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Biocompatibility of nanomaterials in medical applications

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Abstract

Biocompatibility is a critical factor in the application of nanomaterials in medical fields, as these materials must interact safely and effectively with biological systems to be viable for therapeutic and diagnostic use. This article investigates this feature, focusing on the interactions of nanomaterials with cells, tissues, and the immune system. Key properties such as surface chemistry, size, shape, and material composition are examined for their influence on the biological response. The article also explores the role of nanomaterials in medical applications, including drug delivery, diagnostic imaging, and tissue engineering, while discussing the challenges involved in enhancing their biocompatibility. A case study on the calcium oxide (CaO)–calcium phosphate (CaP) binary system is presented, showcasing its potential in bone tissue engineering, particularly its osteoinductive properties and ability to mimic the bone mineral content. The analysis underscores both its therapeutic potential and the biocompatibility concerns of CaO–CaP scaffolds. The article concludes by outlining strategies to optimize nanomaterial biocompatibility and future directions for their translation into medical applications.

Keywords: Biocompatibility; Calcium oxide–calcium phosphate system; Nanomaterials; Tissue-engineering; Osteointegration; Regeneration

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1. Introduction

Modern medicine is witnessing a paradigm shift, shaped by the rise of precision medicine, implantable technologies, and patient-specific treatment regimens. These emerging approaches demand materials that can perform reliably within complex biological systems while enabling fine-tuned control over therapeutic or diagnostic outcomes. However, conventional biomaterials often fall short of these requirements. Their limited biological responsiveness, low adaptability, and potential to trigger immune reactions have created a critical gap in realizing next-generation medical solutions, as highlighted in foundational biomaterials research that emphasizes the limitations of traditional materials in dynamic physiological contexts.[1]

Nanomaterials have emerged as compelling candidates for addressing current biomedical challenges, largely due to their distinctive physicochemical characteristics. Their nanoscale dimensions facilitate interactions with biomolecules, cells, and tissues

at the molecular level, enabling enhanced biological integration. Key features—such as a high surface-area-to-volume ratio, modifiable surface chemistry, and responsiveness to external stimuli—confer functional advantages not typically observed in conventional materials. These advantages have been demonstrated in recent comprehensive analyses focusing on their synthesis, customizability, and wide-ranging biomedical applications of nanomaterials.[2]

The multifunctional nature of nanomaterials enables their incorporation into a wide array of biomedical platforms, including injectable drug carriers and surface-modified implants. Their amenability to large-scale production further enhances their translational potential for routine clinical use, although considerations remain regarding their toxicological profiles and biocompatibility. Prior studies have examined the safety, bioaccumulation, and immune responses of nanomaterials, highlighting both opportunities and challenges in their clinical deployment.[3]

These advantages make nanomaterials particularly attractive for addressing real-world medical demands. In cancer therapy, for example, liposomal formulations such as Doxil® have revolutionized chemotherapy by delivering doxorubicin directly to tumor sites, reducing systemic toxicity and improving therapeutic efficacy. This milestone—recognized as the first Food and Drug Administration (FDA)-approved nanodrug—demonstrates how rational nanodesign can overcome long-standing limitations in pharmacokinetics and safety, as detailed in case studies tracing the translation of nanoparticle-based formulations from bench to bedside.[4]

In diagnostic imaging, ferumoxytol, an iron oxide nanoparticle, has been successfully used off-label as a magnetic resonance imaging contrast agent in various clinical settings, enhancing vascular imaging in patients unsuitable for conventional gadolinium-based agents. This clinical adaptation highlights the flexibility of nanomaterials in addressing diagnostic limitations and expanding imaging capabilities in vulnerable patient populations.[5]

In orthopedic and dental applications, nanostructured coatings and scaffolds—such as those made from calcium phosphate (CaP) or calcium oxide (CaO)—promote bone regeneration and tissue integration due to their osteoconductive nature. These materials, with their nanoscale topographies and bioactive interfaces, offer significant improvements in implant performance and bone-anchoring efficiency.[6] More specifically, nano-hydroxyapatite scaffolds have shown great promise in clinical and pre-clinical bone regeneration efforts, offering high surface reactivity, biomineral mimicry, and superior compatibility with osteoblasts. Their use as bioinspired, osteoinductive matrices has been validated through recent studies examining their structural properties and biological responses *in vivo* and *in vitro*.[7]

Tissue engineering represents another critical domain in which nanomaterials play a transformative role. By mimicking the extracellular matrix, nanomaterial-based scaffolds support cellular activities necessary for tissue regeneration. Their high surface area and controllable porosity facilitate cell adhesion and enable the localized delivery of bioactive agents. Investigations into carbon-based and cellulose-derived nanomaterials have demonstrated their capacity to support tissue integration, promote vascularization, and guide targeted regeneration.[8]

Across these applications, nanomaterials are not only enhancing current medical practices but also enabling previously unachievable technological advances. Despite these promising developments, the clinical use of nanomaterials hinges on their ability to safely interact with biological environments. Their high reactivity, while beneficial for functionality, introduces risks of cytotoxicity, inflammation, or immune system activation. As such, biocompatibility has emerged as a core requirement for their medical use. Defined as a material's ability to perform its intended role without provoking adverse biological responses, biocompatibility ensures that nanomaterials are both effective and safe for clinical use.[1,2]

The next section delves into examining the criteria for assessing biocompatibility, the mechanisms by which nanomaterials interact with biological systems, and the strategies employed to mitigate risks. As the foundation of successful medical applications, biocompatibility serves as the critical bridge linking nanomaterial innovation to real-world patient outcomes.

2. The critical significance of biocompatibility in nanomedicine

2.1. The role of biocompatibility in clinical success

Biocompatibility is a key factor in determining whether a nanomaterial can be successfully translated into clinical applications. For any medical material, especially one designed to work at the molecular or cellular level, it must be able to interact with tissues and fluids in the body without causing harm. If a nanomaterial triggers toxicity, inflammation, or an unwanted immune reaction, it can compromise the therapy entirely. As highlighted in foundational research on the biomedical potential of nanomaterials, ensuring compatibility with the physiological environment is not just important—it is essential.[9]

Unfortunately, there have been many cases where promising nanomaterials performed well in the laboratory but failed *in vivo*. These failures often stem from poor biocompatibility. For example, nanoparticles not designed to avoid immune surveillance may be rapidly cleared from circulation, or, more concerningly, provoke dangerous responses. Studies on targeted delivery have shown the importance of anticipating such reactions during the design phase, underscoring that the clinical success of nanomaterials hinges on proactive biocompatibility assessment and modulation.[10]

2.2. Comparison with conventional biomaterials

Nanomaterials exhibit fundamentally different biological interactions compared to traditional biomaterials. While bulk materials such as metals and polymers are typically inert and used for their mechanical strength, nanomaterials are reactive, customizable, and operate at a scale that enables intimate interaction with biological structures. These features allow for exciting possibilities in medicine—such as targeted drug delivery or real-time monitoring—but they also introduce significant challenges. Studies on nanoparticle surface engineering have shown that poorly designed nanomaterials can adsorb proteins non-specifically, trigger immune responses, or cause cellular damage.[11]

Unlike conventional implants, which typically remain inert and static within the body, nanomaterials are often intended to move, respond dynamically, or break down after fulfilling their function. Their tiny size allows them to enter cells more easily, but it also increases their accumulation in tissues. For instance, particles smaller than 100 nanometers are great for intracellular delivery; however, if they are not biodegradable, they may accumulate and cause harm over time—a concern raised in earlier work on nanoparticle design.[12] Particle shape also significantly influences biological interactions. Spherical nanoparticles tend to be taken up more readily, while rod-shaped particles exhibit distinct uptake pathways and may interact with immune cells differently, potentially altering their safety profile.[13]

2.3. Regulatory emphasis on biocompatibility

Health regulatory agencies around the world—including the U.S. FDA and the European Medicines Agency (EMA)—place a strong emphasis on biocompatibility in the evaluation of nanomedicine products. Developers are expected not only to prove that a treatment works but also to provide detailed evidence about how the material behaves in the body. Key questions include whether the material exhibits toxicity, elicits immune responses, or how it is metabolized and cleared from the body. These concerns are particularly critical for nanomaterials due to their unique and complex properties. Environmental studies on nanoparticle degradation have underscored the importance of understanding material fate as a determinant of long-term safety.[14]

To meet these expectations, developers must prioritize the selection of biocompatible materials and implement surface modifications to improve safety. Organic nanomaterials, such as liposomes or biodegradable polymers, are favored in regulatory assessments due to their inherent capacity to break down into harmless byproducts. On the other hand, inorganic materials such as iron oxide or gold may offer advantages in imaging or durability, but usually require surface coatings to reduce toxicity and prevent accumulation in tissues. These strategies are supported by recent studies showing the feasibility of safely using inorganic nanoparticles in biomedical applications through engineered surface modifications.[15] Additional research has further pointed out the need to manage potential immune effects from inorganic particles, highlighting the value of immunomodulatory surface design.[16]

2.4. Foundation for engineering nanomedicines

Biocompatibility must be integrated into nanomaterial design from the outset—it is not a parameter that can be retroactively optimized. Every physicochemical characteristic of the nanomaterial, including size, shape, surface charge, texture, and chemical composition, plays a pivotal role in determining biological interactions. One widely used method to enhance biocompatibility is PEGylation, whereby polyethylene glycol (PEG) chains are grafted onto nanoparticle surfaces. This modification helps the material stay in the bloodstream longer and reduces detection by the immune system. PEGylation, along with hydrophilic surface coatings, has proven highly effective in improving compatibility, as noted in several design-focused studies.[10,11]

Surface charge also plays a delicate role. Positively charged particles are more likely to enter cells, thanks to their attraction to the negatively charged cell membranes. However, this benefit comes with a downside—a higher propensity for cytotoxicity and pro-inflammatory responses. On the other hand, neutral or slightly negative particles are usually better tolerated, though they might not be taken up as efficiently. Striking the right balance is critical, as highlighted in immunological studies focused on nanomaterial-host interactions.[17]

Another aspect that influences biocompatibility is surface energy. When a nanoparticle enters the bloodstream, it quickly gets coated with proteins, forming

a "protein corona" that changes its biological response. Uncontrolled corona formation may lead to unpredictable pharmacokinetics or off-target effects. Researchers have shown that tweaking surface energy can help control corona composition, thereby guiding biological interactions in a way that supports therapeutic goals.[18]

Finally, the intrinsic nature of the nanomaterial itself matters. Organic nanomaterials, such as liposomes or polymers, are generally safer because the body naturally breaks them down. They are often preferred for treatments requiring repeat dosing or prolonged systemic exposure.[14] In contrast, inorganic nanomaterials such as silica or gold may be preferred for their strength or imaging capabilities, but they often need to be coated or encapsulated to ensure safety. This is especially important in antiviral applications, where precise control over surface charge and hydrophilicity is required to avoid immune activation while preserving efficacy.[19]

3. Methodologies for biocompatibility assessment

Assessing the biocompatibility of nanomaterials involves a multidisciplinary framework, incorporating laboratory assays, animal studies, computational tools, and regulatory evaluation. This integrated approach is essential to understand the complex interactions between nanomaterials and biological systems, ensuring both safety and efficacy for clinical translation. As nano–bio interactions vary depending on material properties and intended application, using a combination of assessment methods helps to identify and mitigate potential risks early in the development process.

3.1. *In vitro* methods

In vitro techniques are typically the first step in evaluating the biological compatibility of nanomaterials. These cell-based assays offer a controlled environment to investigate how nanoparticles influence cellular health, behavior, and morphology. Standard protocols include MTT and resazurin reduction assays, which assess metabolic activity, along with tests for membrane disruption, oxidative stress, and programmed cell death.[19]

For example, Siller *et al.*[20] introduced a real-time live-cell imaging system that continuously monitors the cytotoxicity and morphology of cells in response to 3D-printed biomaterials. This approach enables high-throughput analysis with temporal resolution. Similarly, Wang *et al.*[21] explored the biosynthesis of zinc oxide nanoparticles using plant extracts and evaluated their effect on human osteoblast-like cells. The MTT assay results indicated improved cell proliferation and bone-forming potential.

To better simulate physiological conditions, advanced systems such as 3D cultures and co-culture platforms are increasingly used. These models provide insights into how nanoparticles affect cell signaling, differentiation, and inflammatory pathways in environments that more closely mimic actual tissue architecture. While *in vitro* methods offer speed, scalability, and cost-efficiency, they remain limited in representing the full complexity of a living organism. This limitation highlights the need for complementary *in vivo* evaluations.[19]

3.2. *In vivo* methods

In vivo testing remains a cornerstone of biocompatibility assessment, particularly for assessing systemic distribution, metabolism, excretion, and long-term toxicity. Animal models—especially rodents—enable comprehensive monitoring of biological responses at the organismal level, including immune responses, hematological changes, and potential organ-specific adverse effects.[22]

A practical example involves the implantation of CaO and CaP nanocomposite scaffolds in rat bone defects. Our ongoing *in vivo* studies demonstrated not only effective tissue regeneration but also favorable immune modulation at the site of implantation. Histopathological analysis, a key component of *in vivo* assessments, helped detect subtle tissue-level reactions such as fibrosis and inflammation. Kyriakides *et al.* further highlighted the value of *in vivo* testing in revealing immunological changes such as cytokine production and complement activation, offering critical insights into nanomaterial-host interactions.[23]

Despite their utility, *in vivo* models face limitations due to ethical concerns, regulatory scrutiny, and species-to-species differences, which complicate the extrapolation of animal data to human contexts. To address these challenges, alternative platforms—such as organ-on-chip devices and *ex vivo* perfusion systems—are being explored as more ethically sound and potentially more predictive options.[22]

3.3. Computational models

Computational modeling provides a predictive layer to biocompatibility evaluation using simulations and data-driven algorithms to estimate biological interactions. Molecular dynamics simulations, for example, allow scientists to explore how nanoparticles interact with cellular membranes or proteins at the atomic level, helping to anticipate toxic effects before physical experimentation.[24]

Cao *et al.*[25] demonstrated the utility of computational tools such as nano-quantitative structure–activity relationship models to estimate the toxicity of metal oxide nanoparticles. By analyzing properties such as surface

charge, energy band gaps, and hydration tendencies, they predicted biological outcomes with high reliability, thereby streamlining the screening process. Although these models are powerful, they rely heavily on the quality and diversity of the datasets used for training. Inconsistencies in data reporting and the lack of standardized descriptors can limit their predictive accuracy. As such, computational results are best viewed as complementary to experimental methods, with ongoing improvements necessary to achieve broader regulatory acceptance.[24,25]

3.4. Regulatory standards

The regulatory landscape for nanomaterials is shaped by the guidelines issued by leading authorities, including the FDA, EMA, the International Organization for Standardization (ISO), and the Organization for Economic Co-operation and Development (OECD). These bodies define the protocols and criteria that nanomaterials must meet before clinical application, with emphasis placed on safety, stability, pharmacokinetics, and immune compatibility.[26]

One of the earliest success stories is the approval of Doxil®, a liposomal formulation of doxorubicin, which underwent comprehensive biocompatibility testing for sterility, blood compatibility, and immune responses.[4] However, as nanomedicine continues to evolve rapidly, current regulatory frameworks often struggle to keep pace. The lack of standardized global guidelines poses challenges for developers seeking international approval and commercialization.

In response, regulatory bodies are moving toward greater harmonization, promoting validated *in vitro* and computational models as part of a robust evaluation pipeline. This push not only ensures safety but also facilitates the adoption of innovative technologies.[27]

3.5. Comparative metrics and evaluation criteria

Given the diverse methodologies employed in biocompatibility assessment, the establishment of standardized metrics is essential to ensure reproducibility and facilitate cross-study comparisons. Common evaluation parameters include cytotoxicity thresholds, quantification of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α), cellular uptake rates, tissue biodistribution profiles, and histopathological scoring.

Efforts to integrate these variables into unified frameworks have led to the development of integrated testing strategies, which synthesize data from *in vitro*, *in vivo*, and *in silico* methods into a single evaluative framework. One example is the work by Schloemer *et al*.,[28] who used quantum-level modeling alongside biological tests to assess light-activated nano-upconversion systems, thereby demonstrating a comprehensive route from material design to functional testing. This integration of disciplines improves both predictive accuracy and translational potential. As noted by Seoane-Viaño *et al*.,[29] the successful implementation of 3D-printed nanomedicines hinges not only on their design but also on thorough biocompatibility assessment and regulatory alignment.

4. Scientific challenges in biocompatibility

The integration of nanomaterials into biomedical applications continues to drive innovation in diagnostics, therapeutics, and tissue engineering. However, their clinical translation remains impeded by unresolved challenges surrounding biocompatibility. These include immunological risks, long-term safety concerns, and regulatory uncertainties. This section examines key scientific barriers related to nanotoxicology, immune response, material degradation, and global safety standards.

4.1. Toxicity and immune response

A central challenge in nanomedicine is the potential toxicity and immunogenicity of nanomaterials. Their high surface area and physicochemical reactivity can lead to unintended biological interactions. For instance, nanoparticles may induce oxidative stress, disrupt cell membranes, or trigger inflammatory cytokine release.[3] Surface charge and hydrophobicity strongly influence these outcomes. For example, positively charged particles often facilitate enhanced cellular uptake but are also linked to increased membrane disruption and inflammation.[3]

Furthermore, the adsorption of proteins onto the nanoparticle surface—the "protein corona" effect—alters their biological identity and can lead to immune misrecognition. This dynamic interaction may affect circulation time, biodistribution, and therapeutic efficacy. Importantly, even formulations previously considered inert may provoke immune responses when administered *in vivo*, emphasizing the need for rigorous pre-clinical immunotoxicity testing.[3]

4.2. Long-term stability and degradation

The long-term fate of nanomaterials in the body is a growing concern, especially when they exhibit poor biodegradability. Inorganic nanoparticles, such as those used for imaging and targeted drug delivery, may lack efficient metabolic or excretory pathways. This can result in their accumulation in organs involved in clearance, such as the liver, spleen, and kidneys, potentially causing chronic toxicity over time.[4,5] For example, gold and iron oxide nanoparticles exceeding 50 nm often localize in

the reticuloendothelial system (RES), where they resist renal filtration and remain for prolonged durations. This sequestration may lead to oxidative damage, inflammation, or organ dysfunction.[5] To address these issues, various strategies—such as PEGylation, encapsulation, or size reduction below 10 nm—have been developed to enhance clearance and mitigate RES uptake.[5]

In contrast, biodegradable polymers such as polylactic acid (PLA) and polycaprolactone (PCL) degrade into biocompatible byproducts and offer greater safety for long-term use. Yet, achieving consistent degradation rates across various physiological environments remains challenging.[30] Tailoring polymer composition and nanostructure is essential to balance therapeutic performance with predictable *in vivo* clearance.

4.3. Regulatory and safety concerns

Regulatory pathways for nanomaterials often lag behind the pace of technological advancement. Existing frameworks—originally designed for bulk materials—fall short in addressing the unique risks posed by nanomaterials, particularly those related to long-term biodistribution, individual variability in physiological responses, and complex immunological interactions.[4] Agencies such as the FDA, EMA, and ISO have issued updated guidelines, but significant gaps remain in standardized testing protocols for nanomedicine.

Developers are increasingly expected to adopt a safety-by-design approach, including generating comprehensive toxicology profiles and conducting lifecycle assessments during early-stage development. The need for harmonized global standards is especially urgent for nanotherapeutics intended for systemic or repeat-dose administration.[4,29] Bridging this regulatory gap requires multidisciplinary collaboration and proactive engagement with policymakers.

5. Strategies for targeted improvement

To improve the clinical performance of nanomaterials, targeted design strategies must be integrated early in the development process. These strategies not only reduce adverse biological responses but also enhance the safety, specificity, and real-world usability of nanomedical tools. While many of these methods have proven successful in controlled laboratory environments, translating them into practical applications remains the true benchmark of success. This section outlines four primary approaches: surface engineering, biodegradable material selection, targeted delivery, and hybrid designs. Each strategy offers a framework for enhancing biocompatibility and functionality. These concepts are further illustrated through the case of the CaO–CaP binary system in Section 6.

5.1. Surface modifications

Surface engineering plays a pivotal role in enhancing nanomaterial biocompatibility. Among the most widely adopted techniques is PEGylation, which involves attaching PEG chains to the nanoparticle surface to minimize immune detection and extend systemic circulation.[3,10,18] This "stealth" property allows therapeutic particles to circulate longer, increasing the likelihood of target site delivery.

Modifying surface properties such as charge, hydrophilicity, and the presence of targeting ligands also influences how nanomaterials interact with biological components such as membranes, proteins, and cells.[11,18] These modifications help minimize protein corona formation, reduce immunogenicity, and promote selective uptake by desired cell types. As will be explored later with the CaO–CaP system, such tailoring becomes particularly important when adapting materials to specific physiological environments.

Despite its advantages, PEGylation has limitations. Repeated administration can result in accelerated clearance, and the immune system may develop anti-PEG antibodies. These concerns have prompted ongoing optimization efforts focusing on PEG chain density, molecular weight, and branching to balance stealth effects with immunological safety.[31]

Zwitterionic coatings present an alternative approach. Composed of molecules carrying both positive and negative charges—such as sulfobetaines and phosphorylcholines—these coatings form a densely hydrated shell that resists protein adsorption. Debayle *et al.*[32] demonstrated that zwitterionic polymers could completely inhibit corona formation, outperforming PEGylation in maintaining nanoparticle stealth and physiological stability.

Another innovative approach leverages biomimicry. For example, by incorporating CD47 peptides onto nanoparticle surfaces, researchers can mimic natural "do-not-eat-me" signals. These peptides engage the signal regulatory protein alpha receptor on macrophages, suppressing phagocytosis and allowing for prolonged circulation. However, caution is needed, as excessive immune suppression and potential blood-related toxicities remain concerns in clinical settings.[33]

Another emerging strategy involves cloaking nanoparticles with cellular membranes—harvested from red blood cells, leukocytes, platelets, or cancer cells—to form biomimetic coatings. These membrane-derived surfaces provide immune camouflaging and can even enable tissue-specific homing due to retained surface proteins and antigens. Such carriers have demonstrated promise in drug delivery, detoxification, and vaccine delivery,

offering enhanced biocompatibility and functionality.[34] Collectively, these surface modification techniques form a robust toolkit for tailoring nanomaterials to navigate immune challenges, improving both their safety and therapeutic potential in clinical scenarios.

5.2. Biodegradable nanomaterials

Biodegradable polymers such as PLA and PCL offer significant advantages in terms of biological compatibility and safety.[14] These materials naturally break down into non-toxic byproducts, lowering the risk of prolonged organ retention or chronic inflammatory responses.

Critically, their degradation profiles can be finely tuned to match specific therapeutic timelines, allowing for sustained or controlled drug release. This is particularly beneficial in applications such as tissue regeneration and chronic disease management, where timing and clearance are vital.[10,14] The CaO–CaP system highlights the importance of selecting biodegradable components when developing clinically translatable materials.

5.3. Targeted delivery

Precision targeting has become a cornerstone of effective nanotherapy. By functionalizing nanocarriers with ligands that bind to disease-specific receptors—such as those overexpressed in tumors—therapeutic agents can be concentrated at the site of interest while sparing healthy tissue.[10] In addition, stimuli-responsive platforms that react to environmental cues such as pH, temperature, or enzymatic activity have enabled on-demand drug release tailored to pathological conditions. These adaptive systems reduce off-target effects and enhance therapeutic efficacy, especially in diseases such as cancer, where site-specific intervention is essential.[10,29]

For example, in colorectal cancer treatment, multifunctional nanomaterials have been employed for integrated diagnosis, therapy, and monitoring. These platforms are engineered to selectively accumulate at tumor sites, improving therapeutic precision while reducing collateral damage. Such targeted approaches underscore the importance of using biocompatible materials—such as calcium-based carriers—to meet the safety demands of clinical deployment.[35]

5.4. Hybrid systems

Hybrid nanostructures, which combine organic and inorganic components, offer the best of both functional versatility and biocompatibility. Metallic cores—such as gold or calcium compounds—can be encapsulated within biodegradable or bioactive shells, creating platforms that are both structurally robust and biologically safer.[3,15]

These multifunctional systems are especially well-suited for theranostic applications, where imaging, diagnosis, and treatment are integrated into a single material. However, the complexity of hybrid materials necessitates precise control over properties such as surface chemistry, charge distribution, and degradation kinetics to ensure they are biologically harmonious.[3,18] The CaO–CaP binary system discussed in the next section exemplifies how such hybrid materials can be engineered for enhanced compatibility and targeted performance in a biomedical setting.

6. Case-based empirical analysis: The CaO-CaP binary system

The successful clinical translation of nanomaterials relies on their ability to balance functional performance with biocompatibility. As discussed in the previous section, targeted strategies such as surface modification, biodegradability, and composite design are foundational. The CaO–CaP binary system provides a compelling case study in this regard, illustrating both the promise and the challenges of deploying biocompatible nanomaterials in regenerative medicine. Based on empirical work and laboratory experience, this section explores the material's key features, *in vitro* and *in vivo* findings, clinical challenges, and future strategies in the context of bone tissue engineering.

6.1. Material properties and molecular mechanisms

The binary system comprising CaO and CaP leverages the individual strengths of both materials. CaO is known for its high alkalinity and rapid dissolution, facilitating a bioactive environment that promotes mineralization and bone induction. CaP, being structurally similar to the mineral phase of the bone, contributes to long-term mechanical stability and degradation. As shown in Figure 1, the structural and functional attributes of the CaO–CaP nanomaterial are closely linked to its molecular interactions and phase composition.

6.2. Functional synergy of CaO–CaP composites

The functional benefits of CaO and CaP composites stem from their complementary behavior in biological environments. CaO provides an early burst of calcium ions, initiating mineralization, while CaP maintains structural support for long-term cell attachment and tissue integration. This dual-phase release promotes hydroxyapatite formation and enhances interactions between the scaffold and native tissue—key goals in osteogenic material design.[2,36,37]

Research also highlights that adding trace elements such as magnesium to these systems can further

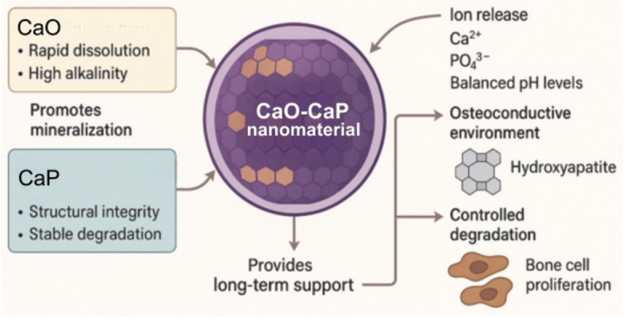

Figure 1. Diagram illustrating the material properties and molecular mechanisms of the CaO–CaP binary system. Image created by the author. Abbreviations: CaO: Calcium oxide; CaP: Calcium phosphate.

elevate performance. For instance, Qi *et al.*[38] found that incorporating magnesium into bioceramics significantly improved cell response and vascular development, both essential for bone healing. This supports the growing view that finely tuned ion release—including calcium, phosphate, and magnesium ions—helps replicate the bone's natural healing environment and bolsters the rationale for materials such as CaO–CaP in regenerative design.

Another valuable trait of CaO–CaP systems is their inherent antimicrobial potential, increasingly important for reducing post-surgical infection risks. The basic nature of CaO elevates the surrounding pH upon dissolution, disrupting bacterial membranes, denaturing proteins, and impairing enzyme function, ultimately killing harmful microbes.[39]

This effect has been demonstrated using CaO and calcium peroxide (CaO_2) nanoparticles. For example, Yu *et al.*[40] reported that polyacrylic acid-coated CaO_2 nanoparticles not only supported wound healing but also combated bacterial growth through the combined release of calcium ions and reactive oxygen species. Similarly, Levingstone *et al.*[41] found that CaP-based scaffolds not only promoted bone regeneration but also resisted bacterial colonization.

Although specific research on CaO–CaP systems remains nascent, our team at Science and Technological Enhanced Laboratory for Advanced Learning and Research (S.T.E.L.L.A.R) Laboratories is actively evaluating their antibacterial potential—especially against *Staphylococcus aureus*, a frequent cause of orthopedic infections. Initial *in vitro* results are promising, showing less bacterial adhesion and better scaffold sterility. This points to the dual functionality of CaO–CaP materials: supporting tissue repair while simultaneously offering protection against infection.

6.3. Biocompatibility studies (*in vitro* and *in vivo*)

A series of *in vitro* and *in vivo* evaluations confirms that CaO–CaP nanomaterials exhibit excellent biocompatibility. In cell culture studies using osteoblasts, these scaffolds supported healthy cell growth, attachment, and differentiation, with minimal toxicity. The controlled release of calcium and phosphate ions also encouraged robust matrix mineralization.[42]

These findings were backed by *in vivo* experiments in rodent models, where CaO–CaP scaffolds were implanted into critical-size bone defects. Tissue analysis showed strong new bone formation, seamless integration with host tissue, and tight bonding at the interface. Compared to conventional grafts, CaO–CaP composites accelerated healing and enhanced defect closure, reinforcing their suitability for clinical use.[43,44]

6.4. Clinical bottlenecks and inflammation response

Despite their clear advantages, CaO–CaP scaffolds face some hurdles in clinical translation, particularly regarding inflammation caused by rapid degradation. The high dissolution rate of CaO can cause spikes in calcium ion levels and increase local pH, which may irritate surrounding tissues and trigger immune responses.

In our own pre-clinical tests, areas where the scaffold degraded quickly showed signs of local inflammation and mild immune cell activation—likely a response to sudden changes in ion concentration and pH. To address this, we applied biodegradable polymer coatings such as poly(lactic-co-glycolic acid) (PLGA) and PEG to the scaffold surface. These coatings help regulate the ion release profile, minimize pH shifts, and reduce inflammatory responses. Our findings align with prior research showing that surface modification of CaO-based materials can delay degradation and mitigate adverse reactions while maintaining regenerative function.[45,46] As illustrated in Figure 2, PLGA-coated CaO–CaP scaffolds appear to activate a more controlled immune response, particularly in relation to cytokine release.

Further analysis of the inflammatory microenvironment revealed that early-stage responses (0–7 days post-implantation) were characterized by elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1 beta. These mediators contribute to tissue swelling, leukocyte recruitment, and vascular changes. In the subacute phase, the inflammatory signal begins to subside, making way for reparative processes. A critical aspect of recovery is the phenotypic transition of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This shift is associated with increased secretion of anti-inflammatory cytokines like IL-10, which downregulate the immune response and promote tissue regeneration. Modulating this immune balance through material design and surface treatment is

key to minimizing long-term tissue damage and enhancing scaffold integration. As shown in Figures 3 and 4, PLGA modification alters the functional behavior of CaO–CaP nanomaterials, while subsequent scaffold degradation triggers a time-dependent inflammatory response marked by shifts in cytokine expression.

6.5. Emerging strategies for clinical translation

Translating CaO–CaP-based systems into clinical practice requires more than just demonstrating biological compatibility; it also demands innovations in material design, delivery mechanisms, and scalable fabrication methods. One notable advancement is the inclusion of osteogenic growth factors such as bone morphogenetic proteins (BMPs) and vascular endothelial growth factor (VEGF), which play key roles in promoting both osteoblast differentiation and vascularization of the implant site.[47]

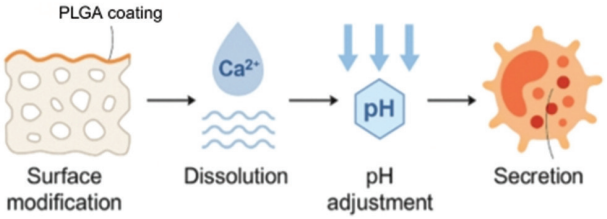

Figure 2. A series of reactions triggered by the surface modification of CaO–CaP. Adding PLGA coating changes the pH and affects the secretion of pro-inflammatory cytokines. Image created by the author.
Abbreviations: CaO: Calcium oxide; CaP: Calcium phosphate; PLGA: Poly(lactic-co-glycolic acid).

Beyond biochemical cues, gene-activated scaffolds have emerged as a powerful tool, enabling the localized delivery of therapeutic DNA or RNA to stimulate regenerative pathways directly within the defect area. These platforms are gaining attention for their potential in treating complex and non-healing bone injuries, where conventional scaffolds often fall short.

A transformative shift is also underway with the adoption of 3D printing technologies, allowing the fabrication of patient-specific scaffolds with precise anatomical conformity. This level of personalization improves not only implant integration and mechanical performance but also healing outcomes. As part of our ongoing investigations, CaO–CaP scaffolds are being combined with bioactive molecules and additive manufacturing techniques to boost regenerative efficiency while enhancing clinical adaptability.[48]

In parallel, ion-doped biodegradable systems—particularly those incorporating magnesium ions—are showing great promise for bone repair. A recent study by Tao *et al.*[49] described the successful development of porous PLA-based microspheres doped with magnesium, which exhibited enhanced biocompatibility, improved osteogenic potential, and controlled biodegradation. These findings align with our own data, underscoring the importance of controlled ionic release and scaffold adaptability in the clinical success of CaO–CaP materials.

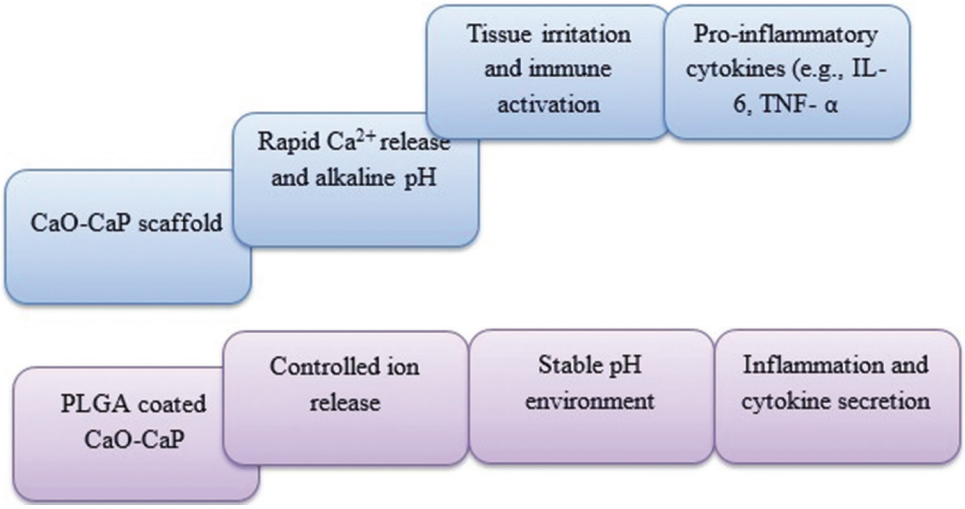

Figure 3. The effect of PLGA modification on the behavior of CaO–CaP nanomaterials. The uncoated pathway results in rapid calcium ion release and pH elevation, which may lead to tissue irritation and upregulation of inflammatory cytokines such as IL-6 and TNF-α. In contrast, the PLGA-coated pathway moderates ion release and stabilizes pH, thereby reducing inflammation and improving biocompatibility. Image created by the author.
Abbreviations: CaO: Calcium oxide; CaP: Calcium phosphate; IL-6: Interleukin-6; PLGA: Poly(lactic-co-glycolic acid); TNF-α: Tumor necrosis factor alpha.

Magnesium, in particular, appears to play a supportive role in modulating osteoblast responses and stimulating new bone matrix deposition. Its inclusion reflects a broader trend toward ion-enhanced strategies for fine-tuning scaffold performance. As highlighted in Tables 1 and 2, nanomaterials used in these systems vary widely in their biocompatibility and regenerative potential, emphasizing the importance of careful material selection and design optimization for translational success.

In pursuit of improved therapeutic outcomes, scaffold systems are increasingly being functionalized with biologically active molecules. Among the most promising are BMP-2 and VEGF, which are well known for promoting osteogenesis and angiogenesis, respectively.[46] These signaling molecules are often embedded within biodegradable carriers—such as PLGA microparticles—which facilitate controlled, localized release while preserving bioactivity over time. In parallel, gene delivery strategies have gained significant traction. For example, plasmid DNA encoding VEGF or BMP-2 has been immobilized within CaP-based scaffolds, forming gene-activated matrices that stimulate site-specific expression of regenerative signals. Although these approaches have demonstrated considerable potential, challenges remain—particularly with maintaining vector stability during scaffold fabrication, ensuring effective gene transfection, and avoiding unintended off-target effects.

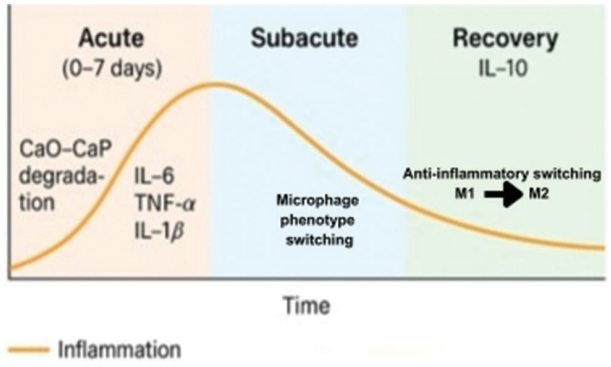

Figure 4. Inflammation and cytokine dynamics following CaO–CaP scaffold degradation. Image created by the author.
Abbreviations: CaO: Calcium oxide; CaP: Calcium phosphate; IL: Interleukin; PLGA: Poly(lactic-co-glycolic acid); TNF-α: Tumor necrosis factor alpha.

Additive manufacturing is also transforming the landscape of scaffold development. In 2022, patient-specific CaP-based craniofacial scaffolds achieved a clinical success rate of over 95%, demonstrating both feasibility and therapeutic promise.[47] Technologies such as fused deposition modeling and stereolithography are now commonly employed to produce custom-fit scaffolds tailored to a patient's anatomical features. These advanced fabrication methods offer superior control over porosity, mechanical strength, and spatial distribution of bioactive

Table 1. Comparative biocompatibility parameters of selected nanomaterials

Nanomaterial	Hemolysis rate	Complement activation	Circulation half-life	Cytotoxicity level	Remarks
AuNPs	Low (<5%)	Moderate (dose-dependent)	Moderate (~24 h)	Low	Excellent imaging agent; surface-dependent immunogenicity
SiNPs	Moderate (10–15%)	High (due to surface silanol)	Short (<12 h)	Moderate	High surface reactivity; surface passivation improves compatibility
LNPs	Very low (<2%)	Minimal	Long (up to several days)	Low	Used in mRNA vaccines; highly biocompatible
CaP	Low (<5%)	Minimal	Biodegradable	Very low	Excellent for bone integration and mineralization
CaO	High (>15%) uncoated	Moderate to high	Fast-degrading	High (alkalinity-induced)	Requires coating to reduce cytotoxicity (e.g., PLGA, PEG)
PLGA-coated CaO–CaP	Low (<3%)	Low	Controlled (tailored by design)	Very low	Reduced inflammation; enhanced osteointegration
CNTs	Variable (type-dependent)	High (can activate immune cells)	Long (>48 h)	Moderate to high	Requires functionalization to improve compatibility
QDs	High (>20%)	High	Long (up to several days)	High	Toxic elements (e.g., Cd); limited clinical use without shielding strategies

Abbreviations: AuNPs: Gold nanoparticles; CaO: Calcium oxide; CaP: Calcium phosphate; Cd: Cadmium; CNTs: Carbon nanotubes; LNPs: Lipid nanoparticles; PEG: Polyethylene glycol; PLGA: Poly (lactic-co-glycolic acid); QDs: Quantum dots; SiNPs: Silica nanoparticles.

Table 2. Comparative biocompatibility metrics of selected nanomaterials

Nanomaterial	Hemolysis rate (%)	Complement activation (C3a level)	Circulation half-life (hours)	Inflammatory response (IL-6/IL-1β)
CaO–CaP	4.5	Moderate	6–8	Low (with coating)
AuNPs	2.1	Low	12–24	Minimal
SiNPs	7.8	High	2–5	Elevated
PLGA nanoparticles	3.3	Low	8–12	Minimal
LNPs	1.2	Very low	24+	Negligible

Abbreviations: AuNPs: Gold nanoparticles; CaO: Calcium oxide; CaP: Calcium phosphate; IL: Interleukin; LNPs: Lipid nanoparticles; PLGA: Poly (lactic-co-glycolic acid); SiNPs: Silica nanoparticles.

components—design features that are challenging to replicate using traditional scaffold manufacturing. As shown in Figure 5, successful bone tissue engineering relies on synergistic integration of scaffold architecture, signaling cues, and responsive biomaterials to drive effective regeneration.

The CaO–CaP binary system exemplifies the delicate balance between biological reactivity and structural stability that defines successful nanomaterial applications in medicine. While its osteogenic potential and favorable integration are well-established, fine-tuning degradation rates and immune compatibility remains crucial. As ongoing innovations in surface coatings, biofunctionalization, and manufacturing techniques evolve, CaO–CaP composites stand poised for greater clinical relevance, offering a tangible example of how theoretical biocompatibility strategies can translate into real-world biomedical impact.

7. Emerging trends and future directions in nanomedicine

Nanomedicine is advancing rapidly, propelled by technological convergence and multidisciplinary collaboration. Next-generation nanomaterials—such as quantum dots, carbon-based structures, and multifunctional hybrid platforms—offer superior optical, electrical, and mechanical properties while maintaining biocompatibility. These attributes make them highly promising for precision drug delivery, targeted diagnostics, and image-guided therapy.[50,51]

Clinical applications of nanotechnology are expanding across therapeutic domains. Multifunctional nanoplatforms have shown significant promise in managing colorectal cancer, where they facilitate early detection, targeted drug delivery, and image-guided interventions, offering a synergistic approach to both diagnosis and treatment.[52] Likewise, surface-engineered nanomaterials have proven

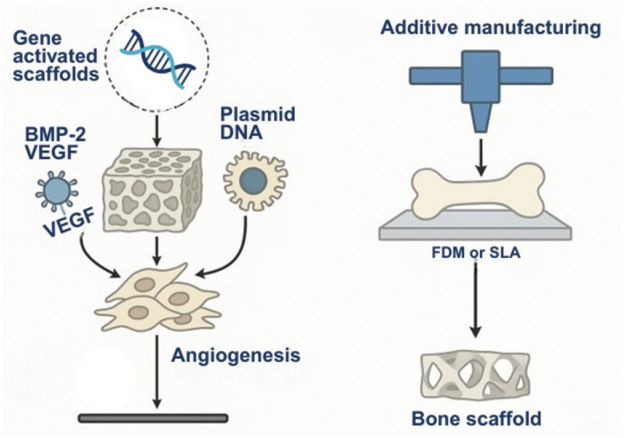

Figure 5. Synergistic strategies of scaffold architecture, signaling cues, and responsive biomaterials in bone tissue engineering. Image created by the author.
Abbreviations: BMP: Bone morphogenetic protein; FDM: Fused deposition modeling; SLA: Stereolithography; IL-6: Interleukin-6; VEGF: Vascular endothelial growth factor.

effective in enhancing immune compatibility and targeted antiviral drug delivery, particularly for managing viral infections.[19]

Addressing the challenges of scalability and reproducibility in nanomaterial production is critical for clinical translation. To this end, spray-drying methods have replaced traditional solvent evaporation techniques, significantly improving nanoparticle uniformity and yield.[51] Automated microfluidic platforms are also being developed to enable continuous nanoparticle synthesis with real-time process monitoring, minimizing batch-to-batch variability. At S.T.E.L.L.A.R. Labs, we are currently integrating AI-guided microfluidic synthesis and in-line spectroscopic monitoring to standardize particle morphology, size, and surface functionality—key parameters for regulatory compliance and clinical-grade manufacturing.

AI and machine learning are also transforming the design and validation of nanomaterials. AI-enabled modeling allows rapid optimization of physicochemical properties while predicting biocompatibility with high accuracy, thereby accelerating preclinical development and reducing experimental costs.[26,53]

In parallel, the field of personalized medicine is evolving, with nanotechnology enabling tailored treatment strategies based on individual genetic and physiological profiles. A landmark application is the use of lipid nanoparticles (LNPs) in delivering mRNA vaccines, as seen during the COVID-19 pandemic. LNPs have proven effective in protecting and transporting nucleic acids to target cells while minimizing systemic toxicity. This platform now

serves as a blueprint for future applications in oncology, genetic disorders, and rare diseases.[54] Nanocarriers are also being designed to function as both immune modulators and delivery systems, making them invaluable tools in managing cancers and infectious diseases.[19,34]

Despite these advancements, regulatory and translational barriers persist. Nanomaterials often evolve faster than existing regulatory frameworks can accommodate. In response, global entities such as the OECD, along with industry–academic consortia, have intensified efforts to harmonize safety assessments, standardize testing protocols, and streamline clinical translation. Progress in this area, fueled by international co-operation and public–private partnerships, is gradually easing these hurdles.[55,56]

As the field moves forward, the future of nanomedicine lies in integrative approaches: Combining smart biomaterials, AI-driven modeling, regulatory foresight, and personalized care. This holistic vision not only enhances the scientific rigor of nanomedicine but also paves the way for meaningful clinical impact in global healthcare.

8. Conclusion

Biocompatibility remains a foundational requirement for the effective use of nanomaterials in medical fields such as drug delivery, diagnostic imaging, tissue regeneration, and antimicrobial therapy. Key parameters—including surface chemistry, particle size, and material composition—critically determine biological responses, as illustrated by the promising performance of the CaO–CaP binary system in bone tissue engineering. The complementary properties of CaO and CaP, when combined with surface modifications, demonstrate strong potential for clinical osteointegration.

As the field progresses, innovations in materials science and cross-disciplinary collaboration are expected to overcome persistent challenges related to toxicity, immune compatibility, and large-scale application. The integration of computational tools and AI will further streamline the design and prediction of safer, high-performance nanomaterials. Although regulatory complexities continue to pose barriers, coordinated efforts among scientists, clinicians, and regulatory bodies will be vital in driving successful clinical translation. By embedding biocompatibility at the core of nanomaterial design and actively addressing translational gaps, nanomedicine is poised to reshape modern healthcare and unlock solutions once beyond reach.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Visualization: Marvellous Eyube
Writing–original draft: All authors
Writing–review & editing: Marvellous Eyube

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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