peptides or proteins along with growth factors through surface modification by grafting enables enhanced biological system integration. Bioactive glass nanoparticles formed through the sol–gel process gain osteoblast differentiation enhancement through peptide surface modification.[36]

2.2 Applications in drug delivery, tissue engineering, and diagnostics

The procedure for developing a controlled drug delivery system relies solely on the sol–gel method. Encapsulation of drugs is done within the frameworks of nanoporous materials, which allow for time-controlled release of medication by the physician. This method is applied for the treatment of cancer because the development of nanoparticles allows for delivering the drugs exactly at the tumor site, which minimizes the negative effects of therapy.[37] The application of biomaterials obtained by the sol–gel method into tissue engineering integrates scaffold structures for constructing tissues. The integration of natural tissues is remarkably enhanced when the hydroxyapatite and calcium phosphate materials are formed through sol–gel processes. The inclusion of peptides or proteins into sol–gel materials is done to ensure increased cell adhesion and cell proliferation.[38]

Performing biosensing and other forms of imaging diagnosis heavily depends on materials based on sol–gel technologies for carrying out the basic processes. The active nanoporous materials used in the diagnosis of diseases are turned into diagnostic devices after they are modified by specific markers to identify the initial stage of such diseases as cancer or infections.[37,38] Section 6 explains in detail the biomedical applications of nanoporous materials synthesized by sol–gel method. Table 1 shows comprehensive information on nanocarriers for drug administration made from sol–gel materials, especially mesoporous silica and hybrid organic–inorganic systems.

3. Mechanisms of the sol–gel process: a molecular insight

3.1 Overview of sol–gel chemistry

The sol–gel process makes it possible to produce metal oxides, silicates, and hybrid materials using a single chemical method. These materials feature controlled porosity, large surface areas, and adjustable chemical properties. The principal feature of this process is the conversion of liquid precursor solutions, or "sols", into solid gel frameworks *via* hydrolysis and condensation reactions. The result is a material with a highly ordered structure, which makes the sol–gel process especially useful in the production of biomedical tools such as drug delivery systems, tissue engineering scaffolds, and sophisticated diagnostic devices.[49]

As sol–gel process is a wet-chemical technique widely used for synthesizing inorganic and hybrid nanomaterials, especially mesoporous silica nanoparticles (MSNPs). The transformation from a colloidal solution ("sol") to a solid network ("gel") is governed by two key reactions: hydrolysis and condensation. Typically, metal alkoxides such as tetraethyl orthosilicate (TEOS) or tetramethyl orthosilicate (TMOS) are used as silica precursors. Under acidic or basic conditions, hydrolysis of the alkoxide groups leads to the formation of silanol groups (Si–OH). These reactive silanols undergo polycondensation to form siloxane bonds (Si–O–Si), generating a growing 3D silica network. Gelation occurs as the colloidal system transitions to a rigid interconnected matrix. Reaction kinetics are influenced by pH, temperature, solvent polarity, and catalyst type, all of which determine the extent of polymerization and structural ordering. Controlling these parameters allows for fine-tuning of nanoparticle morphology, surface functionality, and porosity.[49]

Table 1 Nanocarriers for drug administration made from sol–gel materials

No.	Summary	Key findings	Interventions	Ref.
1	Mesoporous silica nanoparticles (MSNs) have unique properties making them promising carriers for cancer chemotherapy.	MSNs are biocompatible and ideal for targeted drug delivery in cancer. – Noted for customizable surfaces and physicochemical properties.	Not mentioned (no quantitative data reported in abstract).	39
2	MSNs improve solubility, loading, and release of anti-tubercular drugs with favorable cytotoxicity and patient compliance.	Enhanced drug solubility (PA-824 by 20%). – Entrapment efficiency depended on solvent (methanol highest). – Higher loading with 100 nm *vs.* 40 nm MSNs. – Biphasic release profile (60% in 4 h, 95% in 24 h).	Particle size impacted release rate. – Methanol increased loading. – Amorphous drug states prevented recrystallization.	40
3	MSNs are highlighted for their stability, functionalizability, and capacity for targeted delivery.	MSNs suitable for cancer treatment due to low toxicity. – Recent synthetic advances allow surface engineering for better biocompatibility.	Not mentioned (review article; no direct intervention outcomes).	41
4	Structural features of MSNs enable them to serve as multifunctional drug carriers.	Suitable for imaging, multicomponent therapy, and on-demand release. – Customizable surface and pore structure.	Not mentioned.	42
5	Sol–gel MSNs used for anticancer, gene, and plasmonic therapies; PEG/FA coating reduces toxicity.	Sol–gel synthesis supports tunability. – Cornell dots safe for imaging. – AuroLase and plasmonic therapies effective with low toxicity.	PA-824 solubility ↑ 20%. – PEG/FA surface coatings reduced systemic toxicity.	43
6	MSNs are versatile due to surface tunability and ability to respond to external stimuli.	Gatekeeper systems enable targeted, controlled drug release. – Combinations with other carriers increase efficacy.	Not mentioned.	44
7	MSNs possess large surface area/pore volume for drug loading; biocompatibility varies by surface modification.	Useful in combination therapy for cancer. – Coating improves therapeutic performance. – Biological safety still under investigation.	Not mentioned.	45
8	MSNs' adjustable pore size and solubility enhancement make them strong candidates for sustained delivery.	Functionalization improved drug loading (*e.g.*, 10% ↑ in 5-FU loading). – Polymer coatings enabled sustained release.	Hydrophobic groups restricted water penetration. – Bioadhesive polymers prolonged drug release.	46
9	Porous silica nanoparticles were doped with Ag, Cu and Co	Combination of all these nanomaterials led to a synergistic antibacterial activity	Synergistic antibacterial activity of these nanohybrids can lead to development of novel antibiotics, especially against the antibacterial resistance.	47
10	Porous silica nanoparticles were doped with Ag, Cu and Co and combine them to prepare bi and tri metallic silica nanohybrids	Combination of all these nanomaterials led to a synergistic antifungal activity	Synergistic antifungal activity of these nanohybrids can lead to development of novel antibiotics, especially for immunocompromised patients.	48

3.2 Hydrolysis and condensation reactions

The sol–gel process starts with the hydrolysis of metal alkoxide precursors. In this step, the water reacts with the metal alkoxide to break the alkoxy bonds and replace them with hydroxyl groups (–OH). For instance, a popular precursor for silica tetraethyl orthosilicate (TEOS) is hydrolyzed to silanol groups (Si–OH):

$$Si(OR)_4 + 4H_2O \rightarrow Si(OH)_4 + 4ROH$$

The following is condensation, in which the hydroxyl groups produced by hydrolysis couple to release water, or alcohol, forming metal–oxygen–metal (M–O–M) links. The crosslinking reaction forms a three-dimensional network that gradually constructs the gel network. For example, two silanol groups might react, forming water as a byproduct:

$$Si–OH + Si–OH \rightarrow Si–O–Si + H_2O$$

These reactions result in the generation of a high-surface-area nanoporous solid, which is vital for applications like drug delivery, where elevated surface areas may increase loading capacity.[49,50]

3.3 Metal oxides, silicates, and hybrid materials formation

Metal oxides: structural metal oxides, including silica (SiO_2), titania (TiO_2), and alumina (Al_2O_3), are commonly synthesized *via* sol–gel methods. The most common metal oxides are formed by hydrolysis and condensation reactions of metal alkoxides (for example, titanium isopropoxide or tetraethoxysilane (TEOS)). Many of these materials have significant advantages for biomedical applications, including their biocompatibility, high surface area, and the ability to incorporate other molecules (*e.g.*, drugs for drug delivery applications or those molecules needed for biosensors or coatings).[51,52]

Overall, silica-based materials have been widely investigated for biomedical applications due to their high porosity, stability, and ease of functionalization. Tailored sol–gel made silica network from the hydrolysis of TEOS, or other silica precursors, provides customizable pore sizes and surface chemistry. For instance, mesoporous silica nanoparticles (MSNs) have been extensively employed for controlled drug delivery, exploiting their large surface area to achieve high drug load capacity followed by release.[53]

Hybrid materials are a combination of organic and inorganic materials that provide unique properties that come from both the phases. By introducing such organic molecules or functional groups during the gelation phase, these materials

are readily synthesized in a sol–gel network. Such as the introduction of organic polymers or bioactive molecules into the precursor sol, providing a hybrid network with a combination of properties such as improved mechanical properties, biocompatibility, and responsiveness to stimuli. In applications like drug delivery and tissue engineering, where desirable bioactive properties are critical for success, such materials are particularly valuable.[54]

3.4 Significance of the sol–gel method

The elucidation of the sol–gel method dates back a few decades, and despite this fact, researchers from every corner of the earth keep coming up to date with sol–gel technology and scientific achievements. Many researchers from different parts of the globe continue to flock to sol–gel technology and scientific developments even after the discovery of the sol–gel method was made several decades ago.[55] One of the types of bottom-up synthesis can be united with sol–gel and solvothermal methods. The application of sol–gel to modify the surface of substrates is marked to be very efficient and popular.[56] The first and almost self-explanatory advantage of these methods is the fact that they produce large amounts of surfaces with better and uniform finishes. Many researchers regard sol–gel technology as an effective method of creating new nanomaterials, and that the technology has certain features that set it apart from other technologies.[57] It is simple, it is dense and has high uniformity, and it also works at low temperatures. One of its primary advantages is that it can form nanostructures with organic materials because it is compatible obtaining with polymers.[55,56] The end product of this technique is usually highly pure materials. The implementation of this technique enables better control of all the steps in the synthesis of solids and getting the final solid products of the desired characteristics.[55,56] The multi-component complexes are quite easy to synthesize the molecular solutions of the precursors are entirely combined homogeneous blending of oxides. In contrast to other current technologies,[55] it is more commercial and has broad usage in the present era, nevertheless, all the mentioned techniques can synthesize tremendous quantities of nanomaterials. Due to such features, this method can deliver high-quality and reproducible nanostructures suitable for commercial enrollment in large amounts.[57,58] It allows for obtaining functional materials for photocatalysis,[59] ferroelectric materials,[60] and nonlinear optical nanomaterials, including superconductors.[61]

Sol–gel technique for the preparation of metal nanoparticle-doped inorganic and organic hybrid films comprises organically modified silica.[55] Sol–gel processes are widely used for producing ceramic materials, including metal oxides, carbide compounds, and nitrides. In numerous applications, ceramics are made with the sol–gel process as a preform material or as a layer over which thin layers of metal oxides are coated or deposited. Some of the applications that incorporated the materials developed by the sol–gel technique include optical, electrical, energy, surface science, biosensors, medical, and separation technology.[55–58]

The sol–gel technology has the following advantages over other processing technologies: design of processes with large area applicability, high purity, the highest degree of chemical composition control, and low temperature reactions.[55,56] Being one of the most well-known methods for a rather broad range of materials, it can be applied to such objects as thin layers, ultra-fine powders, monolithic glasses, ceramics, and inorganic films.[61] The procedure is still in practice to this date and can be seen being used in the fabrication of 1D nanomaterials. It is also used to perform simple chemical doping, which can be accomplished at room temperature. This technique comes with many benefits that make it rather appealing.[55–61]

The described examples show that the presented sol–gel approaches make it very easy to tune the final morphological characteristics of nanoparticles. owing to the method, it can also generate two or more kinds of nanoparticles at the same time, thereby allowing the formation of an alloy material by adding a specific ratio of two or more metal (or metal oxide) precursors.[47,48] Other one-step methods that can also supply the alloy materials are the electrochemical and plasma. Nevertheless, the distinguishing feature of the sol–gel technique from these other methods is that it is more commercially available. In addition, highly endogenous composites such as the ceramic coatings that are created *via* the sol–gel method, it is possible to prepare them with a purity level of 99%.[55] This approach enables the manufacturing of metal and ceramic nanostructures, and the process temperature is lower than in the other methods; it ranges from 70–320 °C.

It is at low temperatures favor the development of a uniform nanostructure of the sol–gel product, narrow particle size distribution, and high product purity. This method is utilized broadly for the synthesis of metal nano-oxides.[62–65] As mentioned earlier, the sol–gel process entails a transformation of sol to gel employing several methods, which commonly entail moderate drying to expel the solvent. Indeed, one of the mentioned technologies' advantages is its ability to prevent cracks from appearing. In this case, it can interconnect the parts through the formation and solidification of the generated gel. Across the equivalent production of molded or cast products, filters, and membranes are included. The thickness of thin films, which can be prepared by the sol–gel process has a range of 50–500 nm.[66]

Thin films in sol–gel are useful in the chemical as well as the electrical industries. Other optical properties of the material are also changed by applying coatings produced with the sol–gel method. The sol–gel circumstance is usable to make composite or nanocomposite materials. The following is made possible through the nanoscale incorporation of secondary phases into the permanent porosity. Either generated or synthesized components, or some of the components, are taken through sintering processes to create densified portions. The nanoporous gels sinter faster and more efficiently due to their large specific surface area, and this hastens the rate of pressure or compression of the structure.[67,68]

However, it should be noted that in this case, the temperature is increased to develop the grain and to obtain a coarse-grained structure. Thus, sol–gel and solvothermal methods can be viewed as golden standards of nanoparticle synthesis due to

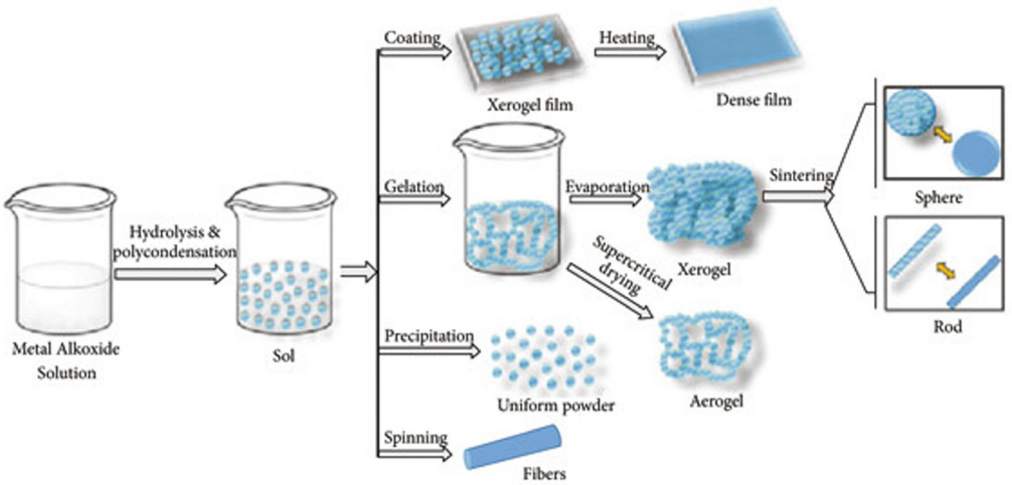


Fig. 2 An overview of the types of processes that can be done with the sol–gel method and the products of each process.[69]

their long-term success proven by numerous applications leveraging the methods' capacity to produce high-quality nanoparticles with enhanced surface features and adjustable compositions for further applications in various fields of nanotechnology and material science as the latter advances into the future.[69] Fig. 2 shows an overview of the types of processes that can be done with the sol–gel method and the products of each process.

4. Synthesis and tailoring nanopore structures

The characteristics of nanoporous materials from sol–gel synthesis strongly rely on precursor types, solvent selection, reaction time, pH, temperature, and catalysts or network modifiers. The gelation process is affected by various factors that produce significant effects on pore dimension and distribution together with morphology of the final material, particularly essential for biomedical applications involving drug delivery and tissue engineering.[55] Fig. 3 shows the fabrication strategies of nanoporous materials with different pore sizes.[70]

4.1 Factors influencing pore size, shape, and surface area

The pore characteristics of sol–gel-derived materials, such as pore size, shape, and surface area, are highly tunable and directly influenced by synthesis conditions and template selection. Surfactants like cetyltrimethylammonium bromide (CTAB) or block copolymers (*e.g.*, Pluronic F127) are often used as structure-directing agents. Under controlled evaporation and self-assembly, these surfactants guide the arrangement of silica around micellar templates, resulting in ordered mesoporous structures. Key parameters such as pH, precursor concentration, template type, reaction time, and temperature can significantly alter the size and distribution of the pores. For example, higher surfactant concentration or lower hydrolysis rates can yield smaller, more uniform pores. The use of swelling agents like triisopropylbenzene (TIPB) or pore expanders like 1,3,5-trimethylbenzene (TMB) can further

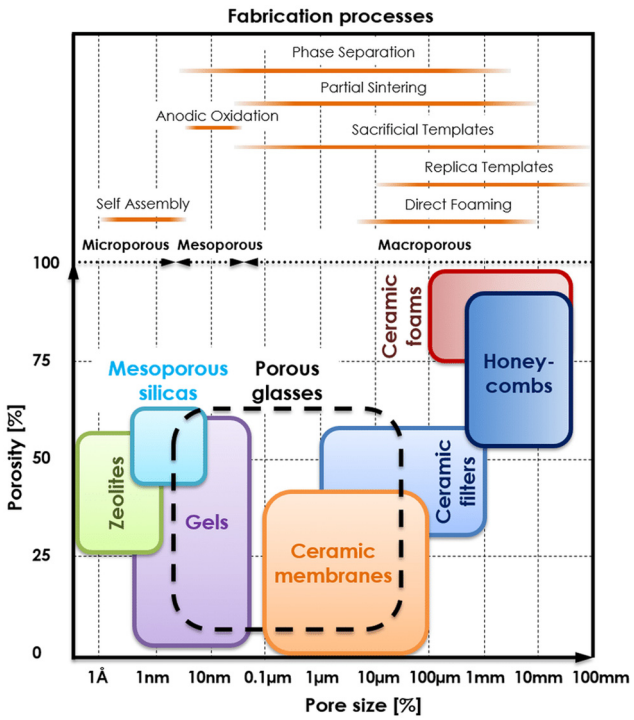


Fig. 3 Pore size and porosity of typical porous materials and fabrication processes.[70]

enlarge pore diameters. These tunable features are critical for optimizing drug loading, diffusion rates, and molecular interactions at the biointerface.[71,72]

4.2 Solvent type and its influence

When performing sol–gel procedures, the characteristics of sol formation together with gel structure depend on the solvent selection. The hydrolysis and condensation reactions occur when alcohols in use as solvents dissolve metal alkoxides. Alcohols serve as solvents to achieve reaction slowing down

while enhancing control of both pore development and the gel solidification process. The gelation speed increases as the dielectric constant rises in solvents or through hydrogen bonding capacity, which both determine material porosity and flow characteristics. The selection of solvents during solvothermal reactions defines how precursors dissolve and controls the growth of crystals, which determines the size and shape, along with the final crystal quality.[55–58]

4.2.1 Reaction time. Materials reach their optimum properties after a sol–gel or solvothermal process that advances for an adequate timeframe. The duration of the reaction usually produces superior network connectivity through polymerization reaction and creates more uniform pores within the network. Material porosity and mechanical strength will deteriorate when reactions exceed optimal times because of over-polymerization and undesirable side effects. The extended time duration in solvothermal reactions leads to improved crystal purity and quality, which are crucial elements for obtaining well-defined crystals for high-end applications.[55–59]

4.2.2 Agitation and stirring. Proper mixture through agitation makes all reactions happen at the same pace to obtain a homogeneous material. Proper mixing helps stop sedimentation to ensure consistent gel formation, together with improved gel structure. During solvothermal processes, stirring provides stability to the reaction because uniform agitation produces high-quality crystals, especially during nucleation and crystal growth. Defects will appear when stirring does not occur in a reaction system.[55]

4.2.3 pH control. The sol–gel method reacts to pH changes through the transformation of hydrolysis and condensation processes. A solution is acidic when hydrolysis occurs rapidly, while basic solutions lead to condensation initiation. The solution pH determines the formation process of the network structure along with the porosity outcome. Large pH changes result in reaction failure and result in unwanted crystallization processes. The reproducibility and quality of materials depend on precise pH control through solvothermal reactions because it alters both precursor solubility and crystal growth speed.[55–61]

4.2.4 Temperature. Both reaction speed and sol–gel product qualities are controlled by temperature. Heat levels determine how gel formation proceeds and influence material porosity, but too much heating creates risks of unsolicited structure changes. The final temperature level of solvothermal reactions enhances nuclei formation with crystallization, yet requires constant monitoring to prevent structural damage.[55]

4.2.5 The size and the shape of pores. During synthesis, the combination of solvent choice and pH value, and temperature controls both pore size distribution and material morphology. The heat ratio between water and alkoxide solution controls the size of pores while adding to network connectivity. The pore size distribution control comes from reaction time along with agitation, which enhances gelation and ensures homogeneous results. The gel network receives additional modifications from Network modifiers consisting of metal salts or organic compounds, which both boost network connectivity and improve stability. Biomedical applications determine suitable properties because these modifiers adjust thermal resistance levels and optical properties of the gel material.[55–57]

4.2.6 Catalysts and network modifiers. Gel texture and porosity end results depend on how catalysts affect the transformation between hydrolysis rates and condensation reactions. Hydrolysis speeds up through acid solutions, yet basic agents work best for condensation reactions. When network modifiers influence the condensation process, the material properties, together with the pore structure, undergo modifications. The optimized implementation of the system creates a network structure while also preventing the formation of mechanical instability defects.[55]

4.3 Common precursors and catalysts: TEOS and TMOS

The two most used silica precursors in sol–gel synthesis are tetraethyl orthosilicate (TEOS) and tetramethyl orthosilicate (TMOS). Both are alkoxysilanes that undergo hydrolysis and condensation to form a silica network. TEOS, due to its ethyl groups, hydrolyzes more slowly than TMOS and is generally preferred for forming denser silica networks with controlled porosity. TMOS, being more reactive due to its smaller methyl groups, tends to produce more uniform nanoparticles but requires careful handling because of its higher volatility and toxicity. In both cases, acidic or basic catalysts (*e.g.*, nitric acid, ammonium hydroxide) are added to modulate the reaction rate and network structure. The selection of precursor and catalyst combinations plays a crucial role in determining not only the physicochemical properties of the nanoparticles but also their suitability for biomedical applications, such as drug delivery or biosensing.[55–59]

4.4 Influence of synthesis conditions on biofunctionality

The biofunctionality of sol–gel-derived nanoparticles is strongly dependent on the conditions under which they are synthesized. Parameters such as pH, temperature, solvent composition, and aging time affect not only particle size and porosity but also the availability of surface functional groups for further modification. For instance, a more acidic environment tends to produce smoother particles with smaller sizes, which may enhance cellular uptake. Conversely, basic conditions often yield more porous structures suitable for high drug loading. Moreover, post-synthesis treatments like calcination, surfactant removal, or surface silanization can drastically affect biocompatibility and functionalization potential.[55–59] Functional groups such as $–NH_2$, –SH, –COOH, or PEG chains are often grafted to enhance hydrophilicity, reduce aggregation, or facilitate ligand attachment. These modifications directly influence biodistribution, circulation half-life, immune response, and targeting ability, making precise control over synthesis conditions critical for biomedical success.[55–59]

4.5 Structural features of sol–gel-derived nanoporous materials

Biomedical applications benefit from the unique properties of nanoporous materials produced through sol–gel methods that include their system of porosity, together with their network connectivity properties and their expansive surface area structure. Different synthesis variables affect these features substantially

because they include both precursor selection and solvent choice, as well as pH value and reaction time and temperature parameters. Advanced understanding of synthesis parameter behavior becomes essential for final design because researchers can thus produce materials tailored for drug delivery platforms and tissue engineering instruments, and diagnostic equipment. Fig. 4 shows the sketch of steps and influencing factors of the method-sol–gel.[67]

4.5.1 Porosity. The basic feature of nanoporous materials derived through sol–gel synthesis exists as porosity since it functions as a defining performance factor. The sol–gel process allows us to develop porous materials whose porosity ranges from microscopic to mesoscale and macroscale. The factors that influence sol–gel porosity development during synthesis include both water-to-alkoxide ratio and reaction-time parameters at specific temperatures. Higher ratios between water molecules and alkoxide groups accelerate both hydrolysis and condensation reactions to develop large, interconnected pores, which aid medical applications requiring controlled drug release mechanisms and high drug content mechanisms.[55–57]

The combination of overall pore volume measurement together with specific surface area measurement determines the maximum molecule storage capacity of the substance, which includes drugs and biomolecules. High porosity in medical applications creates advantages because it promotes cell docking and facilitates cell expansion and distinct cell development rates through these materials serving as tissue engineering scaffold platforms. Both material strength and porosity levels need an exact match because too much porosity could endanger the structure's stability.[55–59] Table 2 shows recent studies on the sol–gel derived nanoporous materials, how to control their porosity, their medical uses, and the ways they can be functionalized.

4.5.2 Surface area. The measured surface area of sol–gel-derived nanoporous materials stands as an essential structural element that determines their potential in biomedical practice. The surface area and scientists analyze material porosity through Brunauer–Emmett–Teller (BET) analysis. High surface area surfaces of the material facilitate better molecular interaction with biological molecules, thus enhancing biological efficacy. The combination of drug delivery systems and controlled release capabilities becomes feasible through improved therapeutic agent adsorption because of their enhanced nanoporous surface area capabilities. Tissue engineering processes receive enhanced benefits from surface area expansion because cells interact better for proliferation along with differentiation.[55]

Surface area manipulation during the sol–gel process depends on solution precursor variations and hydrolysis conditions and condensation rate adjustments. Manufacturers adjust specific parameters to create materials with customized biological surface characteristics for their products.[55–61]

4.5.3 Network connectivity. The intersectoral pore connections of the material component form the basis of network connectivity. The extensive interconnection of pores creates significant effects on both material strength as well as the passage of molecules through the structure. Sol–gel-derived materials achieve their network connectivity through how much condensation reactions that occur during gelation. A high network connectivity enables better mechanical stability as well as equal distribution of functional groups or bioactive molecules across the material substance, essential for drug delivery systems and tissue scaffolds.[55,68,69]

The nanoporous network achieves its density and rigidity through a condensation process that is precisely controlled by reaction time, pH, and temperature. As condensation increases, the structural characteristics of the network change; it creates denser arrangements with restricted porosity. Conversely, when condensation decreases, larger porous networks form that are more flexible but have weaker mechanical properties. The exact

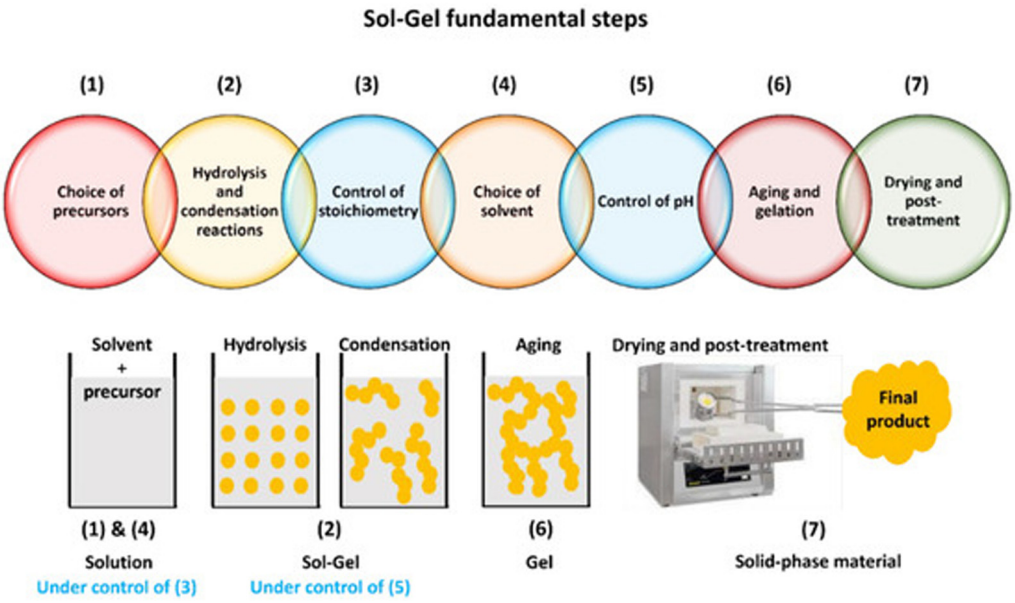


Fig. 4 Sketch of sol–gel steps.[67]

Table 2 Recent studies on the sol–gel derived nanoporous materials, how to control their porosity and their medical uses

No.	Controllability of the porosity	Main findings	Applications	Ref.
1	Sol–gel parameters allow control over pore size/morphology of bioactive glass micro/nanospheres for tissue engineering.	PBGSs synthesized *via* sol–gel and melt-quenching methods show tunable pore structures; applicable in bone regeneration, cancer therapy, and wound healing.	Bone regeneration, wound healing, therapeutic delivery, bioimaging, cancer therapy	73
2	Scaffold pore size affects tissue-specific regeneration; optimal ranges differ across tissue types.	Identifies pore size ranges suitable for bone, cardiac, lung, and skin tissues; emphasizes role in nutrient transport and cellular behavior.	Optimal pore sizes per tissue type; effects on cellular migration, attachment, and tissue formation	74
3	Ice templating offers precise control over pore architecture in polymer-based biomaterials.	Ice templating produces tunable porous structures for biomedical scaffolds; improves biological response and drug release dynamics.	Not explicitly measured (review)	75
4	Quaternary bioglass synthesized *via* sol–gel shows high surface area and bioactivity for bone tissue repair.	Amorphous bioglass stable up to 800 °C; forms apatite in SBF; surface area and crystallinity vary with calcination.	Crystallinity (XRD), Surface area (BET), Bioactivity (hydroxyapatite formation)	76
5	Combines robocasting and laser micromachining to fabricate 3D scaffolds from sol–gel-derived composites.	Hybrid scaffolds (TEOS/gelatin/β-TCP) demonstrated mechanical strength, ion release, and osteoblast compatibility.	Compressive strength (2–3 MPa), biodegradation (ion release), cell viability	77
6	Overview of fabrication techniques and ideal scaffold features for tissue engineering.	Reviews methods to optimize mechanical strength, bioactivity, and degradability in nanostructured scaffolds.	Not specified (review)	78
7	Compares scaffolds made from sol–gel and melt-derived glass powders using robocasting.	Sol–gel scaffolds showed lower porosity (46.7%) but suitable compressive strength, mimicking cancellous bone.	Porosity, sintering behavior, compressive strength, bioactivity, biocompatibility	79
8	Evaluates how templating in sol–gel synthesis affects pore structure and bioactivity of bioglass scaffolds.	Templating improves surface area and interconnectivity, enhancing bone bioactivity and compatibility.	Surface area, pore morphology, bioactivity (qualitative)	80

adjustment of these specific conditions remains essential for manufacturing materials that strike the right middle ground between porosity and surface area and mechanical resistance.[55–61]

4.5.4 Influence of sol–gel conditions on final structure and properties. During sol–gel synthesis, many different process variables shape how the end material will look in terms of structure and properties. Constraints within the synthesis, such as solvent choice and water-to-alkoxide proportions, shape both the dimensions, of pores and their network arrangement. During gelation, the rate of condensation, together with the resulting network structure, depends heavily on the gelation temperature. Temperature influences gelation speed during synthesis, which creates either tight pores with small dimensions or open structures with larger pore dimensions.[55]

Regulation of reaction time determines network polymerization extent, which affects material strength; however, long reactions may degrade pore structure and create additional crystal phases. The control of pH chemical conditions decides gel structure formation through influencing condensation mechanisms that shape material physical properties.[55–60]

5. Functionalization of nanoporous materials: enhancing bioactivity

5.1. Principles of functionalization: chemical bonding, grafting, and surface modification techniques

Functionalizing nanoporous materials is crucial because it enhances their bioactivity and allows for tailored applications in biomedical fields. Through functionalization, the surface properties of these materials can be modified by adding chemical groups and bioactive molecules. This modification improves the attachment to biological systems, facilitating various functions such as drug delivery, tissue healing, and biomolecular detection. The main methods for functionalization include chemical bonding, grafting, surface modification, and the incorporation of bioactive molecules, ligands, and therapeutic agents.[81–83]

5.1.1 Chemical bonding. The binding of chemicals plays a crucial role in providing functional properties to nanoporous substrates. A covalent bond forms on the material's surface because of interactions between bioactive molecules and functional groups. The stability of nanoporous materials is enhanced through the bonding of surface-based functional groups to the interface. This bonding is achieved through silanization processes and other methods that create strong Si–O covalent bonds by enabling alkoxysilanes to connect with the surface hydroxyl groups of silica-based materials.[62–64] This surface transformation method enables the material surface to make various functional groups, like amines, thiols, and carboxylates, available for biological molecule connection.

Metal–ion coordination bonds serve as starting components for surface functionalization efforts of titanium and zirconia metal oxides. The attachment of biomolecules, including proteins and peptides, becomes possible through these interactions for developing therapeutic treatments and diagnostic tools. Fig. 5 shows the SEM characterization of nanoporous ZnO nanoparticles.[67]

5.1.2 Grafting. Surface modification of nanoporous materials works best through the implementation of grafting procedures. Surface modification of materials with biological polymers or biomolecules occurs through covalent and non-covalent bond forms. Nanoporous system functionalization occurs through

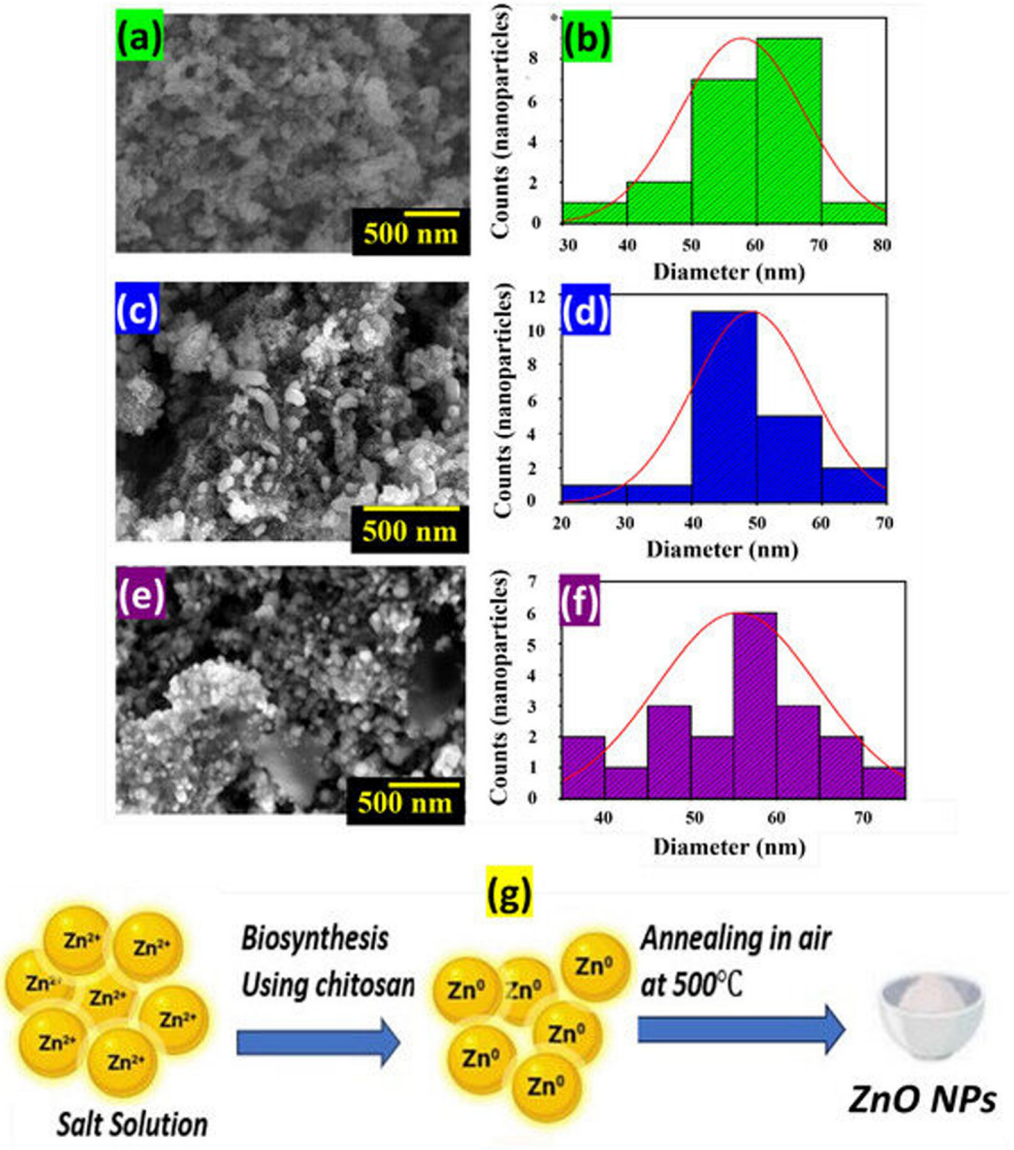


Fig. 5 SEM characterization of ZnO nanoparticles using different chitosan sources: (a) and (b) crab shells, (c) and (d) shrimp shells, and (e) and (f) streptomyces griseus bacteria, and (g) schematic illustration of the synthesis process.[67]

basic "grafting-from" and "grafting-to" modification approaches. Nanoporous surfaces enable attachment of pre-made polymer chains with functional groups through covalent bond connections during "grafting-to" techniques. Bioactive molecules such as peptides or proteins, or DNA achieve attachment as a part of this functional approach.[68]

Scientists implement surface-initiated polymerization for polymer chain growth from surfaces during the "grafting-from" process. Researchers can utilize this method to enhance their ability to control polymer chain parameters for superior substance specificity while improving bioactivity. After grafting implementation on polymers performs a job for subsequent functionalization by attaching specific targeting molecules or ligands, enabling tissue and cell attachment selectivity.[68,69]

5.1.3 Ligand-mediated targeting. Ligand-mediated targeting is a widely employed strategy to enhance the specificity and therapeutic efficiency of nanoparticle-based drug delivery systems. In this approach, targeting ligands such as folic acid, peptides, aptamers, or monoclonal antibodies are conjugated onto the surface of nanocarriers to enable selective binding to overexpressed receptors on diseased cells, particularly cancer cells. For example, folate-functionalized mesoporous silica nanoparticles (MSNPs) have shown significantly enhanced cellular uptake in folate receptor-positive tumor cells. This method not only facilitates precise accumulation at the target site but also reduces off-target interactions and systemic toxicity. The sol–gel process used to synthesize MSNPs offers reactive surface silanol groups that facilitate easy conjugation of targeting ligands through covalent or electrostatic interactions, making ligand-mediated strategies highly compatible with silica-based delivery systems.[55–59]

5.1.4 Responsive surface chemistries. Responsive surface chemistries refer to the functionalization of nanocarrier

surfaces with moieties that respond to specific internal or external stimuli—such as pH, redox potential, temperature, or light—to enable controlled and site-specific drug release. These smart delivery systems remain stable under normal physiological conditions but undergo conformational or chemical changes in diseased microenvironments, triggering drug release at the intended site. pH-sensitive gatekeepers, for example, are commonly integrated onto MSNPs to respond to the acidic tumor milieu or endosomal compartments, ensuring intracellular delivery of therapeutics. Similarly, temperature- or light-responsive polymers can be grafted onto silica nanoparticle surfaces to allow external activation. These chemistries not only enhance therapeutic efficacy but also improve safety profiles by minimizing premature drug leakage. The tunable porosity and modifiable surface of sol–gel-derived nanoparticles make them ideal platforms for incorporating such responsive functionalities.[55–59]

5.1.5 Surface modification techniques. Modifying material surfaces proves essential to incorporate functional groups and bioactive molecules that boost the material's capacity for biological system interactions. These techniques include:

1. Plasma treatment subjects surface nanoporous materials to high-energy gas that generates functional groups, including hydroxyl, carboxyl, and amine groups. By undergoing plasma treatment, surfaces gain increased hydrophilicity that helps them improve their contact with biological fluids as well as cells.[69]

2. Layer-by-layer (LbL) Assembly employs the method of dropping layered polyelectrolytes onto nanoporous surfaces to develop multiple thin films that build at each deposition step. Each layer within this system enables transportation of bioactive molecules and enzymes as well as antibodies, because they provide biochemical targeting features and controlled substance delivery mechanisms.[81]

3. The nanoporous material surface enables self-assembly to spontaneously build ordered multilayers or monolayers of molecules. Nanoscale materials designed to replicate biological environments require this method for developing coatings containing peptides, proteins, or lipids, which help cells to adhere and differentiate and exhibit anti-inflammatory properties.[82]

5.1.6 Strategies for introducing bioactive molecules, ligands, and therapeutic agents. Bioactive molecules, along with ligands and therapeutic agents, require central focus in the functionalization process because they enable nanoporous materials to establish interactions with distinct biological targets. These molecules can be introduced through multiple available approaches.[83]

The surface attachment uses covalent chemistry that bonds proteins or growth factors, or antibodies, through chemical agents. Stable attachment and specific binding occur because of this strategy to receptors on target cells or tissues. The drug delivery applications benefit from peptide or antibody conjugation to nanoporous materials when aiming for targeted cell type delivery.

The introduction of bioactive molecules through non-covalent approaches using electrostatic and hydrophobic interactions mainly serves drug delivery applications. Drugs remain attached to the external surface of nanoporous structures where the controlled release mechanism responds to pH adjustments as well as temperature shifts and selected stimuli.[83–85]

Nanopores provide an encapsulation method by which bioactive agents receive a storage area to support extended-release durations. Nanoporous materials become valuable tools for drug delivery systems because they enable bioactive molecule release at timed intervals in response to environmental triggers.[83–85]

5.2 Common functionalization routes: grafting of organic molecules, peptide and protein conjugation, and bioactive glass modification

The process of functionalizing nanoporous materials contributes substantially to the improvement of their bioactivity, together with their specificity and their performance throughout biomedical applications. Production of functionalized nanoporous materials happens through multiple pathways, which include organic molecule grafting alongside peptide and protein conjugation and bioactive glass modification, and metal and biomolecule, and nanoparticle incorporation methods for better functionality.

5.2.1 Grafting of organic molecules. Nanoporous material surfaces become more bioactive and better compatible with biological systems once organic molecules attach through covalent bonds during grafting processes. Two primary methods exist to perform grafting operations, while the approaches are named ''grafting-to'' and ''grafting-from.'' Using the grafting-to method, researchers bind already produced organic molecules such as poly(ethylene glycol) (PEG) onto surface nanopores to boost material biocompatibility and minimize protein trapping, and avoid immune response.

Microporous surfaces enable ''grafting-from'' reactions by triggering the direct synthesis of organic chain molecules from their surfaces, which creates precise control of functional chain characteristics. Nanoporous surfaces become suitable for modifying their surface properties, such as cell adhesion strength and drug delivery functions, through this approach. The grafting approaches create adapted surfaces which enhance the interfacing between materials and cells, biomolecules, that and drugs.[86,87]

5.2.2 Peptide and protein conjugation. Research groups routinely attach peptides and proteins to nanoporous materials to enhance their ability to target cells properly and to boost both their interactions with cells and their biological effectiveness. The peptide RGD peptides, along with arginine–glycine–aspartate, enable targeting specific cell receptors and enhance cell adhesion and migration. When peptides bind to nanoporous materials, they become suitable for targeted drug delivery purposes along with tissue engineering applications.[88,89]

Nanoporous materials receive therapeutic and diagnostic benefits from the protein conjugation process of adding antibodies and enzymes, together with growth factors. Nanoporous materials linked to antibodies become suitable for pathogen and cancer cell targeting, yet when combined with growth factors, they support tissue repair through cellular differentiation and proliferation stimulation. The ability of nanoporous materials to

strongly interact with biological systems becomes possible through peptide and protein attachment, which makes these materials more effective for therapeutic applications.[88,89]

5.2.3 Bioactive glass modification. The common medical material bioactive glass receives functional improvements for better bioactivity and mechanical performance. The incorporation of bioactive molecules containing calcium phosphate, along with growth factors, improves bioactive glass materials to simultaneously perform bone regrowth while accelerating new bone growth. The bone-forming process leads to tissue integration with surrounding tissue structures that enable vital medical applications in bone repair and regeneration.[90–94]

The addition of silver, copper, and zinc to bioactive glasses enables modification to improve their antibacterial effects. Through their modifying properties, bioactive glasses achieve infection control functions and simultaneously encourage bone healing because of osteogenic effects from specific metal elements.[95–97] Fig. 6 shows the summary of mesoporous bioactive glass (MBG) properties that make these materials highly attractive for biotechnological and biomedical applications.[98]

5.2.4 Incorporation of metals, nanoparticles, and biomolecules. Medically advanced performance of nanoporous materials can be achieved by introducing metals alongside nanoparticles and biomolecules. Nanoporous materials receive added photothermal or magnetic properties after insertion of metal elements, including gold, silver, and iron oxide. Medical practitioners employ therapeutic applications using gold nanoparticles, which absorb light to produce localized heat for cancer treatment. The addition of titanium dioxide and zinc oxide nanoparticles to nanoporous materials produces photocatalytic advancement, antimicrobial protection, and dosage control features.[99]

5.3. Surface modification engages specific biomedical functions

Surface chemistry plays an essential role in nanoporous materials because it defines their biomedical application performance by improving targeting mechanisms, together with biological activities. Surface modification of nanoporous materials adds functional properties that enable them to recognize specific cells or pathogens and tissue targets while temperature and pH triggers precise drug delivery mechanisms.[100]

5.3.1 Using functional surface coatings enables the precise selection of particular cell types or tissues, or pathogens. The main purpose of functionalizing nanoporous materials is to create interaction mechanisms that focus on biological targets of choice. Biomolecules like ligands as well as antibodies, peptides, and functional groups can be bonded to material surfaces to achieve this result. The surface coating of nanoporous materials selects specific target binding, such as particular cell types or tissues, or pathogens, at the expense of preventing unwanted attachment to other cells or tissues.[101]

The specific cell selection process through nanoporous materials works by integrating peptides or antibodies that hook onto cell surface markers. Researchers use the RGD (arginine–glycine–aspartate) peptide sequence to trigger cell adhesion and migration through integrin receptors on cell surfaces when creating materials for bone tissue, cartilage tissue, and skin tissue regeneration applications. When applied to nanomaterials with tumor-associated antigen-specific antibodies, the materials become capable of precise delivery of therapeutic substances to cancer cells, therefore achieving enhanced treatment results with reduced associated complications.[101–103]

Nanoporous materials allow functionalization techniques for the purpose of directing the materials toward tissues. Receivers of bone tissue regeneration benefit from functional groups that embrace calcium and phosphate elements to

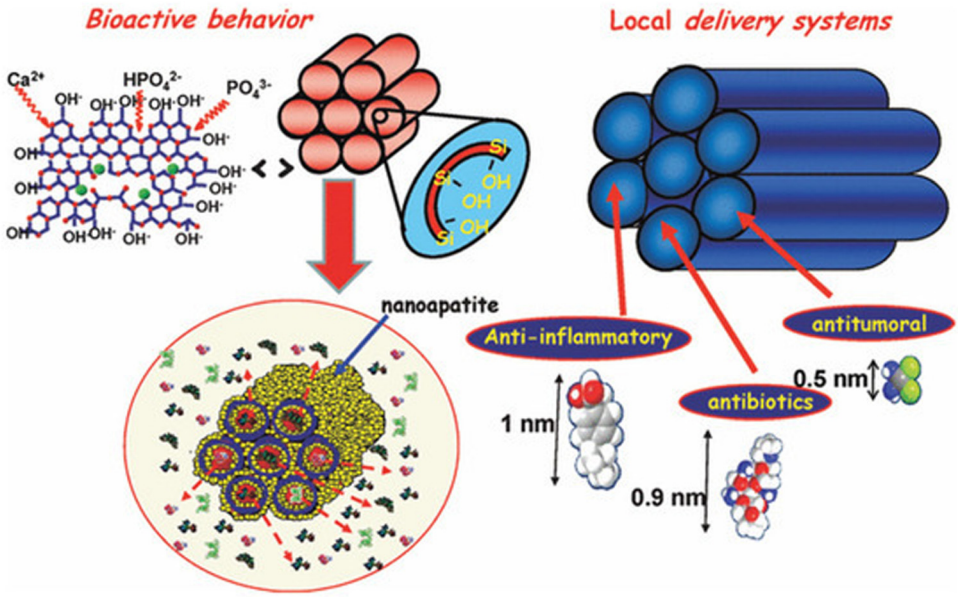


Fig. 6 Summary of mesoporous bioactive glass (MBG) properties that make these materials highly attractive for biotechnological and biomedical applications.[98]

establish osteointegrative bonds. The surface of nanoporous materials receives antimicrobial peptide attachment for wound healing applications, which promotes site injury tissue regeneration through infection prevention mechanisms. Surface-initiated antimicrobial function of nanoporous materials enables the binding and disabling actions against disease-causing pathogens. The surface of nanoporous materials functions as a targeted antimicrobial solution thanks to antibacterial coatings together with specific antibody applications. Nanoporous materials find essential applications in biosensor development and their use in wound treatments and medical infection prevention tactics.[101–103]

5.3.2 Smart functionalization: pH-responsive, temperature-sensitive, and enzyme-triggered systems. Surface-functionalized nanoporous materials possess the ability to adapt their functionality based on changes within the nearby environment. The engineered smart materials possess stimulus-triggered abilities to release their pharmaceutical content, which can also modify their behaviors to specific chemical and physical conditions.[104]

Many biological entities, such as tumors and inflamed body parts, possess exclusive pH environments. Nanoporous materials equipped with pH-sensitive groups, such as carboxyl or amine groups, experience structural variations at pH ranges. Nanoporous drug delivery systems produced with pH-sensitive functionality maintain stability at regular body pH levels and actively release their medications only when the target environment becomes acidic, like within tumors or inflamed areas, providing drug precision while avoiding harm to healthy tissues.[104–106]

Temperature-sensitivity exists in materials that change their physical properties through temperature-controlled effects. Nanoporous materials receive thermosensitive polymers that include poly(*N*-isopropylacrylamide) (PNIPAM), which shows phase transition behavior based on temperature changes. The local temperature rise activates drug release through this material's property, which finds applications in targeted therapy for treating cancer with hyperthermia.[104–106]

Enzyme-responsive functionalization uses specific substrates or peptides that enzymes break down or activate through their activity. The drug delivery strategy finds specific applications in cancer therapy, allowing therapeutic agents to release upon detection of matrix metalloproteinases (MMPs) at tumor sites. The utilization of enzymes in release mechanisms enables physicians to use antimicrobial agents only after detecting infection-specific enzymes in localized areas during treatment.[104–106]

5.4 Hybrid nanoporous structures: combining organic and inorganic components

A new group of biomedical materials known as hybrid nanoporous structures has formed by blending organic compounds with inorganic elements. Hybrid materials that combine organic and inorganic phases yield devices which present superior functionality, that together with better bioactivity and substantial versatility for biomedical applications in drug delivery systems and tissue engineering, and diagnostic systems. Metal–organic frameworks and polymer–inorganic hybrids serve as the main hybrid systems providing high biofunctionalizability and biocompatibility together.[107]

5.4.1 Metal–organic frameworks (MOFs). The building of MOFs occurs through the fusion of metal ions or clusters with organic ligands to develop well-ordered porous crystalline structures. The combination of broad surface area and adjustable pore dimensions produces great advantages for medical implementations. MOFs enhance their biological activity through organic ligands while deriving strong binding strength from metallic components.[108,109]

The high level of porosity within MOF materials allows biomolecules and drugs, along with proteins, to enter their framework for controlled storage, followed by controlled drug delivery. MOF materials retain the capability to bind specific biomolecules *via* peptides or antibodies, which allows scientists to identify chosen tissues or cells. The combination of MOF materials with targeting ligands enables precise drug delivery to cancer cells, thus reducing negative effects on healthy tissue. The selection of metal centers within MOFs derives from their biological activity capabilities. Research validates that zinc-based MOFs function well as wound healing medicine to initiate cellular development while building new tissue and blood vessels.[108,109]

This combination process inside MOFs leads to both components developing enhanced characteristics. An enhancement in MOF diagnostic capacity occurs through CT and MRI contrast enhancement associated with the integration of gold nanoparticles into their composition.[108,109]

5.4.2 Polymer–inorganic hybrids. The development of hybrid composites requires that organic polymers bond with silica and metal oxides and bioactive glasses for inorganic components. Superior materials result from this combination due to their acquisition of flexibility and processability attributes from organic polymers as well as compatibility features from biocompatible components, and rigidity, stability, excellence, and mechanical strength inherited from inorganic components.[110,111]

Hybrid structures combining organic components with inorganic elements serve researchers as vital tissue engineering platforms because they enable the development of mechanical properties according to the scientists' specifications. Composite structures made from hydroxyapatite (HA) together with polymer-based scaffolds create effective structures for bone tissue engineering since these platforms deliver essential bioactive signaling functions alongside maintaining the necessary mechanical integrity needed for bone healing. Modern research has shown that organic–inorganic material combinations enable platform development that directs cell growth and leads to bone tissue recovery applications through bioactive glass and metal oxide particle integration.[110,111]

Systematic design methods used in creating polymer–inorganic blends develop the drug delivery control mechanism. The polymeric framework operates through drug time-based distribution to empty medications, while the inorganic framework makes the structure stable. SENSOR systems designed with silica or metal oxide nanoparticles inside degradable polymer

structures enable anticancer drug kinetics management to enhance therapeutic results and decrease secondary side effects for patients.[110,111]

5.4.3 Synergy between organic functional groups and inorganic support. The fundamental requirement for biological performance and functional enhancement exists in the precise organic–inorganic connection of functional groups within hybrid materials. Inorganic materials combine both supporting roles and catalytic activities with biological systems after they accept organic ligands along with polymers through enzymatic mechanisms and receptor-based mediations.[112–114]

Nanoporous hybrid materials include organic functional groups derived from carboxylates along with amino acids and sugars, which promote exact biological bindings between proteins and enzymes, as well as DNA. Biological interactions between materials at specific sites create reversible connections that trigger cell sticking behaviors as well as movements between positions, and the ability to develop new cell types. Bioactive interactions rely on the inorganic component for structural support as well as regulated active molecule delivery systems.[112–114]

The performance of bone regeneration improves due to better mechanical properties plus enhanced structural integrity when organic substances join with inorganic substances because both strength and biocompatibility prove essential. Hybrid materials unite organic polymers and inorganic ceramics or metal oxides to construct structures that mimic natural extracellular matrix through their framework architecture, which combines mechanical rigidity with biological properties.[112–114]

6. Nanoporous structures for biomedical applications

The scientific community focuses on nanoporous materials because these materials possess three unique characteristics, which include high surface area and adjustable pore sizes, along with advanced surface functionality. Nanoporous materials possess features which enable their use across various biomedical applications within drug delivery as well as biosensing systems and tissue engineering and wound healing and antimicrobial treatment, and diagnostic imaging fields. Nanomedicine, along with biomedical device innovation, benefits significantly from the versatile properties that create a perfect match between these materials and biomedical applications. The design of multifunctional biomedical systems relies heavily on four main categories of materials, which include silica-based materials as well as metal–organic frameworks (MOFs) and hybrid nanoporous composites and metal oxide nanostructures. Fig. 7 shows some biomedical applications of nanoporous materials.[115]

6.1 Drug delivery systems

Medical drug delivery systems evolved thanks to nanoporous material integration that allowed developers to build controlled delivery platforms that offer improved therapy along with decreased adverse effects. Scientists perform extensive analyses on Mesoporous silica nanoparticles (MSNs) because these nanoparticles have two key properties that enable them to encapsulate multiple drugs. The field of news discourse centers on drug delivery control through MSN modifications with targeting ligands combined with stimuli-responsive polymers for precise site-targeting.[116]

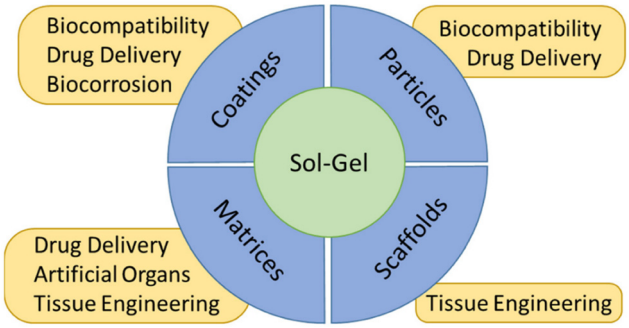


Fig. 7 Different uses of sol–gel materials applied in the biomedical field.[115]

The drug delivery capabilities of metal–organic frameworks (MOFs) stem from their ability to exhibit potent characteristics, which include significant surface area as well as extensive pore volume and adjustable dimensions for pores and multiple functional groups in conjunction with excellent drug encapsulation rates. MOFs undergo design modifications to activate drug release based on pH fluctuations, temperature changes, or light activation, hence reducing likely negative drug delivery impacts.[117]

The drug encapsulation process for hydrophobic agents takes place inside polymeric nanoparticles made from poly(lactic-*co*-glycolic acid) (PLGA). Drugs protected by such nanoparticles experience stability through drug nanoengineering mechanisms that support extensive delivery periods to advance therapeutic effects. PLGA makes an exceptional drug delivery system because it supports biodegradable and biocompatible operation.[116–118]

6.2 Biosensors and diagnostic platforms

Biosensors, together with diagnostic platforms, depend on nanoporous materials for their development because these materials provide high surface-to-volume ratios and adjustable properties. The production of biosensors utilizes nanoporous gold (np-Au) because this material offers both excellent biocompatibility along with high surface area properties. Scientists currently work toward bettering np-Au surface properties to achieve enhanced sensor performance for different biomarkers.[119]

The manufacturing process of biomolecule detection sensors relies on the use of nanoporous anodic alumina material (NAA). The precise structure of its pores enables scientists to place biomolecules for subsequent target detection purposes. The excellent properties of NAA regarding surface area and adjustable pore diameter enable its use in multiple biosensor functions.[119,120]

Researchers have incorporated graphene oxide alongside reduced graphene oxide into nanoporous structures, thus improving sensor functionality. The combination of these materials provides both excellent electrical conductivity and a large surface area property, which enhances biosensor sensitivity. Research advancements in biosensing technology resulted from combining graphene-based materials with nanoporous structures, which produced highly sensitive and selective biosensors for biomedical applications.[121–124]

6.3 Tissue engineering

The field of tissue engineering depends heavily on using nanoporous materials to create scaffolds that duplicate extracellular matrix composition for cell adhesion, as well as cell growth and cell differentiation. Engineering tissue requires scaffolds composed of nanoporous silk fibroin sponges. These porous scaffolds enable cell attachment along with cell multiplication while helping tissue renewal through biological activity only.[125]

Scientists have created a nanoporous structure of hydroxyapatite, which naturally exists as calcium apatite minerals, to enhance bone tissue engineering applications. The materials create an optimal situation for both osteoblast cell attachment and the biological process of bone formation. Nanoporous hydroxyapatite exhibits perfect biocompatibility and osteoconductivity characteristics, which qualify it as an exceptional material for bone tissue engineering applications.

The tissue engineering field has applied PCL and PLGA polymeric materials to manufacture nanoporous scaffolds. The scaffolds act as supportive structures for cell development while creating ideal conditions for tissue emergence in regenerative medicine. The design of tissue engineering scaffolds becomes possible through these materials because they provide adjustable degradation speeds and adjustable mechanical functionality.[126,127]

6.4 Bioseparation and filtration

Bioseparation and filtration operations use nanoporous materials because they have both selective permeability properties and large surface area availability. Filtration processes that depend on membranes having nanoporous structures use this technology to create biomolecule separation through size and charge distinctions. The membranes find practical use for dialysis procedures along with blood filtration applications.[128]

The thematic application of nanoporous materials serves as adsorbents for biological fluid purification through toxin and pathogen elimination. The adsorbents provide both high selectivity along large surface area, which optimizes purification methods. Nanoporous material design allows researchers to generate performance-specific capabilities through precise tuning of pore dimensions as well as surface characteristics for selecting targeted contaminants.[129]

The filtration process benefits from the usage of activated carbon and carbon nanotube-based nanoporous carbon materials because of their high surface area and adjustable pore dimensions. These materials demonstrate an effective ability to absorb impurities that are present in biological fluids. Nanoporous carbon materials exhibit a large surface area and adjustable pore sizes, which enable their use in numerous filtration processes.[130]

6.5 Wound healing

Nanoporous substances demonstrate favorable healing properties because they increase both cellular movement and new vessel formation while supporting tissue reconstruction. Scientists developed silk fibroin sponges containing nanopore structures for medical use in wound treatment. The material structures permit cell adherence while speeding up cell generation, which leads to faster wound healing with better tissue regeneration.[131]

Copper nanoparticles function as an important component within wound dressing materials that boost tissue repair alongside angiogenesis development. The nanoparticles emit copper ions, which provoke blood vessel formation and accelerate the repair process. Copper nanoparticles function as antimicrobial agents, which stop infections from occurring in chronic wounds.[132]

Merits of silver nanoparticles foster antimicrobial effects that guide their incorporation into wound dressings to stop infections. Nanoparticles release silver ions that function as bactericidal agents, thus lowering the chances of wound infection in chronic wounds. Medical wound dressings function better when they contain silver nanoparticles.[133]

6.6 Inflammatory control agents

Nanoporous materials serve for the controlled anti-inflammatory agents delivery which helps control inflammatory responses in medical treatment applications. The release of zinc ions from zinc-based MOFs produces anti-inflammatory effects because these compounds have been developed for controlled zinc ion delivery. Emphasis studies show that these materials provide beneficial effects toward tissue healing processes while decreasing inflammation responses in wound healing contexts.[134]

Nanoparticles of copper serve as an additive to hydrogel structures for directing localized anti-inflammatory responses. The materials achieve their anti-inflammatory effects and simultaneously stimulate collagen deposition while triggering new blood vessel development to accelerate tissue healing processes. Copper nanoparticles exhibit anti-inflammatory characteristics, which provide them with potential for wound healing purposes alongside tissue regeneration needs.[135]

Research has developed anti-inflammatory drug-containing polymeric nanoparticles that serve targeted delivery functions. The nanoparticles activate their therapeutic substance through certain triggers, which helps decrease inflammation at disease sites or areas of injury. The method of using polymeric nanoparticles to deliver anti-inflammatory substances represents an effective technique for managing continuous inflammatory diseases.[136]

6.7 Anticancer drugs

Nanoporous materials function as fundamental delivery methods for anticancer drugs, which provide better clinical outcomes alongside decreased adverse effects. The nanocarriers

being researched for cancer drug delivery include liposomes as well as polymeric micelles and dendrimers and magnetic nanoparticles and mesoporous nanoparticles and gold nanoparticles and carbon nanotubes, and quantum dots. The nanocarriers safeguard drugs from breaking down while enabling precise transport of medications directly to cancerous cells.[137–139]

The drug delivery properties of mesoporous silica nanoparticles have received extensive research because of their high surface area and adjustable pore dimensions. Current developments focus on making MSNs respond to both targeting ligands and stimuli-responsive polymers for controlling drug delivery at tumor locations. The drug-delivery properties of mesoporous silica nanoparticles (MSNs) become more effective for cancer-targeted delivery because researchers attached folic acid or transferrin ligands to these nanostructures. Scientists designed MSNs to detect stimuli found in tumor microenvironment conditions, thereby controlling drug release at targeted sites. The targeted release mechanism both concentrates the medicine at tumor locations and decreases the general toxic effects of treatment, while conventional chemotherapy poses similar problems.[138–140]

Scientists have constructed a pH-triggered MSN drug delivery platform containing doxorubicin and β-cyclodextrin-based cap functionality that behaved as a pH-activated gate at normal pH levels while releasing the content inside cancer tissues with low pH. Academic research involving zirconium-based MOFs brings together UiO-66 and MIL-101 frameworks to simultaneously transport chemotherapeutic drugs and imaging probes for theranostic applications.[141]

The therapeutic potential of cancer treatment includes gold nanoparticles together with carbon nanotubes. Near-infrared light application heats functionalized gold nanoshells while the therapeutic process penetrates cancer cells effectively through photothermal therapy to destroy tumor cells through localized hyperthermia. The unique physical characteristics of carbon nanotubes make them valuable components that transmit small interfering RNA (siRNA) and plasmids containing oncogene suppressor genes for cancer therapy applications.[142,143]

Premature clinical deployment of nanoporous drug delivery systems continues to encounter obstacles regarding their industrial scaling ability, together with their ability to duplicate results and their potential toxic impact on health. The advancement of biocompatible and biodegradable nanocarriers indicates that nanoporous materials will grow more important for cancer therapies in the future.[143]

6.8 Antimicrobial agents

The delivery method and effectiveness of antimicrobial agents benefit significantly from nanoporous materials. Because nanoporous materials exhibit precise control over antibacterial drug and metal ion trapping and releasing functions, they serve as strong antimicrobial agents that fight acute infections and chronic cases despite increasing antimicrobial resistance (AMR).

The research community has extensively studied silver-based nanoporous systems as some of the leading choices. Nanoporous silica, along with polymeric matrices containing silver nanoparticles (AgNPs) functions as an effective system for generating prolonged silver ion release with antimicrobial properties. The bacterial death result occurs when silver ions break cell membranes alongside their interference with protein functions and their production of oxidative stress. The implementation of these systems within dressings for wounds and surgical meshes, and catheter coatings decreases the occurrence of hospital-acquired infections (HAIs).[144,145]

Currently, researchers show equal interest in both copper and zinc ions alongside silver. Antibacterial as well as antifungal properties exist in MOFs composed of copper structures, such as HKUST-1, because they release Cu^{2+} ions gradually. Research done in 2024 established that hydrogels with incorporated copper MOFs demonstrated successful inhibition of two challenging wound infection pathogens: methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* biofilms.[144–146]

Research has enabled the creation of antimicrobial peptide-containing nanoporous lipid structures known as cubosomes that perform encapsulation functions. The immune defense replicating AMPs maintains selectivity to bacteria while lacking harm to human cells through similar biological operations.[147] The protective function of nanoporous carriers helps maintain the stability and effectiveness of their encapsulated materials due to their short degradation times in physiological conditions. Fig. 8 shows the role of the sol–gel synthesis process in the biomedical field and its use to enhance the performance of bioabsorbable magnesium implants.[147,148]

Nanoporous materials maintain vital importance because they possess effective capabilities to break bacterial attachment and bacterial housing networks called biofilms.[147] The small dimensions of nanoporous carriers enable bacteria to remain outside their protective network by stopping their entry, but allow antimicrobial agent release against biofilm surfaces. The latest systems include smart release systems activated by bacterial toxins or enzymes, which provide precise therapeutic benefits.[149] Table 3 shows some examples for biomedical applications of nanoporous materials synthesized by sol–gel method.

7. Advantages of sol–gel method

The sol–gel and solvothermal methods are crucial for large-scale production of nanoparticles, and both methods present special opportunities that cover different stages of the nanoparticle synthesis process. There are several advantages associated with the sol–gel method, among which the following should be mentioned. Most of them are valued with the help of the sol–gel method because of their versatility, simplicity, and applicability in cases when the operation scope should be scaled up.[55,150] This technique entails converting a colloidal solution known as the 'sol' to a three-dimensional network called the 'gel' through the regulation of hydrolysis and condensation reactions of the initial reagents. This allows for one

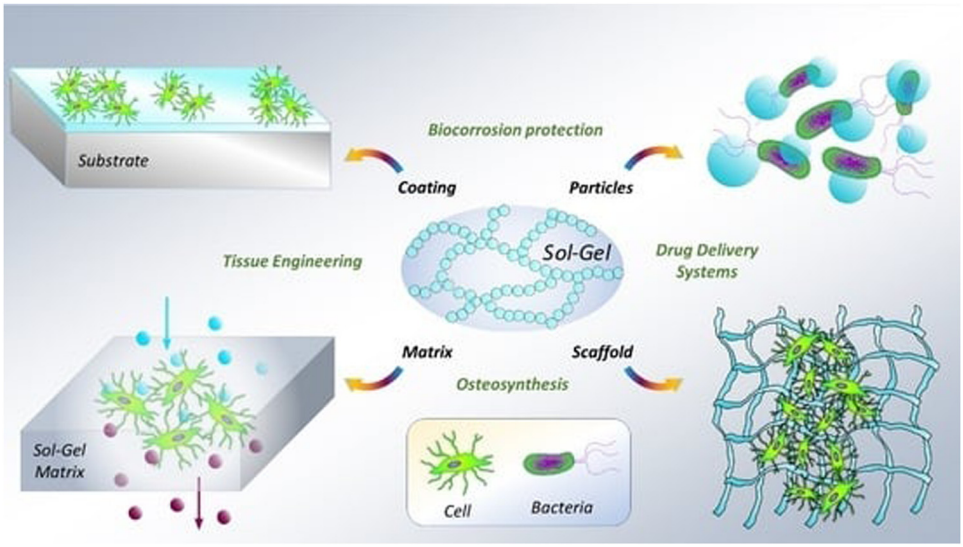


Fig. 8 The role of the sol–gel synthesis process in the biomedical field and its use to enhance the performance of bioabsorbable magnesium implants.[148]

of the primary benefits of the sol–gel process to be highlighted, which is the capability to form high-purity nanoparticles that are uniform in both composition and size distribution. During the sol–gel process, many materials such as metals, oxides, and composites can be added, and as such the process is highly flexible for use in different industries.[160] As sol–gel synthesis, low temperatures of the process help to save energy and corresponding costs and to avoid thermal damage to sensitive materials. Also, the method allows for the introduction of dopants and functional groups during the synthesis stage, which is relevant in defining nanoparticle properties for respective applications.[161,162]

However, solvothermal shows some advantages, which include particle size control, a wide range of materials, and perhaps the kinetics of the reaction.[163] This process harnesses conditions such as high temperature and high pressure in a solvent to cause specific chemical reactions resulting in the formation of nanoparticles. A general feature of the solvothermal process is the size and shape control of the particles by varying the reaction conditions, which include temperature, pressure, and composition of the solvent. The ability to fine-tune the properties of the nanoparticles is important in creating nanoparticles with properties required for certain applications, including catalysis, electronics, and medicine.[164] This makes the solvothermal method suitable when synthesizing nanoparticles of complex materials, which are usually a challenge to synthesize by other methods. For example, it can lead to the synthesis of metal chalcogenides, complex metal oxides, and alloy nanoparticles having high quality with high crystallinities and well-defined structures.[165] Moreover, the solvothermal synthesis process can easily integrate with continuous-flow reactors that are beneficial, especially for large-scale operations.

As previously mentioned, both sol–gel and solvothermal techniques bring unique benefits to the synthesis of nanoparticles and help advance the creation of a wide variety of material systems with desired characteristics. The sol–gel process demonstrates high performance in the formation of homogeneous nanoparticles with definite compositional characteristics at a reasonable cost, while solvothermal synthesis provides fine control for the size, shape, and complexity of particles under high temperature and pressure conditions. The selection of the procedure can be primarily based on the intended application of the nanoparticles under development, in that it is desirable to achieve certain physical and chemical properties at a particular scale of production. In combination, these methods refine the area of nanotechnology and extend the opportunities for nanoparticle usage in various industries.[55,163–165]

8. Limitations of sol–gel method

The sol–gel synthesis processes are effective in synthesizing nanoparticles; however, these methods also have its inherent drawbacks that affect their use on a large scale. It is very important to be aware of these limitations for the effective maximization of production lines and handling of key issues in the synthesis of nanoparticles.

One of the main drawbacks associated with the use of the sol–gel method is that this technique is relatively slow in terms of processing time, especially in the gelation and drying steps. Although the sol can be converted to a gel in a relatively short time, and afterward dried, the whole process of fabricating the composite may take a considerable time, limiting large production possibilities.[55] Moreover, in this process, the gel dries up and it can shrink and there might be chaotic cracking in the gel, which might influence the quality and uniformity of the nanoparticles manufactured. This issue can be somewhat controlled by adjusting the conditions for drying, but it is still a rather important problem.[166]

Another limitation is that an important factor associated with the sol–gel process is the issue with scaling up the

Table 3 Examples for biomedical applications of nanoporous materials synthesized by sol–gel method

No.	Nanoporous material	Summary of the study	Significant findings	Prospects	Ref.
1	Boehmite NPs	Nanoporous structures synthesized *via* the sol–gel method, specifically boehmite nanostructures, serve as effective carriers for drug delivery and protein entrapment, demonstrating biocompatibility and potential in anticancer applications, as well as influencing gene transfer in bacterial systems.	AXNCs release protein at low pH for anticancer drug development. Boehmite NPs enhance gene transfer between bacteria.	Investigate boehmite NPs on gene transfer. Evaluate the safety of boehmite NPs in medicine.	150
2	Nanoporous silica	Nanoporous silica synthesized *via* the sol–gel method serves as an effective substrate for immobilizing biomolecules, enhancing detection efficiency in biosensors, particularly for cardiac markers like troponin I, due to its high surface area and functionalization capabilities.	FRET biosensor detects troponin I with 10–5 ng mL^{-1} sensitivity. Nanoporous silica enhances biomolecule immobilization and detection efficiency.	Optimize antibodies, crosslinkers, and donor–acceptor pairs. Design detection procedures for other cardiac biomarkers.	151
3	Mesoporous hydroxyapatite	Nanoporous hydroxyapatite (HAP) synthesized *via* the sol–gel method exhibits excellent biocompatibility, bioactivity, and osteoconductivity, making it suitable for biomedical applications such as tissue replacement, drug delivery carriers, and biocompatible coatings, particularly when modified with stearic acid.	Mesoporous hydroxyapatite was synthesized using stearic acid as the modifier. Exhibits excellent biocompatibility and drug release behavior.	Investigate the drug delivery efficiency of MT-loaded HAP. Explore other organic modifiers for HAP synthesis.	152
4	PDMS-based porous ORMOSILs	The study synthesized PDMS-based porous ORMOSILs using a sol–gel process, resulting in bimodal nanoporous structures (300–500 μm and 10–50 μm). These materials demonstrated bioactivity through apatite deposition in simulated body fluid, essential for biomedical applications.	Synthesized PDMS-based ORMOSILs using sucrose templates. Materials showed bioactivity and apatite deposition in simulated body fluid.	Explore the mechanical properties of PDMS-based porous materials. Investigate long-term bioactivity and tissue integration.	153
5	Hybrid ZrO_2–PCL materials	Nanoporous structures synthesized by the sol–gel method, specifically hybrid ZrO_2–PCL materials, exhibit good biological properties and bioactivity, enhancing biocompatibility for biomedical applications such as dental implants, promoting osteointegration through apatite formation in simulated body fluid.	Sol–gel coatings enhance titanium's biocompatibility and bioactivity. Apatite formation observed on coated surfaces in simulated body fluid.	Improve the mechanical properties of hybrid materials for load-bearing applications. Explore additional biodegradable polymers for enhanced biocompatibility.	154
6	Multi-wall carbon nanotube/hydroxyapatite nanocomposite powders	The paper discusses the sol–gel synthesis of multi-wall carbon nanotube/hydroxyapatite nanocomposite powders, highlighting their potential for biomedical applications, particularly in bone substitution, due to their biocompatibility and structural reinforcement properties mimicking human bone characteristics.	Homogeneous dispersion of MWCNT in hydroxyapatite matrix confirmed. Biocompatibility of composite powder comparable to monolithic hydroxyapatite.	Explore different concentrations of MWCNTs for enhanced properties. Investigate long-term biocompatibility and integration with bone tissue.	155
7	Mesoporous europo-gadolinosilicate nanoparticles	Nanoporous structures synthesized *via* the sol–gel method, specifically mesoporous europo-gadolinosilicate nanoparticles, serve as bimodal imaging agents for MRI and luminescence, and have potential for drug delivery applications due to their encapsulation and controlled release capabilities.	Mesoporous nanoparticles enhance MRI contrast significantly over Omniscan. Nanoparticles serve as drug delivery and imaging agents.	*In vitro* optimization for *in vivo* studies. Further optimization of dopant levels in nanoparticles.	156
8	Nanoporous $MgAl_2O_4$	The paper does not specifically address nanoporous structures synthesized by the sol–gel method for biomedical applications. It focuses on the preparation of $MgAl_2O_4$ for catalytic uses, highlighting its thermal stability and porosity characteristics.	Nanoporous $MgAl_2O_4$ prepared *via* sol–gel and combustion methods. Pore volumes controlled from 0.7 to 1.1 $cm^3\ g^{-1}$.	Applicability of the method to other metal oxides. Investigate thermal stability at higher temperatures.	157

Table 3 (*continued*)

No.	Nanoporous material	Summary of the study	Significant findings	Prospects	Ref.
9	Sol–gel monoliths	Nanoporous structures synthesized by the sol–gel method exhibit controlled pore sizes, enhancing cell response for biomedical applications. These structures, with micropores around 2 nm, facilitate tissue regeneration and can be tailored for specific cell behavior in regenerative medicine.	Developed sol–gel monoliths with controlled nanopore sizes. Achieved micropores of 2 nm diameter efficiently.	Optimal pore size and shape for different cell types. Investigate the mechanisms of cell response to nanoporous materials.	158
10	Nanocomposite hydroxyapatite/ α-Al_2O_3 powders	The paper discusses the synthesis of nanocomposite hydroxyapatite/α-Al_2O_3 powders using the sol–gel method, highlighting their potential in biomedical applications such as orthopedics, traumatology, and dentistry due to their bioactivity and ability to promote bone tissue proliferation and osseointegration.	Nanocomposite powders show promising biomedical applications. Nanostructured biomaterials enhance mechanical and biological properties.	Explore additional calcium phosphate-based nanocomposites for biomedical applications. Investigate long-term biocompatibility and mechanical properties of nanocomposites.	159

approach. The applicability of the method is not limited to a particular substrate; however, in large it is a little challenging to maintain the uniformity in the particle size and distribution. Potentiometric titration conditions, the extent of precursor mixing, and drying may lead to differences between batches of nanoparticles, which may impact the quality and reproducibility.[167,168]

In addition, to perform sol–gel process, it is necessary to utilize, for example, toxic or environmentally dangerous reagents, for example, metal alkoxides, which is also an issue of safety and environmental protection.[166–168] The use of these chemicals involves certain measures of handling and disposal that pose serious risks, hence leading to a higher cost. Initiatives towards the use of greener precursors and solvents are continuous, however, replacement of such solvents and precursors often brings a permanent solution with the disadvantage of compromising efficiency or even economy.[167,168]

While sol–gel-derived nanocarriers, especially mesoporous silica nanoparticles (MSNPs), offer considerable advantages in drug delivery, several situation-specific challenges can limit their clinical translation. One of the primary concerns is poor bioavailability due to opsonization and rapid recognition by the mononuclear phagocyte system (MPS), which leads to premature clearance from systemic circulation. This limits the effective concentration of the therapeutic payload at the target site. Additionally, clearance pathways are influenced by particle size, surface charge, and hydrophobicity. Nanoparticles smaller than 5–10 nm are often filtered through renal pathways, while larger particles ($>$200 nm) are sequestered by the liver and spleen. Hence, maintaining an optimal size range (typically 50–150 nm) is critical to balance circulation time and biodistribution. Moreover, immune reactions remain a pressing issue; unmodified or bare silica surfaces can activate the complement system or provoke inflammatory responses. To mitigate this, surface modifications such as PEGylation or coating with biocompatible polymers have been widely adopted to improve stealth properties and reduce immunogenicity. These biological barriers underscore the importance of rational nanoparticle design to ensure safety, stability, and therapeutic effectiveness.[55–59,167,168]

The synthesis route plays a pivotal role in defining the physicochemical properties, biological functionality, and scalability of nanoporous materials for biomedical applications. Among these, as aforementioned, the sol–gel method is widely appreciated for its versatility in producing amorphous, porous structures under mild conditions. It enables precise control over pore size, surface area, and composition by manipulating parameters like pH, aging time, and the type of precursors or templates used. In contrast, hydrothermal synthesis, typically conducted at higher temperatures and pressures, favors crystalline nanoparticle formation and is often used to enhance phase purity and mechanical stability. While it allows for good morphological control, it may limit functionalization flexibility and require specialized equipment. Templating approaches (both soft and hard templating) provide superior control over pore architecture and regularity, with soft templating using surfactants (*e.g.*, CTAB) and hard templating relying on solid matrices (*e.g.*, carbon or polymers). These methods are powerful but may involve complex post-synthesis removal steps and organic solvents, potentially impacting biocompatibility. A comparative understanding of these synthesis strategies allows researchers to tailor nanomaterials for specific applications, balancing factors such as drug loading capacity, degradation rates, and clinical safety profiles.[55] Table 4 shows a comparison of sol–gel, hydrothermal, and templating methods for nanoporous biomaterials.

9. Future directions sol–gel method

It should be noted that sol–gel method is still in its developing phase and is expected to receive further developments to overcome its drawbacks and bring improvements to its usability for industrial applications. There are two major future directions: first, enhancing the process efficiency of which gelation and drying may take rather a long time. These are methods like

Table 4 A comparison of sol–gel, hydrothermal, and templating methods for nanoporous biomaterials[55]

Parameter	sol–gel	Hydrothermal	Templating (soft/hard)
Temperature/pressure	Low (ambient to 100 °C), atmospheric	High (100–250 °C), autoclave pressure	Moderate (depends on system)
Material morphology	Amorphous or semi-crystalline	Crystalline (often well-defined)	Highly ordered meso/macropores
Pore control	Tunable (*via* pH, time, templates)	Moderate (depends on mineralizer and time)	Excellent (precise architecture with templates)
Surface area	High (200–1000 m^2 g^{-1})	Medium to high	Very high (depends on template type)
Scalability	Moderate; often batch-based	High (suitable for scale-up)	Limited (hard templating less scalable)
Functionalization flexibility	Excellent (co-condensation or post-grafting)	Limited (post-functionalization needed)	Good (mainly after template removal)
Biocompatibility	High (depending on precursors)	High (if proper precursors used)	Varies (dependent on template residues)
Post-processing complexity	Moderate (aging, drying, calcination)	Minimal (washing and drying)	High (template removal *via* calcination or etching)
Typical applications	Drug delivery, bone scaffolds, sensors	Ceramic coatings, nanoparticles, catalysis	Drug carriers, photonic structures, controlled release systems

microwave or supercritical drying, which could seem to have a major impact on reduced processing time and therefore increased scalability.[45] Moreover, the preparation of green precursors is important for the control of environmentally and safely detrimental precursor materials. Most research is directed toward finding new materials that are non-hazardous to human health and the surrounding environment but that can offer the same performance as currently available materials. The third is improving scalability: to achieve this, structural characteristics and complicated stacks should be eradicated, while tradeoffs should become more consistent between teams. This includes furthering reactor designs, implementing better ways of controlling the processing conditions, and ensuring constant quality within the large quantity batches. Presumably, more exacting measures, such as real-time monitoring and feedback, could also help to maintain the nanoparticle standard.[166] Furthermore, the combination of sol–gel methods with designing intricate forms and constructions of nanoparticles for a particular application enhances the potential of the sol–gel process.[166–170]

Considering the functionalization strategies, especially covalent *vs.* non-covalent approaches, surface functionalization plays a pivotal role in tailoring the biological behavior and performance of sol–gel-derived nanocarriers, especially mesoporous silica nanoparticles (MSNPs).[47,48] Two primary approaches are used: covalent and non-covalent functionalization. Covalent methods involve strong, stable chemical bonds between the nanoparticle surface and functional groups such as ligands, polymers, or targeting moieties. Silane coupling agents (*e.g.*, APTES, MPTMS) are often employed to introduce reactive $–NH_2$, –SH, or –COOH groups for subsequent conjugation. In contrast, non-covalent strategies utilize weaker interactions such as electrostatic attraction, hydrogen bonding, or hydrophobic interactions to adsorb functional molecules onto the surface. While non-covalent methods are simpler and more reversible, they are less stable under physiological conditions. Covalent attachment, especially for PEGylation and targeting ligands, provides enhanced structural integrity, prolonged circulation, and reduced off-target effects, making it the preferred choice for most clinical applications.[55]

Recent *in vivo* studies have provided compelling evidence supporting the use of surface-modified silica nanocarriers in drug delivery. For example, PEGylated MSNPs have demonstrated significantly prolonged blood circulation half-lives and reduced recognition by the mononuclear phagocyte system (MPS), resulting in improved tumor accumulation through the enhanced permeability and retention (EPR) effect.[47,48] Ligand-functionalized systems, such as those conjugated with folic acid, transferrin, or antibodies, have shown receptor-specific targeting capabilities, improving uptake in tumor microenvironments or inflamed tissues. Moreover, dual-functionalized systems combining PEGylation and active targeting moieties have exhibited synergistic effects in biodistribution and therapeutic outcomes. These findings underscore the importance of precise surface engineering to optimize *in vivo* performance, enhance treatment specificity, and reduce systemic toxicity.[55]

Regarding the impact on pharmacokinetics and drug fate, surface modifications on nanocarriers have a profound impact on the absorption, distribution, metabolism, and excretion (ADME) of loaded drugs. Functionalized MSNPs can improve oral bioavailability by protecting labile drugs from enzymatic degradation and enhancing their transport across epithelial barriers. In parenteral formulations, surface coatings such as PEG reduce protein adsorption (the ''protein corona''), minimize rapid opsonization, and delay hepatic and renal clearance—thereby enhancing plasma half-life. Targeting ligands further refine tissue distribution by guiding nanocarriers to specific cellular receptors, which can dramatically alter drug localization profiles. Additionally, surface chemistry influences intracellular trafficking pathways, endosomal escape efficiency, and eventual drug release kinetics. These pharmacokinetic advantages are central to the rationale for advanced surface functionalization in modern nanomedicine.[55,171]

As mentioned before, the field of sol–gel-derived biomedical nanomaterials continues to grow rapidly, but several challenges must be addressed to facilitate clinical translation and broader implementation. Considering the major concern involves regulatory frameworks and standardization, the sol–gel process allows extensive customization of material properties, which, while advantageous, creates inconsistencies in reproducibility and complicates the establishment of universal quality standards. Harmonizing nomenclature, characterization protocols, and biosafety assessments is essential to bridge the gap

between laboratory research and industrial-scale clinical deployment. Furthermore, regulatory approval processes for hybrid organic–inorganic sol–gel systems often face delays due to ambiguity in classification (*e.g.*, drug-device *vs.* combination product) and a lack of harmonized guidelines across regions.[55]

Another critical dimension of future advancement is the integration of sol–gel technologies with emerging biomedical platforms. For instance, coupling sol–gel nanocarriers with nanorobotics may enable precise intravascular navigation and site-specific drug delivery, while CRISPR/Cas-based gene editing tools could be loaded onto mesoporous silica matrices for targeted genome modification. The synergy between sol–gel nanocarriers and AI-assisted diagnostics is another promising direction. Machine learning algorithms can optimize sol–gel formulation parameters for desired therapeutic outcomes and predict *in vivo* responses, reducing the time and cost associated with preclinical development.

From a material design standpoint, future research should focus on the development of fully biodegradable sol–gel matrices that avoid long-term accumulation and offer tunable degradation rates tailored to specific clinical applications. Additionally, next-generation systems should exploit stimuli-responsive behavior, including pH, temperature, redox state, enzymatic activity, or light triggers, to achieve dynamic and controlled therapeutic responses.[172,173] These smart systems could be particularly impactful in oncology, infectious disease management, and precision immunotherapy. The future innovations will hinge on interdisciplinary collaboration across materials science, synthetic biology, pharmacology, and data science to realize the full translational potential of sol–gel-derived nanomaterials in biomedicine.[55]

10. Conclusion

10.1 Summary of key findings

This review highlights the pivotal role of the sol–gel method in the synthesis and functionalization of nanoporous materials for advanced biomedical applications. The sol–gel process offers a versatile and controllable approach to developing nanoporous structures with a broad range of tunable properties, including high surface area, customizable pore size, and chemical functionality. These features make sol–gel-derived materials highly suitable for applications in drug delivery, tissue engineering, diagnostic imaging, and wound healing.

Nanoporous silica-based materials have shown significant potential in drug delivery systems, where pore size tailoring allows for controlled release profiles, and surface modifications enhance targeting and drug loading capacity. Additionally, these materials have proven effective in antibacterial and anti-inflammatory applications, providing a solution for infection control and inflammation management. Metal oxide nanoporous structures, on the other hand, show promise in tissue engineering, particularly in osteointegration and bone regeneration, while also demonstrating valuable photocatalytic properties for antimicrobial and diagnostic purposes.

Further advancements have been made in the synthesis of bioactive glasses and bio ceramics for bone regeneration, particularly in orthopedic and dental applications. Hybrid nanoporous materials have gained attention in diagnostics through their integration into imaging agents and biosensors, offering enhanced diagnostic capabilities for disease detection and real-time monitoring. Functionalization of these materials, such as through grafting or incorporating bioactive molecules, significantly amplifies their efficacy in targeted therapy and precision medicine.

10.2 Future outlook for sol–gel-derived nanoporous materials in biomedicine

The future of sol–gel-derived nanoporous materials in biomedicine is promising, with ongoing innovations in synthesis techniques, material properties, and functionalization strategies. As the scalability and reproducibility of sol–gel processes improve, there will be greater opportunities to transition from laboratory-scale synthesis to large-scale industrial applications. Moreover, advances in multi-functional and stimuli-responsive systems will provide more precise control over drug release, cell differentiation, and tissue regeneration, allowing for personalized therapeutic approaches tailored to individual patient needs.

Emerging combinatorial therapies integrating nanoporous materials with gene therapy, immunotherapy, or targeted drug delivery systems will enable more effective treatments for complex diseases, such as cancer and autoimmune disorders. The synergy between sol–gel-derived nanoporous structures and other therapeutic modalities will be pivotal in enhancing treatment outcomes and improving patient quality of life.

10.3. Final remarks on the role of functionalization in biomedical nanostructures

Functionalization remains at the heart of advancing the biomedical applications of nanoporous materials. By introducing bioactive molecules, ligands, and targeting agents into the surface chemistry, nanoporous materials can be fine-tuned for specific biomedical applications, including precision drug delivery, diagnostic imaging, and tissue regeneration. The ability to control the functional groups at the material surface allows for better biocompatibility, selectivity, and efficacy, making these materials highly promising for clinical use.

As the field progresses, overcoming challenges such as regulatory hurdles, long-term biocompatibility, and ensuring safety in clinical settings will be essential. However, with continued research, development, and clinical testing, sol–gel-derived nanoporous materials have the potential to revolutionize the way we approach biomedical therapies, offering highly efficient, targeted, and minimally invasive treatment options that could significantly impact healthcare in the future.

Statements and declaration

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

P. Yapa – literature search and drafted the manuscript. I. Munaweera – conceptualization, supervision, writing, review, and editing the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

Data availability

All the data are included in this manuscript.

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