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ION-RELEASING INORGANIC PHASES IN OSTEOCHONDRAL SCAFFOLDS AND THEIR REGION-SPECIFIC REGENERATIVE EFFECTS

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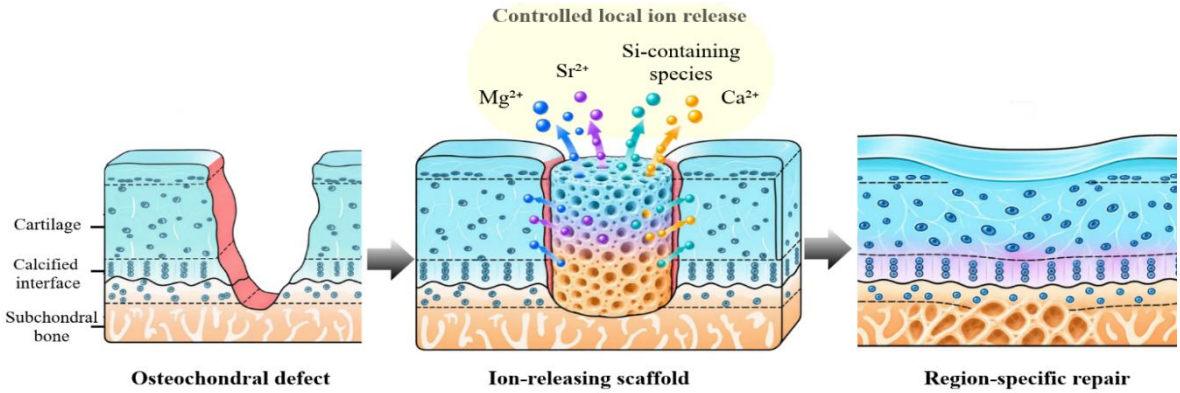
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ABSTRACT

Osteochondral defects affect tissues with distinct matrix compositions, cellular environments, mechanical properties, and healing capacities. Scaffolds intended to repair these defects must therefore support cartilage formation, maintain a functional transition across the calcified interface, and promote subchondral bone repair. Inorganic phases can provide mineral and structural cues while releasing ions that influence local cell behaviour. However, their effects depend on the phase's composition and location, the amount and timing of ion release, and the surrounding scaffold architecture. This review examines ion-releasing inorganic phases used in osteochondral scaffolds, including bioactive glasses, calcium phosphates, ion-substituted apatites, and silicate-based ceramics. The literature is considered across the cartilage, calcified-interface, and subchondral-bone regions, with attention to ion-release characteristics and reported biological outcomes. The review also discusses multifunctional designs that combine mineral cues with features such as controlled release, immunomodulation, or external stimulation. Although preclinical studies report promising region-specific responses, comparisons remain difficult because release-testing methods, experimental controls, outcome measures, and follow-up periods vary. Future studies should report phase location and release profiles alongside region-specific biological and mechanical outcomes. This may help clarify when ion-releasing designs support integrated osteochondral repair.

KEYWORDS: Osteochondral scaffold; ion-releasing biomaterials; bioactive glass; calcium phosphate; hydroxyapatite; controlled ion release; cartilage–bone interface

Graphical Abstract



I. INTRODUCTION

The osteochondral unit comprises articular cartilage, calcified cartilage, and subchondral bone. These regions differ in cellularity, vascularity, extracellular-matrix composition, mineral content, and mechanical properties, yet function together to distribute joint loads. A defect that crosses these regions therefore presents a combined biological and mechanical challenge: cartilage has limited intrinsic repair capacity, while the interface must remain integrated with the underlying bone and withstand repeated loading. Reconstructing the interface is especially difficult because poor bonding or mismatched mechanical properties can contribute to stress concentration and tissue delamination[1]. Scaffolds for osteochondral repair are designed to support cartilage formation, subchondral-

bone regeneration, and integration between them. Inorganic phases can contribute to these functions by providing mineral components, mechanical support, or soluble ions that influence cell behaviour. However, the biological response depends on the ion, its concentration and exposure over time, and the tissue region receiving it. Ion-releasing biomaterials have been investigated for cartilage repair using ions including silicon, lithium, magnesium, strontium, copper, zinc, manganese, and molybdenum; reviews discuss both stimulatory and protective actions, as well as potential interactions between co-released ions[2,3].

The field already includes broad reviews of ion-based cartilage repair and bioactive glasses in osteochondral tissue engineering[2–4]. Accordingly, the present review focuses on a narrower, complementary question: how the location and release of inorganic phases relate to outcomes in cartilage, calcified cartilage, and subchondral bone. This focus also requires distinguishing studies that measure ion release and region-specific effects from studies that report outcomes for a composite scaffold containing an ion-bearing material. The distinction matters because scaffold architecture, mechanical properties, growth factors, and physical stimulation can act alongside ion release. Experimental studies illustrate the range of designs. Molybdenum-containing bioactive glass-ceramic scaffolds have been evaluated for ion release and osteochondral repair in rabbits[5]. Bioactive glass has also been compartmentalized within the bone-facing layer of a biphasic hydrogel and tested in a rabbit defect model[6], while glass-containing fibrous membranes have been designed to support calcified-cartilage repair at the interface[7]. Other systems spatially introduce Mg^{2+} and Cu^{2+} into different hydrogel layers[8], combine a magnesium-phosphate phase with gellan/alginate hydrogels[9], or establish an Mg^{2+} gradient across a bilayer scaffold[10]. Together, these studies show why ion identity alone is an incomplete basis for comparison: the source material, spatial placement, release profile, and accompanying scaffold cues also matter.

More recent approaches include hierarchically structured scaffolds releasing Sr, silicon-containing species, and calcium[11], a whitlockite-containing graft designed to promote calcified-cartilage formation[12], and a porous zinc scaffold paired with a chondroitin-sulfate hydrogel and tested in a porcine osteochondral model[13]. Chemical cues are also being combined with physical stimulation, as in a piezoelectric $SrSiO_3$ scaffold activated by low-intensity pulsed ultrasound[14], and with electrical and structural cues in a biodegradable osteochondral biobattery[15]. A 2026 biphasic design combines a bioactive-glass/nanosilicate bone layer with an IGF-1-containing cartilage layer[16]. These examples broaden the design space, but their multiple components make it important to distinguish ion-associated findings from the overall performance of the hybrid construct. This review therefore examines ion-releasing inorganic phases in osteochondral scaffolds by considering material composition and placement, reported release measurements, region-specific biological outcomes, and the evidence model used. It compares in-vitro studies, animal defect studies, and emerging multifunctional systems, while noting where other cues limit attribution of an outcome to ions alone. The aim is to identify design principles and evidence gaps that can guide more interpretable evaluation of ion-releasing scaffolds for integrated osteochondral repair. To organise the evidence, this review considers how the location of inorganic phases within a scaffold influences local ion exposure, cellular responses, and outcomes across the cartilage, calcified interface, and subchondral bone regions (Figure 1).

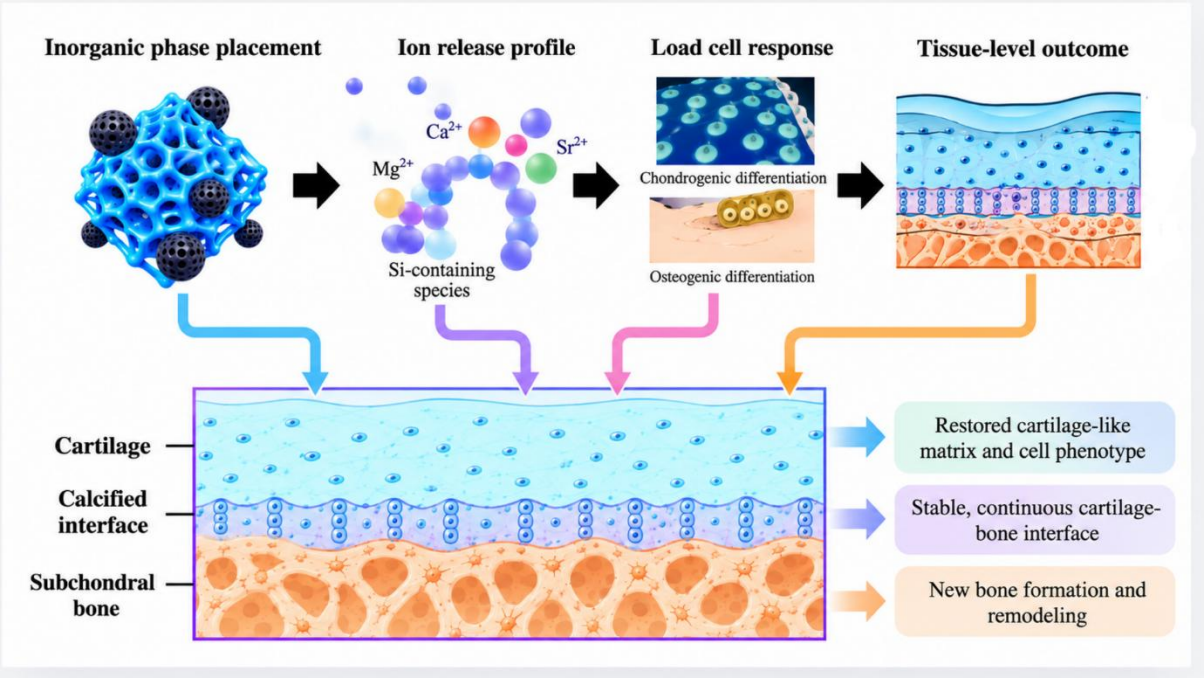


Figure 1. Conceptual framework linking inorganic-phase placement to region-specific responses in ion-releasing osteochondral scaffolds

2. Biological and Functional Requirements of the Osteochondral Unit

The osteochondral unit is a connected tissue system comprising articular cartilage, calcified cartilage and subchondral bone. These regions differ in composition, cell type, vascularity and mechanical behaviour, yet work together to transfer joint loads. A scaffold for osteochondral repair therefore needs to support more than bone

formation or cartilage repair alone: it must help restore tissue-specific functions while maintaining a stable connection between regions[1,17]. The interface is often described as a gradient, although its structure is more complex than a simple, uniform transition[18,19].

2.1. Articular cartilage

Articular cartilage provides a smooth, low-friction surface and distributes compressive and shear forces during joint movement. Its extracellular matrix is rich in water, proteoglycans and collagen, with a depth-dependent organization that contributes to its mechanical behaviour. Because healthy articular cartilage is avascular and contains relatively few cells, repair strategies must support chondrocyte survival and matrix production while enabling nutrient transport through the developing tissue[1,18]. For a scaffold, this means the cartilage-facing region should provide a hydrated, cell-compatible environment that supports cartilage-like matrix formation. It should also limit unwanted mineralization and hypertrophic differentiation in this region, since these changes could compromise the character of the regenerated cartilage[12]. These aims need to be evaluated alongside mechanical performance: a scaffold may encourage matrix deposition in vitro but still fail to reproduce the behaviour of load-bearing cartilage[20].

2.2. Subchondral bone

Subchondral bone supports the overlying cartilage and participates in transferring joint loads. Unlike articular cartilage, it is mineralized and vascularized, and its structure includes cortical and trabecular regions[17]. A scaffold's bone-facing region must therefore support bone-cell attachment, osteogenic matrix deposition and integration with surrounding bone. Its architecture should also allow cell and tissue ingrowth, while providing enough mechanical support during regeneration. Bone formation must remain spatially appropriate. Vascular and mineralizing processes that benefit the bone region should not extend indiscriminately into the cartilage region, where they could disrupt cartilage-like tissue development[18,20]. Thus, the design challenge is not simply to maximize osteogenesis, but to support it in the intended region while maintaining the different conditions needed above it.

2.3. Calcified cartilage and the interface

Calcified cartilage lies between articular cartilage and subchondral bone. It forms a specialized mineralized interface associated with the tidemark and helps connect tissues with distinct compositions and mechanical properties. Its organization is relevant to scaffold design because a poorly integrated boundary may be vulnerable to separation under repeated loading. The interface should therefore be treated as a functional region, rather than as an incidental join between two scaffold layers. Depending on the design, this may involve a gradual change in composition or structure, an intermediate layer, or a securely bonded boundary. The aim is to support integration and load transfer without allowing bone-like mineralization to spread into the cartilage-forming region. The precise native interface is not a perfectly smooth gradient, so gradient designs should be understood as engineering strategies rather than exact replicas of native anatomy[18–20].

2.4. Requirements for an integrated scaffold

These tissue-specific needs translate into several linked design requirements. The scaffold should maintain distinct cartilage- and bone-supportive environments, provide a mechanically stable connection between them, and degrade at a rate compatible with tissue formation and remodelling. Its pore structure and transport properties should support cell access and nutrient exchange, while its mechanical behaviour should be assessed under conditions relevant to joint loading[18,20]. For ion-releasing inorganic phases, the same principles make where, how much and for how long ions are released important design questions. An ion may have useful effects in one region but different effects in another, depending on local cell populations and tissue context[2–4]. Accordingly, scaffold evaluation should report regional outcomes, such as cartilage matrix formation, bone formation, interface integrity and mechanical function, rather than relying on a single overall measure of repair[17].

3. Ion-Releasing Inorganic Phases in Osteochondral Scaffolds

Magnesium, strontium and silicon are among the ions investigated in osteochondral scaffolds because they may influence cartilage and bone formation. Their effects depend on the inorganic phase, its location within the scaffold, and the amount and timing of ion release. Results from a particular ceramic or scaffold should therefore not be treated as evidence that the ion will have the same effect in every formulation or tissue region[2,3,10,11].

3.1. Magnesium-releasing phases

Magnesium-containing silicates have been investigated for their potential to support both osteogenic and chondrogenic responses. In an in vitro study, Yu et al.[21] incorporated magnesium-substituted wollastonite into hydrogel scaffolds and cultured human deep-zone chondrocytes. The magnesium-containing formulation increased markers associated with chondrocyte matrix production and mineralization; the authors proposed it as a candidate material for regenerating calcified cartilage. This finding is relevant to the osteochondral interface, but the study was conducted in vitro and does not establish that the same response would be appropriate in the non-mineralized cartilage region. Gao et al.[10] subsequently used a magnesium gradient in a hierarchical scaffold combining a hydrogel layer and a porous cryo-gel layer. The design was intended to support cartilage and subchondral bone regeneration within one construct. Together, these studies illustrate two different approaches: adding a magnesium-containing ceramic to a scaffold and distributing magnesium spatially within a layered scaffold. For both, the biological outcome needs to be interpreted in relation to where the ion is released and which region is being targeted.

3.2. Strontium-releasing phases

Strontium-containing scaffolds have been studied to support bone and cartilage repair while also modifying the local immune response. Wang et al.[22] compared strontium-releasing calcium-silicate scaffolds with calcium-silicate

controls. Their study reported changes in macrophage polarization and improved cartilage and subchondral bone regeneration in an animal model with the strontium-containing scaffold. This provides evidence for a possible immunomodulatory contribution, although the reported repair outcomes should be understood within the limits of that specific scaffold and preclinical model. Strontium is also combined with other bioactive ions. For example, strontium-containing strontium-phosphate-silicate scaffolds have been investigated for their effects on cartilage and subchondral bone[23], while a later 3D-printed scaffold incorporating strontium-doped bioactive nano glass released strontium, silicon and calcium ions[11]. These multicomponent systems may offer several biological cues at once, but they make it more difficult to attribute an observed effect to strontium alone. Comparisons with otherwise similar scaffolds that differ only in their strontium content would help clarify its contribution.

3.3. Silicon-releasing phases

Silicate ceramics and bioactive glasses can release silicon alongside other ions, such as calcium. In a rabbit osteochondral-defect model, a silicon-containing calcium-phosphate scaffold promoted cartilage and subchondral bone regeneration compared with a calcium-phosphate scaffold without silicon[24]. The study also reported effects on osteogenic and chondrocyte-associated markers. Because the material was a multicomponent ceramic, however, the findings support the performance of that silicon-containing scaffold rather than proving that silicon alone produced every observed effect. Diatomite has been examined as a more defined silicon source. Deng et al.[25] incorporated diatomite particles into a hierarchical GelMA scaffold and reported sustained silicon-ion release, along with outcomes associated with osteogenic differentiation and chondrocyte maturation. The scaffold also promoted cartilage and subchondral bone regeneration in an animal model. This study adds evidence for silicon-releasing materials, while also highlighting the need to assess scaffold architecture and matrix effects alongside ion release.

3.4. Interpreting the evidence across ion systems

The studies reviewed here use different inorganic phases, polymer matrices, scaffold architectures, cell sources and animal models. They also target different parts of the osteochondral unit: magnesium-containing silicate has been investigated for calcified-cartilage formation, strontium-containing scaffolds for combined cartilage and bone repair, and silicon-releasing phases for dual-lineage regeneration. These outcomes are promising, but they do not by themselves establish which ion or release profile is optimal for a given region. A useful comparison should therefore report the inorganic phase and its spatial placement, the ions measured and their release over time, and outcomes for cartilage, the interface and subchondral bone separately. Where several ions are released, suitable material controls are needed to distinguish the contribution of individual ions from the effects of scaffold structure and other components[10,11,21–25]. Representative ion-releasing inorganic phases, scaffold configurations, experimental models and reported regenerative outcomes are summarized in Table 1.

Table 1. Representative ion-releasing inorganic phases in osteochondral scaffolds and their reported regenerative effects

Study	Inorganic phase and spatial design	Evidence model	Main reported outcomes	Interpretation
Yu et al.[21]	Mg-substituted wollastonite in a hydrogel scaffold	In vitro human deep-zone chondrocytes	Increased matrix-associated responses and mineralization; responses included calcified-cartilage and hypertrophy-associated markers	Supports investigation for the calcified-cartilage interface; does not establish suitability for the non-mineralized cartilage zone.
Deng et al.[23]	3D-printed strontium-phosphate-silicate ceramic (SPS)	In vitro chondrocytes and in vivo osteochondral repair model	Reported chondrocyte responses, cartilage and subchondral-bone regeneration, and reconstruction of the interface	A multion source; the effects cannot be assigned to strontium or silicon alone.
Wang et al.[22]	Strontium-containing calcium-silicate ceramic scaffold	In vitro immune and cell studies; in vivo osteochondral repair model	Continuous strontium release; reported changes in macrophage response and improved cartilage and bone repair versus calcium-silicate controls	Includes a comparison scaffold that helps assess the contribution of strontium.
Asensio et al.[26]	Gradient scaffold with strontium and zinc folate derivatives in preferential regions	Human osteoblast and articular-chondrocyte cultures; rabbit-condyle defect model	Sustained release of Sr^{2+} and Zn^{2+} was reported alongside cartilage-like tissue and osteochondral tissue formation	A regionally organized, multicomponent design; ion effects are combined with folate, hyaluronan and scaffold architecture.

Gao et al.[10]	Mg^{2+} gradient in a hydrogel–cryogel hierarchical scaffold	In vitro studies; rabbit osteochondral-defect model	Upper and lower regions supported different chondrogenic and osteogenic responses; the combined design was assessed for dual-lineage repair	Illustrates spatially differentiated ion exposure, combined with other cues such as deferoxamine and pore structure.
Li et al.[11]	Strontium-doped bioactive nanoglass in a 3D-printed PCL scaffold; hierarchical pores	In vitro cell studies; rat osteochondral-defect model	Released Sr, Si and Ca ions; reported cartilage-related responses and defect repair	Ion release and nanotopography act together, so their individual contributions need separation.
Xu et al.[27]	Sr-enriched amorphous calcium-phosphate granules added to a collagen/collagen–Mg-hydroxyapatite scaffold	In vitro studies; goat weight-bearing bone-defect model	Reported improved subchondral-bone repair with Sr-enriched granules	Provides large-animal evidence for bone-focused augmentation; it does not establish equivalent benefit in cartilage or interface regions.
Deng et al.[25]	Gradient diatomite particles in a GelMA hierarchical scaffold	In vitro studies; rabbit osteochondral-defect model, assessed at 8 and 12 weeks	Sustained silicon release and reported cartilage and subchondral-bone regeneration	A gradient silicon source; outcomes also depend on particle distribution and scaffold architecture.
Liu et al.[14]	$SrSiO_3$ in a piezoelectric pPLLA scaffold, combined with LIPUS	In vitro cell studies; rat osteochondral-injury model	Sustained Sr and Si release plus electrical signaling; reported integrated cartilage and bone repair	The design combines ionic and electrical cues, so results should not be attributed to ion release alone.
Xu et al.[28]	Magnetic hydroxyapatite@Fe_3O_4 particles with Mg and Mn distributed in a continuous gradient hydrogel	In vitro studies; rat osteochondral-defect model	Magnetic-field-assisted fabrication established a gradient; the scaffold was assessed for cartilage and bone repair	Magnetic organization is a fabrication strategy in this study; it does not by itself demonstrate magnetic triggering of ion release.
Liu et al.[29]	Layered hydrogel designed to spatially organize Mg^{2+} and Cu^{2+} with a biomimetic calcified-cartilage interface	In vitro and in vivo validation	Reported maintained regional ion distributions and distinct tissue-associated responses	A recent example of spatially differentiated ion cues; assess the separate effects of scaffold structure, ion concentration and other signals.

Abbreviations: BG, bioactive glass; GelMA, gelatin methacryloyl; LIPUS, low-intensity pulsed ultrasound; PCL, poly(ε-caprolactone); pPLLA, piezoelectric poly(L-lactic acid); SPS, strontium phosphate silicate.

4. Region-Specific Regenerative Effects

The biological value of an ion-releasing scaffold depends on the tissue region in which its effects occur. A response that supports calcified-cartilage formation may be undesirable in the articular cartilage, while an effect that improves subchondral bone repair does not by itself demonstrate restoration of the cartilage or interface. Studies should therefore report outcomes separately for the cartilage, calcified-cartilage interface and subchondral bone[17–20].

4.1. Effects in the cartilage region

In the cartilage-facing region, the aim is to support chondrocyte survival and cartilage-associated matrix formation. Relevant outcomes include glycosaminoglycan deposition and expression of markers such as SOX9, aggrecan and type II collagen[20,24,25]. For ion-releasing materials, these measures should be considered alongside markers of hypertrophy and mineralization, since not every chondrogenic response is evidence of stable articular cartilage formation[21]. The magnesium-gradient scaffold developed by Gao et al.[10] illustrates why location matters: the upper hydrogel region provided a different magnesium environment from the lower cryo-gel region, and the combined design was evaluated for cartilage and bone repair. Other multicomponent systems, including the strontium/silicon/calcium-releasing scaffold, have also reported chondrocyte-related outcomes[11]. These studies support assessing the cartilage region directly, rather than inferring cartilage regeneration from whole-defect scores alone.

4.2. Effects at the calcified-cartilage interface

The interface requires a controlled transition between cartilage-like and mineralized tissue. Here, localized mineral deposition and expression of calcified-cartilage-associated markers may be desirable, provided the mineralization remains confined to the intended region. In vitro, Mg-doped wollastonite/hydrogel scaffolds promoted mineralization and hypertrophy-associated responses in human deep-zone chondrocytes, suggesting potential for calcified-cartilage formation. The result should be interpreted in that context: the study supports a possible interface application, rather than indiscriminate use of the same formulation throughout the cartilage layer. This distinction is central to evaluating multifunctional scaffolds. An increase in type X collagen or mineral deposition could indicate a useful interface response in one region but would require a different interpretation if observed in the articular cartilage zone[18,19,21]. Region-resolved histology and molecular outcomes are therefore needed to determine whether the scaffold is generating a transition between tissues or simply promoting mineralization across the construct.

4.3. Effects in the subchondral-bone region

In the subchondral-bone region, key outcomes include bone formation, mineralization, integration with host bone and recovery of the supporting architecture[17,20]. Silicon-containing bio ceramic scaffolds have been evaluated for dual-lineage outcomes in animal models[24], while diatomite-containing scaffolds were designed to provide a silicon source within a hierarchical construct and were assessed for cartilage and bone regeneration[25]. These studies illustrate the need to report bone outcomes separately from cartilage outcomes, even when both are observed in the same implant. A study by Xu et al.[27] offers a more bone-focused example: adding strontium-enriched amorphous calcium-phosphate granules to a collagen/collagen–magnesium-hydroxyapatite scaffold improved its reported subchondral-bone repair capacity. This finding is relevant to targeted augmentation of the bone compartment, but it does not alone establish that the cartilage and interface regions were equivalently improved. The three regions need their own outcome measures when a scaffold is presented as supporting whole-unit repair.

4.4. Coordinating repair across the osteochondral unit

Some studies report repair in both cartilage and subchondral bone. Examples include magnesium-gradient scaffolds, silicon-releasing systems and strontium/silicon/calcium-releasing scaffolds [24,25]. Such findings support the possibility of dual-lineage repair, but they do not make the regional outcomes interchangeable: cartilage matrix quality, interface continuity and bone restoration remain distinct endpoints[17–20]. For this review, region-specific effect refers to a biological response linked to a defined scaffold region and supported by an outcome measured in that tissue. This framing helps distinguish ion activity from the effects of scaffold architecture, other released ions or additional cues such as growth factors and mechanical stimulation[10,11,14,16]. It also sets up the next section, which examines how scaffold design and release control can localize these effects.

5. Spatial Organization and Control of Ion Release

The biological effects discussed in the previous two sections depend not only on which ions a scaffold releases, but also on where they are released and how exposure changes over time. Spatial organization can be achieved by placing an inorganic phase in a particular layer, distributing it as a concentration gradient, or incorporating it into a matrix with region-specific structure. The goal is to align the local ionic environment with the intended response in cartilage, the calcified-cartilage interface or subchondral bone[6,10,11,25].

5.1. Positioning the inorganic phase

A straightforward approach is to confine an ion-releasing phase to a selected scaffold region. For example, compartmentalized bioactive glass in a biphasic hydrogel scaffold was used to distinguish the cartilage-facing region from the glass-containing, bone-facing region. Layered placement can also be combined with different pore structures and mechanical properties to create distinct local environments. A continuous gradient offers a less abrupt transition. Gao et al.[10] incorporated a magnesium gradient across a hydrogel–cryogel scaffold, while Deng et al.[25] used gradient diatomite content in a GelMA-based scaffold to distribute a silicon source across the construct. In a separate study, a magnetic field was used during fabrication to position magnetic, magnesium-containing hydroxyapatite particles in a continuous gradient hydrogel[28]. In that example, the magnetic field helped establish the scaffold's spatial organization, it should not be interpreted as evidence that magnetic stimulation directly controlled ion release after implantation.

5.2. Release over time and external stimulation

The timing of ion exposure is another design variable. A short-lived release may create an early local signal, whereas continued release may extend exposure during tissue formation. Neither profile is automatically preferable: its value depends on the target region, the cell response and the scaffold's degradation behaviour. Studies should report release curves and relate them to the timing of biological outcomes rather than describing release as controlled or sustained without measurements[10,11,25]. External stimulation may add another control layer, but it is important to specify what the stimulus controls. In a pPLLA/$SrSiO_3$ composite, low-intensity pulsed ultrasound was used with a piezoelectric scaffold that released strontium and silicon ions while also generating electrical signals[14]. The study therefore combines ionic and electrical cues; the reported design should not be simplified to ultrasound-triggered ion release unless release itself was shown to vary with ultrasound exposure. A 2026 sandwich-scaffold study provides a further example of spatial and temporal control. They designed a scaffold with distinct ion-associated functions across its layers and reported limited cross-diffusion between magnesium and copper environments, supporting a maintained biochemical gradient[29]. This highlights a practical issue for any layered design: the intended regional differences need to persist long enough to influence repair, despite diffusion and scaffold degradation.

5.3. Connecting release measurements to regional outcomes

To compare designs, studies should report the composition and location of each inorganic phase, the identity and number of ions released, the release medium, sampling times and scaffold mass, and whether release was measured from the whole scaffold or from individual regions. Where gradients are intended, spatial measurements are needed to show that the gradient exists and persists. These measurements should be interpreted alongside region-specific outcomes, such as cartilage matrix formation, interface mineralization and subchondral bone formation[10,11,28]. This approach helps separate three related but distinct questions: whether a scaffold releases ions, whether those ions reach the intended region, and whether the regional tissue response is associated with that exposure. Clear reporting across all three would make evidence from different scaffold systems easier to compare and would strengthen claims of region-specific regenerative effects[6,25,29].

6. Evidence Gaps and Translational Considerations

The studies reviewed here show that inorganic phases can deliver ions within osteochondral scaffolds and influence cartilage- and bone-associated outcomes. However, these findings come from different materials, models and outcome measures. They support further investigation, but do not yet establish a generally effective ion, dose or scaffold architecture for osteochondral repair.

6.1. Strength and scope of the evidence

Much of the evidence for multiphasic osteochondral scaffolds remains preclinical. A review of animal studies found that rabbits were commonly used and that most studies relied on small-animal models, it also cautioned that ectopic implantation does not directly demonstrate repair in a load-bearing osteochondral defect[30]. Results from cell culture or small animals should therefore be distinguished from evidence of durable repair under joint loading. Clinical evidence does exist for some cell-free osteochondral scaffolds. For example, a multicentre randomized trial reported five-year outcomes for an aragonite-based implant[31]. This is relevant evidence for scaffold-based repair, but it does not establish the efficacy of the newer magnesium-, strontium- or silicon-release strategies reviewed here, or demonstrate that their proposed ion-specific mechanisms account for clinical outcomes. Those questions require direct testing of the ion-releasing designs themselves.

6.2. Separating ion effects from other scaffold effects

An inorganic phase can alter several properties at once: ion release, surface chemistry, porosity, stiffness and degradation. A scaffold containing multiple ions or additional cues, such as growth factors, ultrasound-induced electrical signals or magnetic particles, may produce a useful overall response, but it can be difficult to attribute that response to any one component[11,14,16,28]. Studies would be easier to interpret if they included matched controls that isolate the inorganic phase or ion of interest, alongside measurements of the released ions and the scaffold's structural properties. Dose also needs careful interpretation. Higher inorganic-phase content does not necessarily mean better regeneration: magnesium-doped wollastonite, for instance, was investigated for mineralization and hypertrophy-associated responses in deep-zone chondrocytes, making its intended use and location relevant to how the result is interpreted. Studies should report the ion concentration or release profile associated with biological outcomes, including evidence of adverse responses at higher exposures where available[10,21,29].

6.3. Demonstrating durable, integrated repair

Short-term tissue staining or defect filling cannot by itself show that regenerated tissue will remain integrated and functional under repeated loading. Longer follow-up should assess cartilage matrix quality, interface continuity, subchondral-bone restoration, scaffold degradation and mechanical function together[20,30]. Where a study reports dual-lineage repair, cartilage and bone outcomes should be presented separately, with interface outcomes reported as well when the scaffold is designed to affect that region[17–19].

6.4. Steps toward clinical evaluation

Future studies would benefit from a consistent reporting framework covering scaffold composition and regional phase placement; ion identity and release over time; controls that distinguish ion effects from architecture and other signals; and region-specific biological and mechanical outcomes. Testing should progress from in vitro assessment to relevant orthotopic animal models and longer follow-up, with larger-animal studies considered before clinical evaluation where appropriate. Manufacturing and implantation also matter. A gradient or multilayer scaffold needs reproducible composition and architecture, reliable joining between regions, stable performance after sterilization and storage, and a practical surgical workflow. These requirements are especially important for ion-releasing systems, because changes in phase distribution or degradation could alter the exposure profile after fabrication[20,29,30]. The translational case will be strongest when a scaffold's regional ion delivery, biological effects and mechanical performance are demonstrated together, rather than inferred from any single outcome.

7. CONCLUSION

Ion-releasing inorganic phases offer a way to add biological cues to osteochondral scaffolds, but their effects depend on the ion, its source material, the scaffold region in which it is placed, and the resulting release profile. Evidence involving magnesium-, strontium- and silicon-containing systems suggests potential to support cartilage, calcified-cartilage interface or subchondral-bone repair, although these outcomes are not interchangeable and should be assessed separately. The main design principle emerging from this review is to match the location and timing of ion release to the biological needs of each region. A convincing assessment should connect scaffold composition and regional ion exposure to cartilage, interface and bone outcomes, and then to mechanical integration and function. Current evidence for many of these ion-delivery strategies remains preclinical. Clinical

outcomes reported for other scaffold implants do not, by themselves, validate the specific ion-release designs reviewed here. Progress in the field will depend on studies that measure ion release, demonstrate where the ions reach, separate their effects from other scaffold cues, and follow repair long enough to assess integrated function. Reporting these elements together would make results across scaffold systems more comparable and help establish which ion-releasing designs provide reproducible, region-specific benefits.

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