



Degradation pathways and translational challenges of Mg-6Zn-xCa biodegradable alloys in physiological environments: a critical review

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Abstract: Magnesium-based alloys that are biodegradable receive increased interest as temporary metallic implants because alloys are compatible with bone, have intrinsic biocompatibility, and elicit the possibility of no secondary removal surgeries. Mg-Zn-Ca alloys, and in particular Mg-6Zn-xCa alloys have received particular attention, owing to the fact that zinc and calcium are biologically important elements which can both strengthen the alloy and alter degradation behavior. Nevertheless, even with the substantial amount of research, the reported corrosion and biodegradation rates of nominally similar Mg-Zn-Ca alloys differ widely in the literature, which prevents consistent comparison and prevents clinical translation. This review critically analyzes the corrosion behavior of alloys Mg- 6Zn-xCa ($x = 0.1, 0.3, 0.5$ wt) in physiologically relevant conditions with a particular focus on the combined contribution made by microstructure, second-phase chemistry, processing route, and testing conditions. We suggest that the conflicting nature of the reported degradation kinetics is not due in large part to alloy composition, but to poor control and reporting of local physicochemical physiological boundary conditions, especially pH development, protein-mediated surface interactions, fluid renewal and micro-galvanic coupling of Ca- and Zn-rich intermetallic phases. Based on this discussion, the review offers a site-specific environment-microstructure interactive framework through which alloy design, physiological exposure conditions and degradation mechanisms are interrelated to allow a more significant reconciliation of in-vitro outcomes with in-vivo performance. This study, through the approach of using electrochemical and biomedical principles, uncovers important research gaps in contemporary testing methods, the weaknesses of composition-based approaches to interpreting results, and proposes a recommendation on how to achieve standardized and physiologically relevant testing of Mg-6Zn-xCa alloys. The framework provided is to rationalize, comparatively assess, and translate the biodegradable magnesium orthopedic and biomedical biomaterials using translation qualifications.

1. Introduction

The invention of biodegradable metallic implants represents a paradigm shift in the science of biomaterials, aiming to solve the long-standing problems with permanent metallic implants, including stainless steel, cobalt-chromium alloys, and titanium-based materials. Even though they lead to outstanding mechanical stability, the long-term retention rate of these materials in the body is often linked to stress shielding, chronic inflammatory reactions, imaging artefact, and, in most instances,

the necessity to undergo secondary surgery once the tissue has healed (Zhou *et al.*, 2021; Tan *et al.*, 2023; He *et al.*, 2024). These restrictions have fueled the furious research into temporary, bioresorbable metals which can offer sufficient mechanical support during healing and then degrade subsequently.

Magnesium and magnesium alloys have stood out as the most promising type of candidate biodegradable metal in load-bearing biomedical applications (Zhang *et al.*, 2022; Aikin *et al.*, 2025). Compared to traditional implant metals, magnesium has a higher density and elastic modulus, and thus, a lower mechanical mismatch and stress-shielding effect (Narayanan *et al.*, 2021; Zhou *et al.*, 2021). Furthermore, magnesium is an essential physiological element in enzyme action, bone remodelling, and cellular signaling, which generally gives it the overall positive biocompatibility image (He *et al.*, 2023; Istrate *et al.*, 2024). These properties have placed Mg-based alloys at the centre of the investigations into the temporary orthopedic fixation device, vascular scaffolds, and other technologies associated with implants (Tan *et al.*, 2023; Zhang *et al.*, 2024).

These advantages are accompanied by the primary obstacle to clinical translation the high and uncontrolled degradation of magnesium in the presence of chloride in physiological environments (Azadani *et al.*, 2022; Wang *et al.*, 2022). Excessive corrosion can result in an untimely loss of mechanical integrity, the creation of hydrogen gas and alkalization of the locality, which can interfere with tissue healing and implant performance (Song *et al.*, 2020; Kraus *et al.*, 2022). Thus, the rate of degradation of magnesium alloys, without compromising mechanical performance and biological response has become the focus of the field. Alloying, microstructural refinement, and surface modification techniques have been widely considered to deal with this problem in the last ten years (Narayanan *et al.*, 2021; Jafari *et al.*, 2025).

In this respect, particular focus has been given to Mg-Zn-Ca alloys. Zinc affects solid-solution and precipitation strengthening and is needed in biological functions to develop the bone and cellular metabolism, and calcium affects grain refinement and osteogenic responses and bone mineralization pathways (Gong *et al.*, 2021; Istrate *et al.*, 2022). Even though Zn and Ca additions may lead to improvements in the mechanical performance and biocompatibility, as well as provide a pathway to tuning corrosion behavior when carefully balanced (Fu *et al.*, 2022; Zhang *et al.*, 2023). Consequently, Mg-Zn-Ca systems, particularly those containing moderate Zn and low Ca additions are commonly suggested as potential good cases of biodegradable implantation use (Sun *et al.*, 2024; Moussa *et al.*, 2024).

Nevertheless, there is increasing evidence to suggest that the nominal composition is not the only factor that determines the corrosion behavior of Mg-Zn-Ca alloys. The formation, dispersion, and electrochemical activity of Ca- and Zn-containing intermetallic phases, processing route-imposed grain size, and crystallographic texture, and the existence of trace impurities all have a strong impact on local electrochemical heterogeneity and degradation morphology (Istrate *et al.*, 2022; Fattah-Alhosseini *et al.*, 2024; Cai, 2024). At the same time, the physiological environment (e.g., the pH and buffering chemistry, the concentration of chlorides, protein adsorption, fluid movement) itself has a determinant effect on the corrosion kinetics and mechanisms (Mei *et al.*, 2021; Wei & Gao, 2023; Ferroni *et al.*, 2024). Consequently, the degradation behavior that is seen in simple laboratory environments is not expected to be predictive of in-vivo performance (Wei *et al.*, 2023; He *et al.*, 2024).

Of particular importance, even though the body of published research in the Mg-Zn-Ca alloys is vast, claims of corrosion and biodegradation of ostensibly similar compositions often vary by over an order of magnitude when the results are reported (Castano-Gonzalez *et al.*, 2024; Kovacevic *et al.*, 2025). These discrepancies are usually ascribed to variations in alloy chemistry, but the closer examination shows that there is a significant diversity of the experimental methods, environmental control and reporting of the results (Wei and Gao, 2023). This puts some basic questions in the trustworthiness of composition-based interpretations, and the accuracy of direct comparisons across studies. Specifically, the benefits in the relative role of local pH development, second-phase-driven micro-galvanic coupling, protein-surface interactions, and fluid renewal have been largely underresearched or undercontrolled, even though they have been long known to influence magnesium corrosion (Mei *et al.*, 2021; Dai *et al.*, 2024; Kovacevic *et al.*, 2025).

It is against this background that this review is critically and integratively oriented towards Mg-6Zn-xCa alloys ($x = 0.1, 0.3, 0.5$ wt), a composition regime that is concomitantly mechanically and biologically relevant. This review does not look at degradation behavior as an intrinsic material constant, but rather as a challenge to the interaction of alloy microstructure, processing history, and environmentally relevant conditions of physiological processes. The review attempts to highlight controlling variables that have not been appreciated or understood in the literature with a synopsis of the recent developments in the scientific field of corrosion and medical materials research. Thus, it includes a site-specific environment-microstructure interaction framework which will resolve the conflicting in-vitro measurements and enhance the predictive correlation between lab-testing and in-vivo functioning.

2. Physiological, Anatomical And Fluid-Environment Considerations

In the case of biodegradable implant materials, the service environment, i.e. the type of body-fluid, ionic composition, pH, protein content, fluid flow/shear and cellular interactions has a dominant effect on the corrosion kinetics, morphology of attack, and transport and fate of corrosion by-products (Zhang *et al.*, 2022; Wei *et al.*, 2023). The ionic species of physiological media (in particular, Cl^- , HCO_3^- , PO_4^{3-} , Ca^{2+}) change the surface film and solubility of corrosion products reducing or enhancing Mg dissolution depending on composition and buffering capacity (Amukarimi *et al.*, 2021; Zohdy *et al.*, 2023). Changes in pH, both local and temporary, e.g. acidic microenvironment surrounding inflamed or infected tissue, significantly affect the rate of Mg corrosion and alter the corrosion morphology which turns uniform to highly localized (Kovacevic *et al.*, 2025; Zohdy *et al.*, 2023). Cathodic kinetics is changed by adsorbed proteins and organic molecules (serum albumin, fibrinogen, hyaluronic acid), which can inhibit or promote corrosion, respectively, through adsorption, shear and competitive displacement (Wei *et al.*, 2023; Dai *et al.*, 2024). In addition, shear (i.e. in vasculature or synovial spaces) and fluid flow are effective in mass transporting reactants/products and often increase the rate of corrosion and alter film stability relative to stagnant tests (Shang *et al.*, 2022; Ferroni *et al.*, 2024). Finally, cellular (macrophages, osteoclasts/osteoblasts) and tissue reactions to corrosion products (local alkalization and hydrogen evolution) also change the degradation pathways and tissue outcomes, which emphasizes the need of the multi-condition testing that reflects the target anatomical location (He *et al.*, 2024; Mota-Silva *et al.*, 2025).

2.1 Body-fluid analogues and corrosion drivers

Common in-vitro fluids to test biodegradable metals are Hank's Balanced Salt Solution (HBSS), simulated body fluid (SBF), phosphate-buffered saline (PBS), cell-culture media (with/without serum proteins) and synovial-fluid mimics, and the medium used has a severe impact on the observed corrosion behaviour (Amukarimi, 2022; Zhang *et al.*, 2022; Wei & Gao, 2023). Besides the composition of solutions, buffering system ($\text{CO}_2/\text{HCO}_3^-$ vs. HEPES/Tris) and flow/shear conditions (static vs. dynamic) also significantly vary the film formation, mass-transport of ions and elimination of corrosion-products and should thus be adjusted to the target anatomical site (Amukarimi, 2022; Mei *et al.*, 2021; Yavuzyegit *et al.*, 2024). In the case of Mg-based alloys the protective $\text{Mg}(\text{OH})_2$ / carbonate layers formed in the beginning are broken by the chloride ions: Cl^- transforms the $\text{Mg}(\text{OH})_2$ into the soluble MgCl_2 that deteriorates the passivation and speeds up the localised attack (Zhang *et al.*, 2021; Wei and Gao, 2023). The electrochemical process of Mg degradation is controlled by anodic dissolution of Mg - Mg^{2+} and cathodic proton/water reduction (sometimes oxygen reduction can also play a role under special conditions), which leads to the production of OH^- and local pH change and alteration of corrosion products (Zhang *et al.*, 2022; Wang *et al.*, 2020). Lastly, as local pH can be a determiner in in-vitro Mg biodegradation in numerous realistic scenarios, pH regulation and $\text{CO}_2/\text{HCO}_3^-$ buffering are vital considerations when developing physiologically relevant corrosion experiments (Kovacevic *et al.*, 2025; Wei & Gao, 2023).

2.2 Anatomical sites & implications

In orthopaedic systems like bone fixation screws and plates, the magnesium-based implants are subjected to interstitial bone fluid, which has common ionic strength, low flow and temporary local pH change that occurs in bone repair and inflammatory mechanisms (Liu *et al.*, 2022; He *et al.*, 2024). The neutral pH may occur below those of these microenvironment, particularly at the acute healing period, which can affect the rate of corrosion and hydrogen release (Gao *et al.*, 2021). It should then be allowed that the implant should be mechanically stable at least 6-12 weeks to favor bone consolidation, and that biodegradation should then occur gradually (Kraus *et al.*, 2022; Mota-Silva *et al.*, 2025).

The blood and plasma environment, which is characterized by high protein concentrations, constant flow of fluids, and pH within the close physiological range of 7.35 - 7.45, persists in a vascular environment (biodegradable stents and guidewires) (Shang *et al.*, 2022). The situation results in a high rate of ion movement and mechanical shear destabilizing corrosion films, which necessitates more tightly regulated degradation behaviour alloys or coating (Zhang *et al.*, 2021; Li *et al.*, 2024).

In the case of articular joints, surface charge and corrosion film formation is altered by adsorption of organic macromolecules in a complex medium, which is provided by the presence of viscous synovial fluid that is rich in hyaluronic acid, lubricin, and proteins (Meyer *et al.*, 2021; Ferroni *et al.*, 2024). It has been demonstrated that uniform corrosion is slowed down by high viscosity and limited oxygen diffusion, and that this may increase localized corrosion at protein-metal interfaces (Sung *et al.*, 2023). On the other hand, in soft-tissue or wound settings, the implants are exposed to potentially acidic environments (pH 5-6) with inflammatory cells and reactive oxygen/nitrogen species, which increase the rate of corrosion, and alter the chemistry of the $\text{Mg}(\text{OH})_2$ / oxide films (Song *et al.*, 2020; Kovacevic *et al.*, 2025). The series of Mg-6.0Zn-xCa alloys that the research is investigating in the current thesis therefore supplies such a relevant model with which to investigate a variety of corrosion behaviors across a variety of physiological media, representing different anatomical conditions of the bone versus vascular and soft-tissue locations - a timely and necessary method to

translate biodegradable Mg systems into a reliable clinical practice (Wei & Gao, 2023; He *et al.*, 2024).

Table I: Physiological environment-sensitive corrosion drivers which control the degradation behavior of magnesium-based implant materials.

Anatomical Site	Key Fluid Components	Dominant Corrosion Driver	Risk
Bone	HCO ₃ ⁻ , PO ₄ ³⁻	pH fluctuation	Gas pockets
Blood	Proteins, shear	Film destabilization	Rapid thinning
Joint	HA, proteins	Localized attack	Tribocorrosion

3. Microstructure And Alloying Effects On The Degradation Behavior Of Mg–Zn–Ca Alloys

The microstructural features have a decisive influence on the corrosion and degradation behaviour of Mg-Zn-Ca alloys, and can have an impact that is as large as or larger than the influence of nominal alloy composition (Yang *et al.*, 2024). Although this alloying with Zn and Ca is often cited as one of the main approaches to enhancing the mechanical performance and biocompatibility, increasingly there is a growing body of evidence that corrosion behavior of such systems is governed by measurable microstructural limits instead of qualitative compositional trends alone (Kovacevic *et al.*, 2025).

3.1 Microstructural Refinement and Grain Size.

It has also been well documented that the grain refinement of magnesium alloys is important in improving their corrosion resistance by increasing the uniformity of passive film formation and reducing localized anodic behavior. In the case of Mg-Zn-Ca alloys, it has been shown through extrusion, rolling, and severe plastic deformation studies that the reduction of the grain size between coarse (> 30 μm) and fine (< 10 μm) can reduce measured rates of corrosion by about 30-60 % under identical conditions of immersion (Narayanan *et al.*, 2021; Sun *et al.*, 2024). In finer grain sizes, at grain sizes below 8-10 μm on average, quantitatively reported fine-grain Mg-Zn-Ca alloy corrosion rates in simulated body fluids are generally below 0.5 mmyr⁻¹, whereas coarse-grain counterparts generally report corrosion rates between 1.5 mmyr⁻¹ and higher (Istrate *et al.*, 2022; Cai *et al.*, 2024).

But this positive influence does not have limitless power. The high levels of corrosion have been linked to ultra-fine grain structures (< 2 μm); especially those formed during high-strain processing routes, which is connected to the high density of grain boundaries, and the increase of diffusion paths of aggressive species (Fattah-Alhosseini *et al.*, 2024). These observations suggest that there exists an optimal grain size range, the maximum corrosion resistance of Mg-Zn-Ca alloys which is usually in the range of ~5 to 15 μm.

3.2 Zinc role Solid Solution vs. Precipitation Effects.

Additions of zinc to about 4-6 wt % are usually advantageous to enhance Mg-based alloys and could moderate enhance corrosion resistance by means of solid-solution and grain refinement (Zhang *et al.*, 2022; Fu *et al.*, 2022). The most common reported corrosion rates under this range are about 0.3 to 1.0 mmyr⁻¹ in case of a minimal corrosion rate with a restricted formation of secondary phases under

static immersion conditions (Sun *et al.*, 2024). At higher concentrations above this limit, however, excess Zn will favor the development of Zn-rich intermetallic phases like MgZn and Ca₂Mg₆Zn₃ that bring about strong electrochemical heterogeneity. Potential differences of as much as 150-250 mV have been observed between these intermetallics and the a-Mg matrix with the aid of electrochemical measurements, and this sufficiency is capable of propelling localized micro-galvanic corrosion (Gong *et al.*, 2021; Istrate *et al.*, 2022). This means that alloys with large amounts of Zn can develop a shift in more uniformly degrading alloys to localized attack, especially with the inclusion of calcium additions.

3.3 Calcium Content: Quantitative Galvanic Coupling Thresholds.

In Mg-Zn-Ca alloys, calcium also works over two functions, first enhancing grain refinement and biocompatibility, and secondly, facilitating the formation of second phases that are electrochemically active. The quantitative analysis of various studies reveals that Ca contents lower than about 0.2 wt % normally support refined, mostly single-phase microstructures with the corrosion rate of these usually lower than 1 mmyr⁻¹ (Mei *et al.*, 2021; Zhang *et al.*, 2023).

Conversely, additions of Ca above a homogenous level of circa 0.3 wt % are always associated with the shift of quasi-uniform to localized corrosion behavior regardless of the processing pathway (casting, extrusion, or additive manufacturing). With this transition, the creation of continuous or semi-continuous Ca₂Mg₆Zn₃ networks existing along the grain boundaries takes place and acts as potent cathodic positions relative to that of Mg matrix (Fu *et al.*, 2022; Cai *et al.*, 2024). Alloys with ≥ 0.5 wt % Ca are believed to be many times slower than allegedly similar test condition degradation behaviour, such is the sensitivity of the degradation behaviour to fairly small changes in compositions (Fattah-Alhosseini *et al.*, 2024; Kovacevic *et al.*, 2025).

3.4 Intermetallic Phase Distribution and Morphology.

In addition to the contribution of phase fraction, intermetallic phase morphology and place distribution have a first-order effect on corrosion mechanisms. Individual Ca-Zn intermetallics are dispersed and discrete and typically result in isolated micro-galvanic cells that do not produce significant spatial effects but rather interconnections between networks that allow permanent localized attack and deep penetration corrosion (Istrate *et al.*, 2022; Dai *et al.*, 2024). Quantitative electrochemical impedance experiments have indicated that the charge transfer resistance can change by more than an order of magnitude when intermetallic phases are discontinuous or percolating at the same global compositions (Wei and Gao, 2023).

3.5 Reported Corrosion Rates Variability:

Corrosion rates reported by industry and government vary widely; this fact is thus reflected in the data provided in this article. The variability in the reported rates of corrosion by the industry and government is great; therefore, it is represented in the data presented in this article. The literature synthesis indicates that a very broad range of corrosion rates is reported under nominally comparable alloy compositions and test conditions ranging as low as 0.2 mmyr⁻¹ to values exceeding 5 mmyr⁻¹ of Mg-Zn-Ca alloys (Wei *et al.*, 2023; Kovacevic *et al.*, 2025). Such variability cannot be explained by composition only and highlights the prevailing power of microstructural condition, surface, and environmental control. Specifically, the variations in pH buffering, solution renewal, and protein

content have been demonstrated to change the corrosion rate by 3-10 times of the same alloy microstructure (Mei *et al.*, 2021; Ferroni *et al.*, 2024).

3.6 Design Implication of Alloy.

Taken together, these results indicate that the proper design of biodegradable Mg-Zn-Ca systems through alloy design should be informed by quantitative microstructural design rather than compositional design (Ferroni *et al.*, 2024). The level of calcium should be kept to less than about 0.3 wt. unless there are well-known methods of carefully managing intermetallic formation, the grain sizes must be designed to lie within a range of optimum values, and the intermetallic morphology must be thought of in a manner that is explicit to the processing. The possibility to ignore these quantitative constraints is dangerous as it may erroneously ascribe corrosion behavior to alloy chemistry and ignore more powerful microstructure-controlled processes (Kovacevic *et al.*, 2025).

4. Corrosion Mechanisms Of Mg–6Zn–xCa Alloys

The electrochemical kinetics, micro structural characteristics and environmental stimuli interact to determine the corrosion behavior of magnesium alloys (Wei *et al.*, 2023). Although generic models of corrosion have been used to explain magnesium anodic dissolution and film breakages in chlorides-based solutions, Mg-6Zn-xCa alloys have mechanistic nuances of difference compared to both lean binary Mg-Ca and Mg-Zn alloys (Ferroni *et al.*, 2024). The causes of these differences are the joint action of Zn on cathodic kinetics, the multifaceted influence of the Ca-containing intermetallics and the conditionality of the formation of protective and deleterious surface layers in physiological conditions (Kovacevic *et al.*, 2025).

4.1 Anodic Dissolution and Zn-Modified Cathodic Kinetics

In magnesium corrosion, magnesium anodic dissolution reaction of Mg to Mg^{2+} and hydrogen cathodic reaction are coupled reactions. Zn has a dominant effect on corrosion in the form of grain refinement and solid solution strengthening in the alloys (Mg-Zn-without Ca), and a minor effect on the kinetics of hydrogen evolution at standard biomedical concentrations (approximately 3-6 wt. Zn) (Zhang *et al.*, 2022). Nevertheless, in Mg-6Zn-xCa alloys, Zn has a strong influence on cathodic operations on two routes:

- I. Disturbed hydrogen evolution dynamics: Zn affects physiological electrolytes by enhancing the overpotential of hydrogen evolution, which inhibits the cathodic reaction rate in the presence of Zn in solid solution (Narayanan *et al.*, 2021).
- II. Intermetallic-driven micro-galvanic activity: In the case of Zn and Ca, when Mg contains an intermetallic phase, Ca_2Mg_6Zn or $MgZn$, the cathodic activity of the intermetallics in comparison with the a-Mg matrix may increase the local hydrogen evolution rate and form favorable corrosion sites (Gong *et al.*, 2021; Istrate *et al.*, 2022).

The bifurcated nature of the cathodic currents found by the quantitative measurements on the Mg-6Zn-0.5Ca alloys with high contents of $Ca_2Mg_6Zn_3$ may be 2-3 times higher than those in the lean Mg-Zn systems under the same operating conditions, which highlights the particularity of the Zn-rich intermetallics in Mg-6Zn-xCa alloys (Cai *et al.*, 2024).

4.2 Calcium-Containing Phases: Cathodic Sites Versus Protective Layer Precursors

The effect of calcium on Mg alloys corrosion is complex. Ca is more likely to form Mg_2Ca , which is highly anodic compared to the Mg matrix, and greatly promotes homogeneous corrosion in lean Mg-Ca systems (e.g., Mg-1Ca) (Mei *et al.*, 2021). The Mg-6Zn-xCa ones, on the other hand, create $Ca_2Mg_6Zn_3$ and other ternary phases, which are largely cathodic in comparison to the Mg matrix and thus cause micro-galvanic corrosion (Fu *et al.*, 2022; Zhang *et al.*, 2023).

But in definite physiological regimes, Ca has a two-fold role:

- I. Galvanic attack promoter: Continuous networks of $Ca_2Mg_6Zn_3$ at Ca contents ≥ 0.3 wt%, sustain localised corrosion penetration by increasing the local cathodic density (Fattah-Alhosseini *et al.*, 2024; Kovacevic *et al.*, 2025).
- II. Precursor of protective layer In fluid conditions, with phosphate and carbonate present, dissolved Ca^{2+} may react with PO_4^{3-} and HCO_3^- to produce layers of calcium phosphate (Ca-P) at the interface between the metal and the fluid. These precipitates can block active surfaces, and prevent corrosion at a particular place particularly in situations where the precipitation rate is slow compared to dissolution (Wei and Gao, 2023; Ferroni *et al.*, 2024).

The shift in cathodic-based deterioration to protective Ca-P layer domination is highly dependent on the environment. To use the example, Ca-P layer coverage (which is above 20-30 percent of the surface) can be found to cut the effective corrosion rates up to 30-50 percent in phosphate-buffered saline with pH regulation and the presence of proteins (Wei *et al.*, 2023), which is hardly achievable in chloride-dominated electrolytes without buffering.

4.3 Localized vs. Uniform Attack: Phase Distribution, Texture, and Defects

Corrosion does not occur homogeneously in Mg-6Zn-xCa alloys. The location and form of $Ca_2Mg_6Zn_3$ intermetallics, coupled with the processing-related texture and defect systems, control the nature of such degradation to be localized or uniform in nature.

- i. Micro-galvanic initiation: Intermetallic phases can act as cathodic hub which provides an accelerated anodic dissolution of the rest of the Mg matrix. When the stages are connected together in continuous networks or clusters, the local attack prevails and the pitting becomes deep and provides an increased rate of mechanical weakening (Istrate *et al.*, 2022; Dai *et al.*, 2024).
- ii. Even, non-connected dispersions: Smaller, high-pressure corrosion-forming dispersions, which can be obtained by means of a fine thermo-mechanical treatment, have a tendency to evenly distribute mass, thus slower corrosion process on average and reduced pit depths (Sun *et al.*, 2024).

In practice, interconnected $Ca_2Mg_6Zn_3$ alloys have pitting corrosion depths of more than 200 mm after 14-21 days in simulated physiological conditions, whereas intermetallics dispersed alloys have pitting corrosion depths of less than 100 mm (Cai *et al.*, 2024). Such discrepancies highlight the key mechanistic nature of intermetallic topology in the Mg-6Zn-xCa corrosion.

4.4 Protein Adsorption and Biological Conditioning Layers

Effects of protein interaction also make Mg-6Zn-xCa systems unique to more simple binary Mg systems. Serum proteins selectively adsorb to the cathodic intermetallic phases changing local electrochemical activity and changing corrosion patterns (Wei & Gao, 2023). Selective binding of proteins to $Ca_2Mg_6Zn_3$ surfaces in Mg-6Zn-xCa alloys may either promote local dissolution or under

steady-state adsorption promote the growth of a conditioning layer that inhibits the aggressive access of ions. This kind of protein-intermetallic synergy is not present or is considerably smaller in both binary Mg-Ca and Mg-Zn alloys, which underscores a mechanism that is unique to ternary Mg-Zn-Ca alloys with physiological conditions (Kovacevic *et al.*, 2025).

Table II

4.5 Summary of Mechanistic Distinctions

Mechanistic Feature	Lean Mg–Ca	Lean Mg–Zn	Mg–6Zn–xCa
Primary second phase	Mg ₂ Ca (anodic)	MgZn (neutral/moderate)	Ca ₂ Mg ₆ Zn ₃ (cathodic)
Cathodic kinetics	Elevated HER from matrix	Slightly modified	Significantly enhanced around intermetallics
Galvanic coupling	Moderate	Low	High at ≥ 0.3 wt % Ca
Protective layer formation	Limited	Limited	Conditional (Ca–P)
Protein adsorption effects	Minor	Moderate	Mechanistically influential

The following Table II is a conceptual summary of how the compositional synergy, phase chemistry, biological interface interactions have led to the aberrant corrosion behavior of Mg-6Zn-xCa alloys relative to binary analogues.

5. In-Vitro Testing And Standardisation: Toward Reliable, Reproducible Assessment Of Mg–Zn–Ca Alloys

Strong in-vitro testing is the basis to the knowledge behind corrosion processes and translation of biodegradable magnesium (Mg) alloys into the clinical environment. Nevertheless, the state of in-vitro corrosion testing of Mg-6Zn-xCa alloys portrays extensive paradigm deficiencies that undermine the comparability of the data and the mechanistic interpretation. The shortcomings can no longer be accepted in a discipline that aims at clinical relevance, and they indicate compelling deficiencies in standardisation (Kovacevic *et al.*, 2025).

5.1 Criticism of the bad practices in the present in-vitro testing.

Even though there are formal standards available (e.g. ASTM G31-21 Standard Practice of the Laboratory Immersion Corrosion Testing of Metals, ISO 10993-15 Biological Evaluation of Medical Devices - Chemical Characterisation of Materials) many published studies continue to utilise flawed methods that compromise the use of corrosion data (Istrate *et al.*, 2022; Zhang *et al.*, 2023; Cai *et al.*, 2024; Guo *et al.*, 2025).

5.1.1 Static PBS Without pH Control

The widespread use is the immersion testing with the use of static phosphate-buffered saline (PBS) without regulation of pH or renewal of solution. In these circumstances, the quick dissolution of Mg stimulates local alkalisiation (pH > 9) in a few hours and radically changes the kinetics of corrosion, leaving artefacts that have little similarity to physiological buffering in vivo (Kovacevic *et al.*, 2025;

Ferroni *et al.*, 2024). Reporting of the immersion in PBS only without any control of the pH evolution or even reporting of the same will never be sufficient and discouraged.

5.1.2 Short (< 14 Day) Immersion Tests

Short-term immersion tests (e.g., < 7 days) are well-reported, but they do not give much information on the degradation modes of clinical timescales. The kinetics of magnesium corrosion is time-dependent, initially surface film forms, then divides, and finally stays longer than the first week in the stages of repassivation or pit expansion (Wei and Gao, 2023). Thus, experiments terminated below 14 days are at risk of poor characterisation of corrosion rates and mechanisms.

5.1.3 Reporting Corrosion Rates in the absence of Surface Area normalisation.

The other widespread weakness is the presentation of the corrosion rates without proper surface area normalisation. Since geometry, roughness and intermetallic distribution apparently have a strong effect on the local current densities it can give misleading results when corrosion rates are given on the basis of mass loss per specimen (e.g. mm/year). Proper normalisation of the valid comparisons should be with electrochemically active surface area (ECSA), or at least with geometric surface area in topography correction (Narayanan *et al.*, 2021; Istrate *et al.*, 2022).

5.2 ASTM and ISO Standards Weaknesses.

The existing ASTM and ISO standards offer a structure of corrosion experiments, yet, they were not created keeping biodegradable Mg alloys in physiology in focus. For example:

- a. ASTM G31-21 is focused on immersion testing, and it does not demand pH and fluid renewal schedules as well as protein/media composition as compared to in-vivo.
- b. ISO 10993-15 is more biological in its assessment but it does not provide explicit protocols to assess electrochemical evaluation of Mg alloys, such as hydrogen evolution content and normalisation of surface area.

These loopholes give rise to non-uniform implementation of standards and allow further release of incomparable sets of data (Narayanan *et al.*, 2021; Wei and Gao, 2023).

5.3 A Minimum Reporting Checklist of Mg-Zn-Ca Corrosion Studies.

To further develop the discipline to the level of reproducibility and comparability, the following are the minimum reporting criteria that we propose to apply to in-vitro corrosion research of Mg-Zn-Ca alloys:

1. Environment specification:

- ✓ Full formulation (ion concentrations, buffering agents) and identity of base solution (e.g. DMEM, PBS).
- ✓ Protein (e.g., albumin) inclusion or exclusion.
- ✓ Gas composition (e.g., 5% CO₂, 37 °C).

2. pH control and monitoring:

- ✓ Preliminary pH and all pH.

- ✓ Time resolved pH measurements or programmable pH (e.g., titration or automated buffering).
- ✓ Temporality and conditions of renewing solutions.

3.Surface condition:

- ✓ Elaborated surface finishing (grit size, polishing sequence).
- ✓ Measurement method Roughness metrics (e.g., Sa, Ra).

4.Electrochemical tests parameters:

- ✓ Working electrode area (ECSA were available).
- ✓ Specifications of reference and counter electrodes.
- ✓ Scan rates, stabilization criteria and impedance fitting models.

5.Normalisation of the rate of corrosion:

- ✓ Surface area (geometric or ECSA) normalisation.
- ✓ Mass loss analysis and quantification of hydrogen evolution provided that area normalisation is also done.

6.Duration and time points:

- ✓ Shortest duration of immersion should be 14 days or reasons why.
- ✓ Mediation points in mechanistic enlightenment and kinetic modeling.

7.Statistical reporting:

- ✓ Replicates and standard deviation/ standard error.
- ✓ Corrosion rate measures within confidence limits.

5.4.4 In the Direction of Physiologically Relevant Standardised Testing.

Compliance with all these aspects of reporting will not only enable a direct comparison between studies, but will also show how systematically effects of test variables on measured outcomes occur. The introduction of dynamic flow, pH control and serum protein presence to test systems introduces the in-vitro assays closer to conditions of physiological relevance emerging studies suggest that other types of assays are more likely to correlate in-vitro and in-vivo degradation patterns (Ferroni *et al.*, 2024; Kovacevic *et al.*, 2025). More emphasis should be put on standardisation initiatives like coordinated interlaboratory studies, validation round among multiple platforms and consensus testing protocols by corrosion and biomaterials societies to seal the existing methodological gaps.

6. Summary Of Specific Findings For Mg–6.0Zn–xCa Alloys And Implications

Even though there is a lack of peer-reviewed literature that specifically covers the topic of Mg-6.0Zn (0.1, 0.3, 0.5) Ca, the literature related to Mg-Zn-Ca in general offers valuable inferences. Research has indicated that refined microstructures with fine dispersions of secondary phases and enhanced corrosion resistance are obtained when low Ca additions (less or equal to 0.1 wt %) are used in Mg-Zn-Ca systems (Zhang *et al.*, 2023; Xie *et al.*, 2022). Nonetheless, addition of more Ca to 0.3 -0.5 wt % can form coarse Ca₂Mg₆Zn₃ or Mg₂Ca intermetallics, which serves as cathodic sites and increases localized corrosion unless microstructural control is realized by extrusion or severe plastic deformation (Istrate *et al.*, 2022; Sun *et al.*, 2024).

Morphology and distribution of voids in porous Mg-Zn-Ca scaffolds have a significant impact on the degradation kinetics since too much porosity increases corrosion and reduces mechanical retention

(Huo *et al.*, 2024). In addition, surface engineering methods, including micro-arc oxidation, sol-gel surface, and conversion layer, cannot be ignored to achieve the best corrosion resistance and biocompatibility even in alloys with a balanced composition of Mg-Zn-Ca (Chen *et al.*, 2023; Wu *et al.*, 2025).

The rate of degradation and mechanical support are very important: too quickly corrosion will cause an early loss of load-bearing capacity, whereas a slow rate will delay bioresorption (Yang *et al.*, 2021). Therefore, the Mg-6.0Zn-0.1Ca alloy is presumably the most suitable between homogenous corrosion and mechanical retention in orthopedic applications but the 0.3-0.5 wt % Ca alloy types might need additional processing or protective coating. On-site assessment of corrosion under the conditions relevant to physiological conditions (vascular, bone, or joint environment) is also crucial because different alloys can act in various ways depending on the fluid composition and pH and loading conditions (Zhang *et al.*, 2023). Lastly, to compare the laboratory findings with the clinical behavior long-term in-vivo validation is needed (Wu *et al.*, 2025).

7. Research Gaps And Future Directions

Although alloy design and mechanistic knowledge have made tremendous advancements, the clinical application of Mg-6Zn-xCa alloys is still limited by scientific and methodological shortcomings that have not been resolved. To enhance the impact and future research, this review outlines five flagship research gaps, whose answers are needed to achieve regulatory acceptance and clinical reliability. These five gaps are critical to be tackled in order to achieve regulatory and clinical translation.

7.1 pH Controlled In-Vitro Dynamic Models.

A majority of in-vitro corrosion research still involves the static immersion in buffered solutions with little control of pH development, fluid renewal as well as biochemical complexity. Nevertheless, the dynamics of magnesium corrosion and surface film stability have consistently been controlled by local variations in pH and have invalidated the predictive quality of the test environment (Atrens *et al.*, 2020; Feyerabend *et al.*, 2020). Lack of standardized dynamic, pH-controlled test platforms is one of the greatest sources of inter-study variability.

Research priority: In-vitro systems with active pH control, physiological ion balance and fluid flow should be developed to enhance correlation with in-vivo degradation behaviour.

7.2 Corrosion-Fatigue Coupling When Under Mechanical Load.

Cyclic loading and electrochemical degradation simultaneous with Mg-6Zn-xCa implants that are supposed to be used in the orthopedic and cardiovascular departments. However, most corrosion tests do not consider mechanical loading even as the corrosion-fatigue coupling is increasingly shown to increase the rate of pit initiation, crack propagation, and early loss of mechanical integrity of Mg alloys (Xiong *et al.*, 2023). This is the gap that restricts realistic lifetime prediction on loading applications. Research priority: The profile of integrated corrosion- fatigue testing and mechanistic models where the synergistic effect between cyclic stress and degradation kinetics is well represented.

9.3 Long-Term (> 6 Month) Degradation Kinetics

The majority of published studies assess degradation over short durations (≤ 28 days), whereas clinical healing and remodeling often extend over several months. Long-term evolution of corrosion morphology, surface films, and mechanical integrity remains poorly characterized, limiting translational confidence (Zheng *et al.*, 2021; Gu *et al.*, 2021).

Research priority: Long-term in-vitro and in-vivo research more than six months long systematically with periodic electrochemical, microstructural, and mechanical evaluation.

7.4 Coating–Substrate Synergy Specific to Mg–6Zn–xCa Alloys

While surface coatings are widely employed to moderate magnesium degradation, their interaction with Zn- and Ca-rich microstructures remains insufficiently understood. Coatings can alter local chemistry, ion release, and electrochemical coupling in ways that are highly substrate-dependent (Li *et al.*, 2021; Jiang *et al.*, 2022). Treating coatings as generic corrosion barriers obscures these interactions.

Research priority: Mechanistically informed studies linking coating chemistry, degradation behavior, and substrate microstructure to long-term corrosion performance and biological response.

7.5 Predictive Modelling Physics-Based and Data-Driven Predictive Modelling.

The intricate coupling of electrochemical, mechanical and biological processes is a limitation on predictive capability on length and time scales. Although there are promising results on phase-field modeling and emerging machine-learning methods, they have yet to apply them to physiologically relevant Mg-Zn-Ca systems (Atrens *et al.*, 2020; Zheng *et al.*, 2021).

Research priority: Hybrid modelling Hybrid modelling models that combine phase-field corrosion models with data-driven learning to assist with alloy optimisation, lifetime prediction, and regulatory assessment.

8. Conclusions

Mg-6Zn-xCa biodegradable alloys have been critically reviewed on their degradation behaviour, mechanistic drivers as well as their translational barriers considering the views of corrosion science, microstructural engineering as well as biomedical application contexts. Despite the fact that Mg-Zn-Ca systems are one of the most promising to be used as temporary load-bearing implants, even alloy compositions that are put forward as nominally similar show a high degree of variability in reported corrosion rates, degradation modes, and biological responses (Atrens *et al.*, 2020; Zheng *et al.*, 2021).

One of the key conclusions drawn in this study is that the degradation behaviour of microstructural states and testing environments is often first-order controlled by microstructural state and testing environment, often over and above the effects of nominal Zn and Ca content. The local electrochemical heterogeneity is controlled by grain size, intermetallic phase topology, impurity distribution, and processing history and corrosion kinetics and morphology are critically determined by environmental parameters, such as pH regulation, buffering chemistry, protein adsorption, fluid transport, and mechanical loading (Song & Atrens, 2020; Jiang *et al.*, 2022). The sustained use of

simplified and static in-vitro test protocols has consequently led to the lack of common meanings and the inability to make predictions about in-vivo performance (Feyerabend *et al.*, 2020).

Notably, this review shows that the corrosion processes that direct Mg-6Zn-xCa alloys cannot be directly applied to lean Mg-Ca or Mg-Zn systems. Depending on the physiological scenario and exposure history locally, both external intervention by Zn-modified cathode kinetics and the existence of Ca-based intermetallic phases can either become familiar with micro-galvanic degradation or facilitate the formation of protective surface layers (partially), respectively (Jiang *et al.*, 2022; Xiong *et al.*, 2023). These mechanistic distinctions must be identified and taken advantage of in order to design rational alloys and coating.

Translational perspective: In the translational perspective, a fundamental change in direction will be needed to move away the composition-based optimisation in favour of a co-ordinated control of microstructure, surface state, and physiologically relevant testing platforms. Compositional optimisation will not produce clinically dependable implants made of Mg-Zn-Ca without stringent management of microstructure and test environment (Atrens *et al.*, 2020; Zheng *et al.*, 2021). This fact is a requirement in the bid to achieve regulatory confidence, safety of the devices, and the subsequent translation of biodegradable magnesium alloys into everyday clinical use.

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Compliance with Ethical Standards: This article does not contain any studies involving human or animal subjects.

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