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Review

Vanadium-free Ti-based high- and medium-entropy alloys as next-generation biomedical implant materials: a critical review

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Abstract: Load-bearing biomedical implants in severe physiological environments must compromise mechanical compatibility, corrosion resistance, and long-term biocompatibility. The fear of the long-term liberation of vanadium and aluminum has provoked the creation of vanadium-free options, despite Ti-6Al-4V remaining clinically viable. This has proved promising, with high- and medium-entropy alloys (HEAs/MEAs) of titanium containing non-toxic two stabilizing elements such as Nb, Ta, Mo, and Zr. Concentrating on the interdependent nature of alloy composition, microstructural development, phase stability, corrosion characteristics, ion release, and biological response, the present critical review article discusses vanadium-free Ti-based HEAs/MEAs and their potential use in biomedical implants. Ti-based HEAs/MEAs have been found to possess low elastic modulus values, corrosion resistance (owing to the presence of multicomponent passive oxide films), and good in vitro cytocompatibility compared to conventional Ti-6Al-4V alloys. This review highlights that microstructural heterogeneity, particularly in additively produced alloys, may have a significant influence on corrosion and biological performance, and that high configurational entropy is not sufficient to ensure improved performance. The challenges that are left to overcome include the lack of standardized testing procedures and long-term in vivo validation. This review presents research priorities so that the clinical translation of vanadium-free Ti-based HEAs/MEAs to be used in load-bearing applications is carried out safely.

Keywords: Vanadium-free alloys; high-entropy alloys; medium-entropy alloys; biomedical implants; corrosion resistance; biocompatibility; complex concentrated alloys; multi-principal element alloys

1. Introduction

Implants with load-carrying capabilities must meet stringent criteria for mechanical strength, corrosion resistance, and biocompatibility in biological environments [1,2]. Titanium and its alloys, particularly Ti-6Al-4V, have emerged as the most commonly used materials for orthopedic and dental implants owing to their high specific strength and superior corrosion resistance [3,4]. Nevertheless, the long-term release of V and Al ions from Ti-6Al-4V alloys is known to induce adverse biological responses and may cause neurological disorders [5–7].

HEAs are defined as multi-principal element alloys containing at least five principal elements in near-equimolar compositions (5–35 at.% each). HEAs are characterized by high configurational mixing entropy ($\Delta S_{mix} \geq 1.5R$), which facilitates the formation of simple solid solution structures instead of intermetallic compounds. Medium-entropy alloys (MEAs) containing three to four principal elements have a slightly lower configurational entropy ($1R \leq \Delta S_{mix} < 1.5R$) than HEAs. HEAs and MEAs are often referred to as molt principal element alloys (MPEAs) and complex concentrated alloys (CCAs), respectively. Hence, to cover all literature related to HEAs/MEAs, it is essential to survey literature containing terminologies such as MPEAs and CCAs [8,9].

The emergence of HEAs/MEAs offers new opportunities in material design owing to their composition-dependent flexibility and unique phase stability behavior [10–12]. HEAs/MEAs offer significantly more freedom in designing alloys with optimized mechanical strength, elastic modulus, and corrosion resistance than conventional alloys containing a dominant element [10,11]. For instance, Ti-based HEAs/MEAs containing non-toxic β-stabilizing elements like Nb, Ta, Mo, and Zr have gained considerable attention for potential use in implants owing to their superior corrosion resistance and phase stability in Ti-based alloys [12–15].

Several studies have indicated that vanadium-free Ti-based HEAs/MEAs tend to have elastic modulus values closer to those of cortical bone, which has an elastic modulus of 10–30 GPa, thereby reducing the likelihood of stress shielding, which is often experienced in conventional Ti-based implants [16,17]. The elastic modulus values of these Ti-based HEAs/MEAs range between 55 and 90 GPa, whereas Ti-6Al-4V has an elastic modulus of 110–120 GPa. Moreover, stable passive oxide layers comprising TiO_2, Nb_2O_5, and Ta_2O_5 have been reported to form on the surface of these Ti-based HEAs/MEAs, thereby improving their corrosion resistance and reducing metal ion release in physiological environments [18–20]. However, there are still gaps in the literature, as most of the research carried out so far has only focused on the phase constitution and mechanical properties of these Ti-based HEAs/MEAs, while corrosion behavior, ion release, and biological response are often studied separately under different conditions [21,22].

Additive manufacturing (AM) techniques, such as directed energy deposition (DED) and selective laser melting (SLM), have further enhanced the applications of HEAs/MEAs for developing Ti-based implants, owing to their ability to produce complex geometries and controllable porous structures [23–25]. However, AM processing may affect the corrosion resistance, corrosion behavior, and biological response of these Ti-based implants, owing to the presence of defects, elemental segregation, and microstructural diversity, which may be formed during AM processing [26–28].

Despite recent progress, the relationships between AM-induced microstructures, corrosion behavior, ion release, and the biological response of vanadium-free Ti-based HEAs/MEAs are still not well understood [29–31].

This critical review article presents an integrated assessment of vanadium-free Ti-based HEAs/MEAs as load-bearing biomedical implant materials. Emphasis is placed on the correlations between composition, microstructure evolution, corrosion response, ion release, and biological response, with a focus on additive manufacturing technologies.

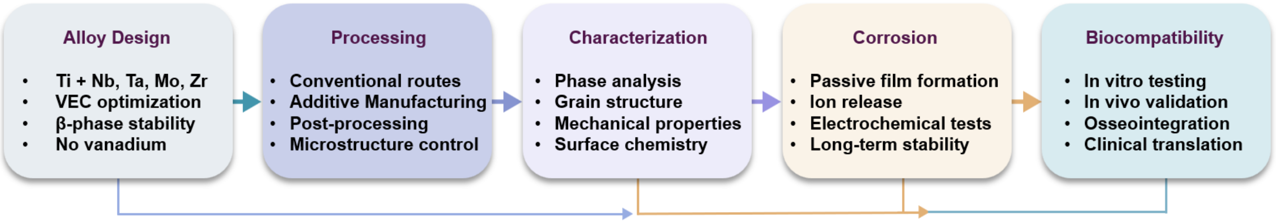

Figure 1. Schematic overview of the review paper.

2. Research landscape and emerging trends

In the last decade, studies on vanadium-free Ti-based high- and medium-entropy alloys have been increasing rapidly, meaning that the perception of their potential in biomedical device applications is becoming clearer. There has been a notable rise in publications in this field since 2015, as shown in Figure 2, with a significant increase in studies that specifically discuss biomedical performance, as revealed by corrosion resistance, ion release, and biocompatibility. This indicates a shift in the field of initial alloy development to research that is application-oriented, in which clinical significance, and not merely structural performance, is the concern. The observed trend serves to show the level of scientific maturity of the field and the necessity of a critical and integrative assessment of current knowledge, which is the basis of the present review.

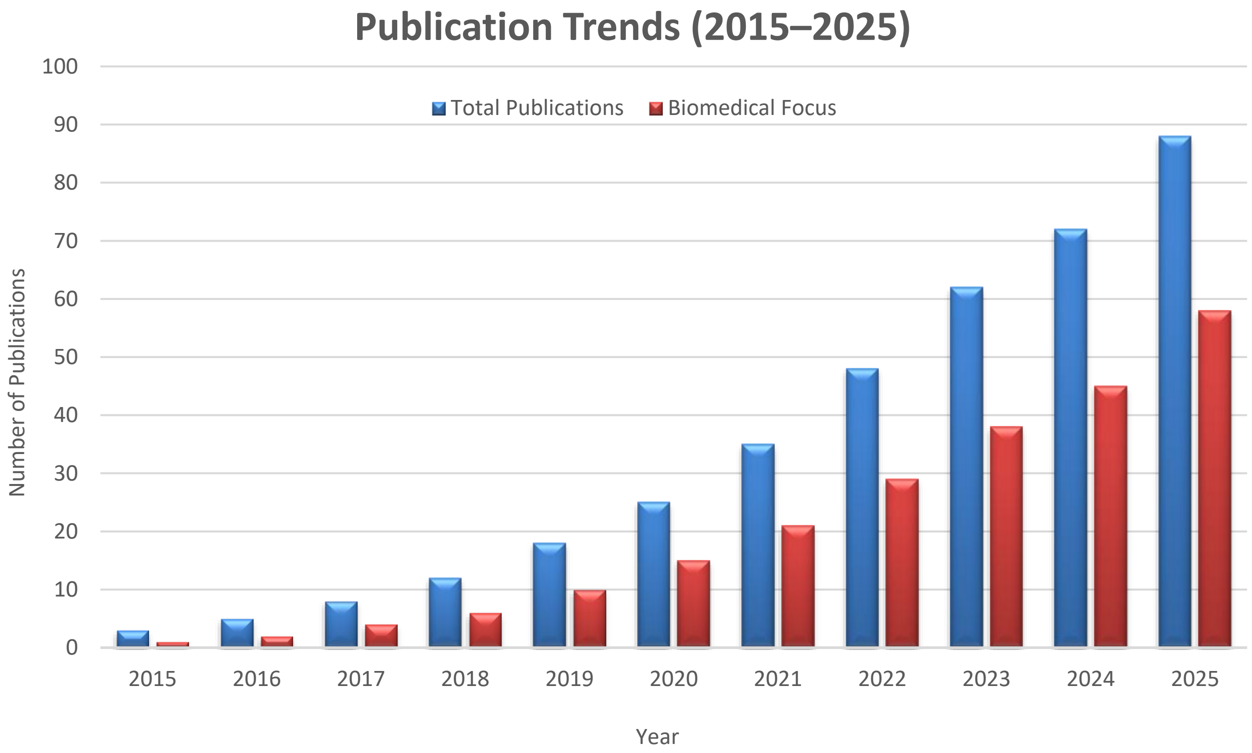

Figure 2. Publication trends related to vanadium-free Ti-based high- and medium-entropy alloys (HEAs/MEAs) for biomedical applications since 2015. There has been a sharp increase in publications and biomedical-centered research, show growing clinical applicability and interest.

3. Alloy design principles of vanadium-free Ti-based HEAs/MEAs

3.1. Elemental selection criteria for biomedical applications

The primary factors that determine the design of vanadium-free Ti-based high- and medium-entropy alloys for use in biomedical implants are biocompatibility, phase stability, and mechanical compatibility with human bone [32–34]. Owing to its proven biological safety, high affinity for oxygen to form a stable TiO_2 passive layer, and long clinical record in load-bearing implants, titanium is traditionally used as the basal element. Vanadium's cytotoxicity and potential adverse neurological and inflammatory actions on the long-term release of the ions are motivating factors that drive the selective elimination of vanadium [15,35].

Ti alloys are also composed of other non-toxic elements that replace the β-phase-stabilizing role of vanadium. Table 1 shows that niobium (Nb) and tantalum (Ta) are especially attractive owing to their better corrosion properties, established biocompatibility, and capability to stabilize the body-centered cubic (β) phase in Ti-based systems [36–38]. Even though zirconium (Zr) is neutral with regard to phase stability, it enhances corrosion and solid solution strengthening, yet it does not impair the biological response [39,40]. Molybdenum (Mo) is used to increase the stability and strength of the β-phase, but should be controlled carefully to avoid unwanted density and elastic modulus [41].

Table 1. Representative vanadium-free Ti-based HEAs/MEAs for biomedical applications.

Alloy system	Composition (at.%)	Classification	VEC	Phase constitution	Elastic modulus (GPa)	Yield strength (MPa)	Ref.
TiNbTaZr	$Ti_{25}Nb_{25}Ta_{25}Zr_{25}$	HEA	4.5	Single β (BCC)	68–72	850–920	[42,43]
TiNbTaZrMo	$Ti_{20}Nb_{20}Ta_{20}Zr_{20}Mo_{20}$	HEA	4.8	Single β (BCC)	78–85	980–1050	[24,44]
TiNbZr	$Ti_{33.3}Nb_{33.3}Zr_{33.3}$	MEA	4.33	β + minor α	62–67	720–790	[29,45]
TiNbTa	$Ti_{33.3}Nb_{33.3}Ta_{33.3}$	MEA	4.33	Single β (BCC)	71–76	830–900	[46,47]
TiZrNbMo	$Ti_{25}Zr_{25}Nb_{25}Mo_{25}$	HEA	4.75	Single β (BCC)	74–80	910–980	[48,49]
TiNbTaZrHf	$Ti_{20}Nb_{20}Ta_{20}Zr_{20}Hf_{20}$	HEA	4.4	Single β (BCC)	82–89	920–1020	[50,51]
TiNbMo	$Ti_{40}Nb_{30}Mo_{30}$	MEA	4.6	β + ω traces	69–74	780–850	[52,53]
TiZrTa	$Ti_{35}Zr_{35}Ta_{30}$	MEA	4.3	Single β (BCC)	66–71	740–810	[54,55]
TiAlFeCoNi	$Ti_{20}Al_{20}Fe_{20}Co_{20}Ni_{20}$	HEA	7.2	BCC + ordered phases	70–90	–	[56]
TiNbZrTaHf	$Ti_{20}Nb_{20}Zr_{20}Ta_{20}Hf_{20}$	HEA	4.3	Single β (BCC)	79	–	[57]
TiZrHfNbTa	$Ti_{20}Zr_{20}Hf_{20}Nb_{20}Ta_{20}$	HEA	4.4	BCC + ω	69	2130 (UTS)	[57]
Ti-6Al-4V (reference)	$Ti_{90}Al_{6}V_{4}$	Conventional	4.18	α + β	110–120	880–950	[58,59]
Cortical bone	-	Natural tissue	-	-	10–30	-	[60,61]

Notes:

- VEC = Valence electron concentration
- BCC = Body-centered cubic
- Values represent ranges from multiple studies under different processing conditions
- The elastic modulus reduction compared to that of Ti-6Al-4V is critical for minimizing stress shielding
- All compositions are equiatomic unless otherwise specified
- The reported ranges originate from different studies that employed various processing routes and testing conditions

3.2. Phase stability and β-phase promotion

Phase constitution has a strong influence on mechanical properties of a high-entropy alloy and multi-component alloys. Specifically, the single-phase solid solutions compared to the multi-phase microstructures are formed to play a more significant role in the overall behavior of the mechanical stability of the solid solutions [62–64].

Figure 3 illustrates how phase stability in vanadium-free HEAs/MEAs is achieved through the combined effect of non-toxic β-stabilizing elements such as Nb, Ta, Mo, and Zr.

When properly adjusted, the high configurational entropy associated with the structure of HEAs/MEAs may help prevent the development of brittle intermetallic phases and promote the development of simpler solid-solution phases. However, it is still difficult to guarantee the stability of the phases using the entropy effect, with complex phases developing, particularly after processes such as heating, shaping, or even 3D printing. To achieve the phase stability required for biomedical applications, a precise equilibrium between enthalpic interactions and atomic size differences is required [65,66].

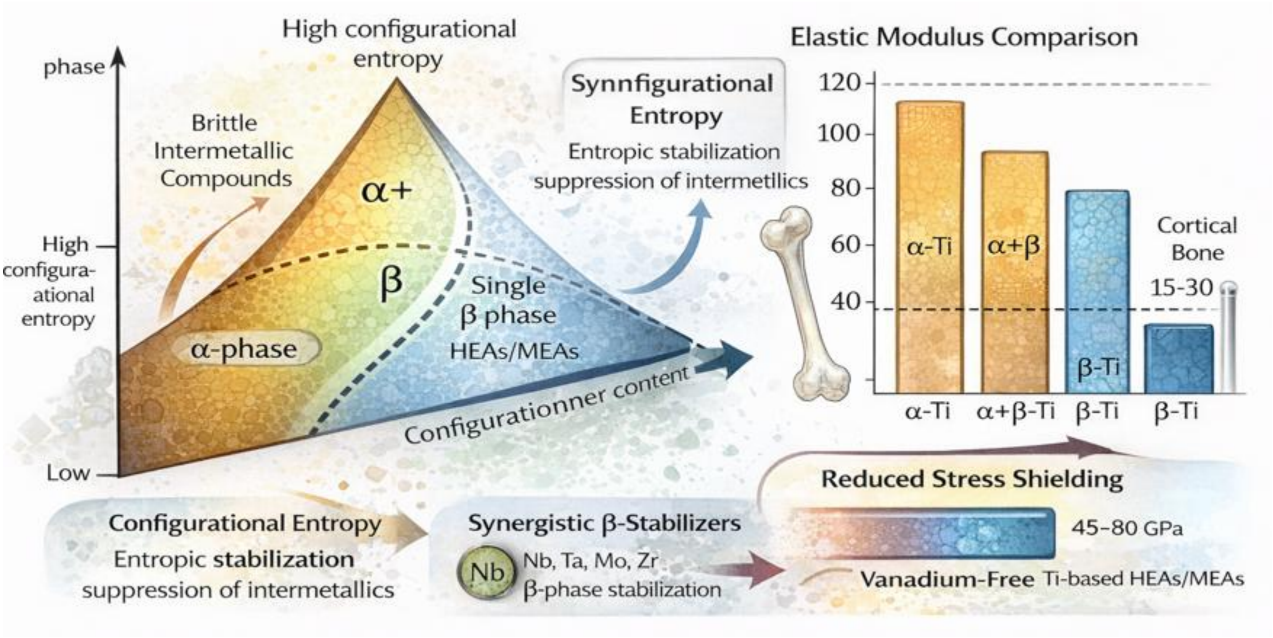

Figure 3. Phase stability and β-phase promotion in Ti-based HEAs/MEAs without vanadium. The diagram shows the synergetic impact of various non-toxic β-stabilizing elements and configurational entropy on the encouragement of β-dominant or single-β phases and the resultant low elastic modulus relative to α- and α + β microstructures, which provides a mechanical benefit in biomedical terms.

3.3. Thermodynamic and empirical design parameters

A variety of thermodynamic and empirical parameters have informed the compositional design of vanadium-free Ti-based HEA/MEAs. Several parameters have been used to predict the tendency of phase formation in multi-principal element alloys, including the atomic size difference (δ), mixing enthalpy (ΔH mix), valence electron concentration (VEC), and Ω parameter [67–69]. According to Table 2, the single-phase solid solution is usually favored in cases where both δ and ΔH coincide within typical numbers, but in Ti-based ones, VEC values exceeding approximately 4.2–4.4 are likely to encourage stabilization of the two (BCC) phases [70,71].

These parameters are useful; however, when fabricating alloys used in biomedicine, they must be employed cautiously. Most predictive criteria have been designed to work with structural HEAs and do not directly consider the biological response, ion release, or corrosion behavior. Therefore, alloy compositions that are merely optimized in terms of mechanical strength or phase stability might not be as efficient in a physiological environment [72,73]. This highlights that corrosion and biocompatibility issues, along with thermodynamic design issues, must be considered at an early stage in the alloy development process.

Table 2. Thermodynamic and empirical design parameters for vanadium-free Ti-based HEAs/MEAs.

Alloy system	δ (%)	ΔH_mix (kJ/mol)	ΔS_mix (J/K·mol)	VEC	Ω	Predicted phase	Actual phase	Agreement	Ref.
TiNbTaZr	4.8	−4.2	11.53	4.5	5.8	Single β (BCC)	Single β	✓	[31,74]
TiNbTaZrMo	5.2	−3.8	13.38	4.8	7.2	Single β (BCC)	Single β	✓	[31,50]
TiNbZr	4.2	−5.1	9.13	4.33	4.5	β + minor α	β + α traces	✓	[29,48]
TiNbTa	4.6	−4.5	9.13	4.33	5.1	Single β (BCC)	Single β	✓	[47,74]
TiZrNbMo	5	−4	11.53	4.75	6.5	Single β (BCC)	Single β	✓	[49,50]
TiNbTaZrHf	5.4	−3.5	13.38	4.4	7.8	Single β (BCC)	Single β	✓	[24,51]
TiNbMo	4.5	−4.8	9.13	4.6	4.9	β + ω possible	β + ω traces	✓	[48,53]

Notes:

- δ = Atomic size difference: $\delta = 100\sqrt{[\Sigma c_i(1-r_i/\bar{r})^2]}$
- ΔH_mix = Mixing enthalpy: $\Delta H\_mix = \Sigma_{i=1}^{n} \Sigma_{j=i+1}^{n} 4\Delta H\_ij\text{^}mix\ c_i c_j$
- ΔS_mix = Configurational entropy: $\Delta S\_mix = -R\ \Sigma c_i \ln(c_i)$
- VEC = Valence electron concentration: $VEC = \Sigma c_i (VEC)_i$
- Ω = Thermodynamic parameter: $\Omega = T\_m\ \Delta S\_mix / |\Delta H\_mix|$
- General criteria for single-phase BCC: VEC > 4.2–4.4, δ < 6.6%, -15 < ΔH_mix < 5 kJ/mol
- Design parameters show reasonable predictive power but not absolute
- The reported ranges originate from different studies that employed various processing routes and testing conditions

3.4. Design trade-offs and current limitations

These materials have a high degree of flexibility in modifying their properties; however, trade-offs between the mechanical and elastic moduli, corrosion, and processability simultaneously generate inherent limitations in the design of vanadium-free Ti-based HEAs/MEAs. Refractory 2-stabilizers such as Nb, Ta, and Mo may be increased to enhance strength and corrosion resistance, although this usually results in higher density and elastic modulus, which is not favorable for load-bearing implants [60,75]. However, lowering the alloying content to a lower modulus would be at the expense of phase stability and mechanical reliability.

Moreover, compositional complexity can make manufacturing difficult, especially in additive manufacturing methods, where elemental segregation and microstructural heterogeneity can be favored by differences in the melting points and diffusion behavior [76,77]. These problems highlight the significance of adopting a comprehensive approach to alloy design that incorporates a balance between manufacturability, composition complexity, long-term in vivo performance, and biomedical performance.

Although many alloy compositions have been proposed for the development of HEA/MEAs for biomedical applications, most research has focused on the evaluation of the mechanical properties without entirely addressing corrosion properties and biocompatibility. Thus, optimization of the alloy composition for the development of HEAs/MEAs for biomedical applications is still a complex challenge.

4. Microstructural evolution and processing effects

4.1. Phase constitution and microstructural features

The phase constitution of vanadium-free Ti-based high- and medium-entropy alloys (HEAs/MEAs) is of interest for determining the mechanical compatibility, corrosion behavior, and biological performance of these materials in load-bearing biomedical applications [72,73,78]. Owing to its reduced elastic modulus and superior mechanical compatibility with cortical bone, the stabilization of the body-centered cubic (β) phase is normally favored over that of α or α + β microstructures in titanium systems. Consequently, most vanadium-free Ti-based HEAs/MEAs have been designed in such a way that they promote a single-phase or β-dominant BCC microstructure.

The tendency toward stabilization of the β-phase in titanium alloys can be explained by the basic phase equilibria of titanium alloys. Figure 4 indicates that the temperature and alloying elements influence the stability domains of the α, 80, and 88 phases. At room temperature, β-stabilizing elements such as Nb, Ta, and Mo inhibit the occurrence of α and omega phases in the traditional Ti alloys by tipping the phase lines to the beta direction [79–81]. Equivalent stabilization processes occur in Ti-based HEAs/MEAs that do not include vanadium, and the joint ability of multiple non-toxic β-stabilizers to stabilize β-phase retention is promoted over a wide compositional and temperature space.

In addition to the effect of the elements, the large configurational entropy of HEAs/MEAs favors the development of simple solid-solution structures and discourages the development of complex intermetallic phases [79,82]. However, entropy alone cannot provide single-phase stability. Several studies have reported the formation of secondary phases, particularly α-Ti or the metastable omega phase, after thermomechanical processing or additive manufacturing under non-equilibrium cooling conditions [83,84]. Secondary phases can significantly influence electrochemical heterogeneity and local mechanical response, which can have long-term biological stability and corrosion resistance implications.

Thus, microstructural homogeneity is a critical requirement for biomedical-grade vanadium-free HEA/MEAs. Alloys with a homogeneous β-dominant microstructure are generally more predictable in their mechanical behavior than their multiphase counterparts and are less likely to develop localized corrosion [9,85]. Conversely, phase boundaries and chemically heterogeneous regions may be favorable sites for local ion release and passive film breakdown under physiological conditions [86]. These aspects underscore the importance of controlling phase constitution during the optimization of mechanical properties and ensuring corrosion resistance and biocompatibility.

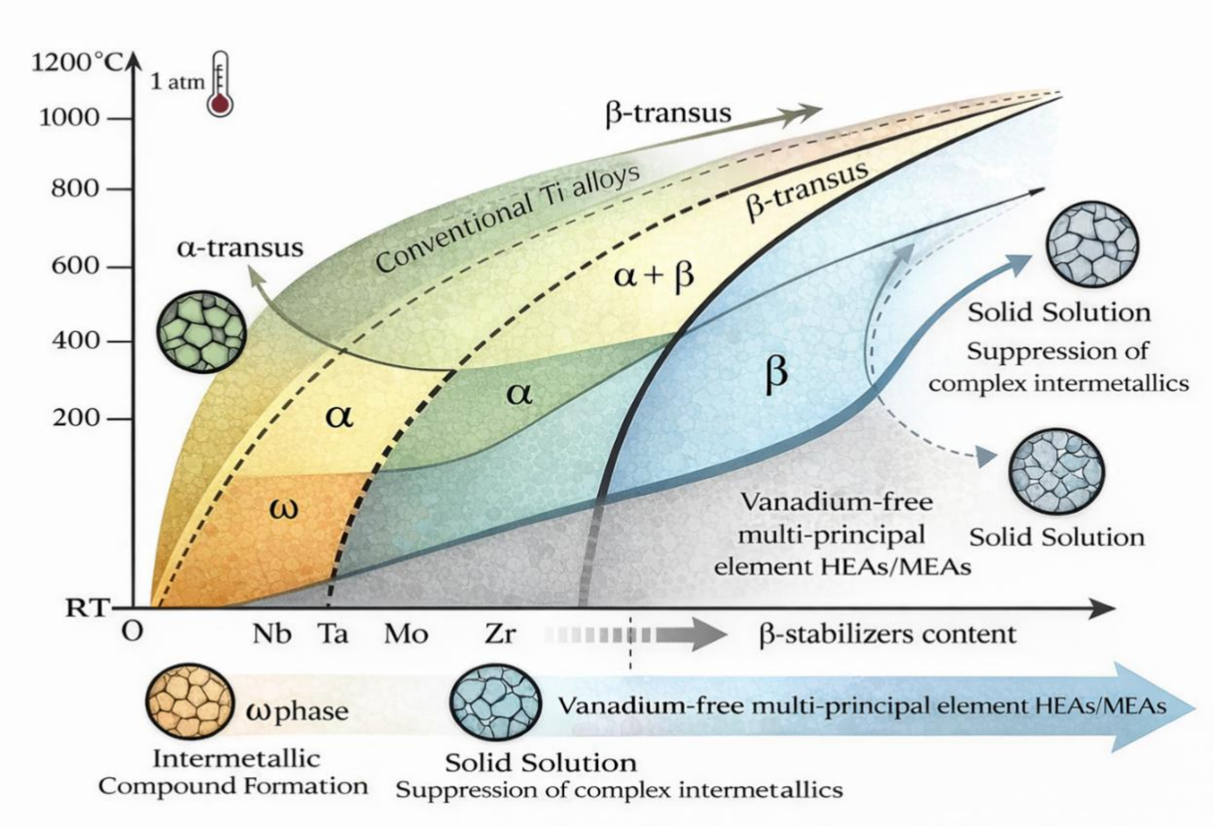

Figure 4. Phase diagrams of titanium alloys showing the α, β, and ω phase stability regions relevant to vanadium-free Ti-based HEA/MEAs.

4.2. Grain size, lattice distortion, and solid-solution effects

The high lattice distortion caused by a mismatch in the atomic size between the constituent elements is one of the features that distinguishes HEAs/MEAs. This distortion influences the grain boundary properties and dislocation movement, as well as the diffusion behavior, in addition to enhancing the solid solution [80,81]. Fine-grained microstructures are commonly desirable in the context of biomedical Ti-based HEAs/MEAs owing to the ability of grain refinement to enhance strength at a relatively low elastic modulus.

Grain size also plays a major role in corrosion behavior. Under certain conditions, finer grains may hasten the development of passive films and enhance corrosion resistance because they increase the density of the grain boundaries. Conversely, when chemical inhomogeneities exist, a large grain boundary density may become the desired site for localized corrosion [82,83]. Such antagonistic effects, instead of blindly refining the grains, highlight the importance of a refined microstructure.

4.3. Effects of thermomechanical processing

Thermomechanical processing, such as hot forging and rolling, and subsequent solidification heat treatments, such as annealing, are commonly employed to tailor the microstructures of vanadium-free Ti-based high- and medium-entropy alloys (HEAs/MEAs). It has been shown that controlled annealing treatments can preserve or stabilize a dominant body-centered cubic (BCC, β-type) solid-solution phase in Ti-based bio-HEAs, change the grain morphology, and reduce microstructural heterogeneity, enhancing mechanical reliability and biomedical use [61].

Chemical uniformity may be further promoted by proper homogenization heat treatments by minimizing the elemental segregation caused by solidification or additive manufacturing processes. Because enhanced chemical homogeneity has been directly associated with greater corrosion resistance and more desirable biocorrosion and cellular reactions in simulated physiological settings, these decreases in compositional heterogeneity are particularly essential to biomedical HEAs/MEAs [87,88].

However, long-term exposure to high temperatures can result in undesirable microstructural evolution, including phase breakdown, coarsening, and alloy element redistribution. These modifications can damage electrochemical performance and compromise the mechanical compatibility by reintroducing local chemical heterogeneities or secondary phases that are preferred for corrosion [89].

The nature of HEAs/MEAs as multi-principal element alloys indicates that their response to thermomechanical processing is more complex than that of standard titanium alloys. Despite the conventional description of diffusion behavior in HEAs as slow, recent work on diffusion has also demonstrated that not all diffusion can be described as sluggish, and that, to a large extent, the diffusion behavior in alloy systems and individual elements depends on the alloy system and its constituents. Nonetheless, phase control and homogenization may become more challenging during processing when utilizing multicomponent diffusion; therefore, detailed thermomechanical schedules are necessary for biomedical-grade HEAs/MEAs [90].

Besides the commonly used names of high-entropy alloys (HEAs) and medium-entropy alloys (MEAs), wider categories, such as multi-principal element alloys (MPEAs) and complex concentrated alloys (CCAs), are often mentioned in research. These categories include several titanium-based alloys made for medical use, such as $Ti_{35}Zr_{35}Nb_{15}Mo_5Fe_5Cr_5$, TiZrNbHfTa, and TiZrNbTaMo, which have shown good strength, resistance to corrosion, and compatibility with the body. Recent studies have found that Ti-based CCAs can have good elasticity, high strength, and better resistance to corrosion under conditions that mimic the human body, which makes them promising options for biomedical implants [91,92].

In addition, knowing how biomedical structures respond to forces and how stress is spread within them is important for assessing how well implants work and how reliable they are [93].

4.4. Microstructural implications of additive manufacturing

Additive manufacturing (AM) creates additional microstructural complexity in vanadium-free Ti-based HEA/MEAs. AM processes such as directed energy deposition (DED) and selective laser melting (SLM) often generate microscale elemental segregation, residual stresses, steep thermal gradients, and repeated thermal cycling, owing to their rapid solidification, steep thermal gradients, and repeated thermal cycling [24,48,94]. Segregation and compositional changes, as indicated in Table 3, can result in localized electrochemical cells, which promote corrosion initiation, although AM-induced grain refinement can enhance strength.

In addition, AM-specific defects, such as porosity and lack of fusion, may undermine mechanical integrity and biocompatibility and serve as stress concentrators and favorable corrosion locations [95,96]. Post-processing techniques, such as hot isostatic pressing and heat treatment, are important to minimize such issues and generate microstructures that are suitable in the biomedical field in the long term [97].

Table 3. Additive manufacturing processing parameters and microstructural outcomes.

Alloy system	AM technique	Laser power (W)	Scan speed (mm/s)	Layer thickness (μm)	Grain structure	Relative density (%)	Phase constitution	Ref.
TiNbTaZr	SLM	200–250	800–1200	30–40	Fine columnar	98.5–99.8	Single β	[98,99]
TiNbTaZrMo	SLM	250–300	600–1000	30–50	Cellular/columnar	97.2–99.5	β + trace ω	[42,100]
TiNbZr	L-PBF	180–220	1000–1400	30–40	Fine equiaxed	99.0–99.7	β dominant	[38,101]
TiNbTa	DED	800–1200	400–800	200–400	Coarse columnar	98.0–99.3	Single β	[102,103]
TiZrNbMo	SLM	220–280	700–1100	30–50	Fine cellular	98.2–99.6	β + minor α	[73,104]
TiNbTaZr + HIP	SLM + HIP	200–250	800–1200	30–40	Homogenized	99.7–99.9	Single β	[105,106]

Notes:

- SLM = Selective laser melting; L-PBF = laser powder bed fusion; DED = directed energy deposition
- HIP = hot isostatic pressing (typically 900–1000 °C, 100–150 MPa, 2–4 h)
- Relative density measured by the Archimedes' method or CT scanning
- Post-processing (HIP, heat treatment) significantly improves density and homogeneity
- Elemental segregation is common in the as-built condition, reduced after heat treatment

4.5. Critical assessment and knowledge gaps

Despite these advances, certain limitations exist with reference to the correlation of microstructural properties with functional properties in vanadium-free Ti-based HEAs/MEAs. Most studies on HEAs/MEAs have focused on microstructural properties, with no clear correlation with their corrosion, ion release, and biological properties. The use of microstructural observations as predictors is restricted because most studies provide them without systematic correlations with biological results or corrosion processes [34,107]. Moreover, owing to the lack of standardized characterization protocols, the definition of optimal microstructural configurations is blurred, and cross-study comparisons are complicated.

Future studies should prioritize the use of integrated methods that simultaneously measure the microstructure, corrosion behavior, ion release, and biological response under clinically relevant conditions. Such an approach is necessary to establish strong structure–property–biocompatibility relationships and to develop vanadium-free Ti-based HEAs/MEAs for reliable clinical use.

Although there are a number of studies showing improved microstructural stability in Ti-based HEAs/MEAs, results were found to be largely dependent on processing routes and cooling procedures, making it challenging to compare the results of different studies.

5. Corrosion behavior and ion release in physiological environments

5.1. Electrochemical corrosion mechanisms in vanadium-free Ti-based HEAs/MEAs

The corrosion characteristics of vanadium-free Ti-based HEAs/MEAs are a major factor that determines their long-term reliability in biomedical implants that must bear loads. There are complicated interactions among the surface chemistry, microstructure heterogeneity, alloy composition, and electrolyte composition surrounding the corrosion processes under physiological conditions [108,109]. The creation of uniform and cohesive passive oxide layers contributes significantly to the corrosive properties of Ti-based HEAs/MEAs, as in conventional titanium metal alloys [88].

In several studies, vanadium-free Ti-based HEAs/MEAs have been demonstrated to generate passive layers enriched in TiO_2, Nb_2O_5, Ta_2O_5, and ZrO_2, which have low ionic conductivities and are thermodynamically stable under body fluid conditions [17,110,111]. Nb and Ta are also particularly beneficial, as demonstrated in Figure 5, because these oxides enhance the stability of passivation and reduce the susceptibility to localized corrosion in the presence of chloride-rich environments. However, the passive continuity of the film may be broken, and micro-galvanic corrosion may be promoted by variations in chemical homogeneity, particularly when added during processing or additive manufacturing [112,113].

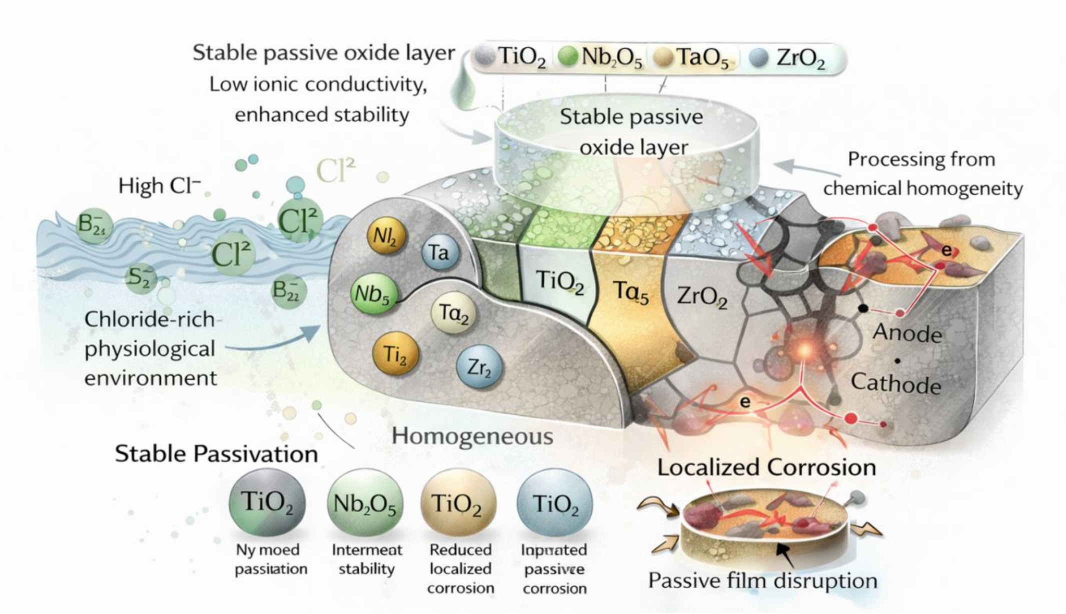

Figure 5. Electrochemical corrosion behavior of Ti-based HEA/MEAs without vanadium under physiological conditions. Although passivation may be disrupted by chemical heterogeneity due to processing or additive manufacturing, which encourages micro-galvanic coupling and allows localized corrosion and ion release, the formation of a stable passive oxide film enriched with TiO_2, Nb_2O_5, Ta_2O_5, and ZrO_2 provides better corrosion resistance.

5.2. Influence of microstructure and processing on corrosion performance

Examples of microstructural characteristics that significantly influence the corrosion behavior of vanadium-free HEAs/MEAs are grain size, phase distribution, and elemental segregation. Compared with multiphase systems, which have phase boundaries that are often preferred locations of localized attack, single-phase or β-dominant microstructures tend to exhibit more homogenous corrosion behavior [112,114]. Fine-grained microstructures can be used to accelerate passive film formation; however, when compositional variations exist, their excess heterogeneity can also promote corrosion susceptibility at grain boundaries [115].

Processing routes have a significant influence on corrosion performance. Cast and wrought HEAs/MEAs often exhibit different corrosion behaviors because of differences in microstructural homogeneity, whereas additively manufactured alloys might exhibit enhanced corrosion behavior following appropriate post-processing treatments, such as hot isostatic pressing [116,117]. These findings illustrate the importance of the relationship between corrosion data and in-depth microstructural characterization instead of considering corrosion resistance as an intrinsic material property.

5.3. Ion release and its biological implications

The direct relationship between the release of metal ions in implant materials and cytotoxicity, inflammatory response, and tissue compatibility in the long term is a significant issue in biomedical engineering. Even though the elimination of vanadium significantly reduces the chances of introducing potentially dangerous ions in vanadium-free Ti-based HEAs/MEAs, other alloying metals, such as Mo and, to a lesser extent, Nb and Ta, should also be taken into consideration cautiously [118,119].

In experimental studies performed in cell culture media and simulated body fluids, low ion release rates of vanadium-free Ti-based HEAs/MEAs have often been observed; these rates are often similar to or lower than those of Ti-6Al-4V [120]. Owing to differences in the duration of the tests, solution chemistry, surface finish, and analytical methods, different ion release values have been reported across studies, as summarized in Table 4. The lack of standardized ion-release testing procedures is a major challenge that complicates direct comparisons and risk assessment [121].

Table 4. Corrosion performance of vanadium-free Ti-based HEAs/MEAs in simulated body fluids.

Alloy system	Testing solution	E_corr (V vs. SCE)	i_corr (μA/cm^2)	Passive film composition	Ion release rate	Ref.
TiNbTaZr	Hank's solution (37 °C)	−0.18 to −0.12	0.08–0.15	TiO$_2$, Nb$_2$O$_5$, Ta$_2$O$_5$, ZrO$_2$	<5 ppb/cm^2/day	[122,123]
TiNbTaZrMo	PBS (pH 7.4, 37 °C)	−0.15 to −0.09	0.12–0.19	TiO$_2$, Nb$_2$O$_5$, Ta$_2$O$_5$, MoO$_3$	<8 ppb/cm^2/day	[61,124]
TiNbZr	Ringer's solution (37 °C)	−0.22 to −0.16	0.15–0.23	TiO$_2$, Nb$_2$O$_5$, ZrO$_2$	<6 ppb/cm^2/day	[15,125]
TiNbTa	0.9% NaCl (37 °C)	−0.20 to −0.14	0.11–0.18	TiO$_2$, Nb$_2$O$_5$, Ta$_2$O$_5$	<4 ppb/cm^2/day	[72,126]
TiZrNbMo	Hank's solution (37 °C)	−0.16 to −0.10	0.14–0.21	TiO$_2$, ZrO$_2$, Nb$_2$O$_5$, MoO$_3$	<7 ppb/cm^2/day	[88,127]
Ti-6Al-4V	Hank's solution (37 °C)	−0.28 to −0.22	0.25–0.35	TiO$_2$, Al$_2$O$_3$	10–18 ppb/cm^2/day (V)	[15,128]

Notes:

- E_corr = Corrosion potential (more positive = more noble)
- i_corr = Corrosion current density (lower = better corrosion resistance)
- SCE = Saturated calomel electrode
- Ion release rates vary significantly with surface finish and testing duration
- Most vanadium-free HEAs/MEAs show improved corrosion resistance compared to Ti-6Al-4V

5.4. Comparative performance with conventional titanium alloys

Enhancing the corrosion and ion release capacities of conventional titanium alloys while maintaining their mechanical compatibility is an important objective in the design of vanadium-free HEAs/MEAs. Comparative studies have been conducted under simulated physiological conditions, with a variety of Ti-based HEAs/MEAs showing lower corrosion current densities and more noble corrosion potentials than Ti-6Al-4V [120,124,129]. Such improvements are often attributed to multi-element passive film chemistry and reduced susceptibility to localized corrosion.

Nevertheless, without the addition of vanadium, not all HEA/MEA have shown improved performance compared to conventional titanium alloys. For some, the performance of the HEA/MEA has been shown to be dependent on the microstructural homogeneity, which makes the results difficult to generalize, particularly where the composition is complex enough to give rise to corrosion due to segregation or where microstructural control is wanting [129]. Rather than presuming inherent superiority under the banner of high entropy only, these results indicate the necessity of rigorously designing alloys and optimizing their processing.

5.5. Critical challenges and future directions

Notwithstanding the encouraging corrosion and release characteristics, several critical problems must be addressed before vanadium-free Ti-based HEAs/MEAs can be considered viable for use as clinical implants. These include insufficient correlation between corrosion information and biological performance, the absence of standardized electrochemical testing procedures, and the absence of long-term immersion and in vivo corrosion experiments [34,130]. Another significant limitation is that standardized tests for electrochemical testing do not exist. Differences in the composition of the used electrolytes and exposure times may prevent direct comparisons and may give inconsistent conclusions in terms of corrosion performance.

Future research should include a systematic and comparative analysis of corrosion testing under clinically relevant conditions, including cyclic loading and fretting-corrosion conditions. Corrosion information should be combined with ion-release data and biological hazards to establish reliable safety profiles and accelerate the entry of vanadium-free HEA/MEAs into biomedical applications.

Although enhanced corrosion resistance is generally reported in many Ti-based HEAs/MEAs, there are significant differences in various alloy compositions and environments. Variations in electrolytes, surface treatments, and electrochemical measurement techniques have also been reported.

6. Biocompatibility and biological response

6.1. In vitro cytocompatibility and cellular response

In vitro biocompatibility is an important initial step toward establishing that vanadium-free Ti-based HEAs/MEAs can be used as biomedical implants. In most studies that have been presented to date using conventional cytocompatibility tests, osteoblast-like cells, mesenchymal stem cells, or fibroblasts have been cultured on alloy surfaces or subjected to alloy extracts to test their cell viability, proliferation, and adhesion [42,120,131]. Cellular responses to vanadium-free Ti-based HEAs/MEAs were positive, as shown in Table 5, and the reported cell viability and proliferation levels were comparable to or better than those of Ti-6Al-4V.

Surface chemistry and topography play a major role in cell–material interactions. It has been established that the growth of stable layers of oxides enriched with Ti, Nb, Ta, and Zr prevents the release of potentially dangerous metal ions but enhances protein adsorption and attachment of cells [132,133]. Cross-body comparisons are not aided by variations in surface preparation, including polishing, passivation, and surface roughness, which are known to significantly influence reported biological results [133].

Table 5. In vitro biocompatibility assessment of vanadium-free Ti-based HEAs/MEAs.

Alloy system	Cell type	Viability (%)	Proliferation vs. control	Adhesion	Cytotoxicity grade	Test duration	Ref.
TiNbTaZr	MC3T3-E1 osteoblasts	96–102	1.15–1.25×	Excellent	Grade 0 (non-toxic)	1–7 days	[134,135]
TiNbTaZr	hMSCs	94–99	1.10–1.18×	Good	Grade 0	3–14 days	[136,137]
TiNbTaZrMo	MC3T3-E1 osteoblasts	92–98	1.08–1.15×	Good	Grade 0–1	1–7 days	[138,139]
TiNbZr	MG-63 osteoblasts	95–101	1.12–1.22×	Excellent	Grade 0	1–5 days	[140,141]
TiNbTa	L929 fibroblasts	97–103	1.05–1.12×	Good	Grade 0	1–7 days	[135,142]
TiZrNbMo	MC3T3-E1 osteoblasts	91–96	1.06–1.14×	Moderate	Grade 0–1	1–7 days	[139,143]
TiNbMo	hMSCs	93–98	1.08–1.16×	Good	Grade 0	3–10 days	[138,144]
Ti-6Al-4V	MC3T3-E1 osteoblasts	88–95	1.00× (control)	Good	Grade 0–1	1–7 days	[134,145]

Notes:

- Viability measured by MTT, CCK-8, or live/dead assays
- Cytotoxicity grading per ISO 10993-5: Grade 0 = none, Grade 1 = slight
- hMSCs = human mesenchymal stem cells
- Most vanadium-free HEAs/MEAs show equal or superior performance to Ti-6Al-4V
- Surface finish and roughness significantly influence results across studies

6.2. Effects of ion release on cellular behavior

The biological effects of other alloying elements, particularly molybdenum, remain a major consideration, even though vanadium-free HEAs/MEAs do not cause any concerns regarding vanadium toxicity. In vitro experiments usually release low concentrations of noncytotoxic ions that are not toxic when the exposure period is brief [42,120]. However, little is known about the biological consequences of the low-level but long-term release of ions, especially under dynamic physiological conditions with fluid flow and mechanical loading.

More importantly, some studies exclusively employed cytotoxicity assays using indirect extracts, which may be insufficient to measure localized biological consequences at the implant–tissue interface.

Hence, direct contact tests and long-term exposure experiments are essential to obtain a more realistic estimate of the biological threat posed by the ion release of vanadium-free HEAs/MEAs [146]. Moreover, biological tests are usually based on short-term in vitro studies that do not reflect the complex biological environment encountered in vivo.

Moreover, molybdenum (Mo) is highly identified as a powerful effect of β-phase stabilization in titanium-based alloys and is the most important influence on improving mechanical properties and resistance to corrosion. Ti-based HEAs/MEAs alloys containing Mo have enhanced electrochemical stability in physiological conditions as the formation of stable passive oxide films. Moreover, incorporation of Mo helps to enhance mechanisms and enhance microstructural stability. Nevertheless, just like other metallic metal ions in biomedical alloys, the long-term biological impacts of released metal ions are a field where future studies need to be done [147,148].

It is important to note that although good results have been obtained in various studies, it is essential to highlight that there is still a lack of understanding of the biological effects of long-term ion release from multi-element alloys. For this reason, it is essential to establish standardized experimental procedures to properly assess the biological safety of Ti-based HEAs/MEAs.

6.3. In vivo evidence and current limitations

In vivo studies on vanadium-free Ti-based HEAs/MEAs are still rare, as the number of in vitro studies has been growing. A limited number of animal studies have documented minimal inflammatory responses and satisfactory osseointegration behavior in the short term after implantation [149,150]. Although the results are encouraging, as summarized in Table 6, there are insufficient in vivo data to make solid conclusions regarding the long-term safety, systemic ion distributions, and potential accumulation effects.

Additionally, variations in animal models, implantation sites, and evaluation processes make it difficult to make meaningful comparisons between studies. The absence of common in vivo testing models is one of the biggest challenges in clinical translation and regulatory approval [151,152].

Table 6. Summary of in vivo studies on vanadium-free Ti-based HEAs/MEAs.

Alloy system	Animal model	Implantation site	Duration	Inflammatory response	Osseointegration	Bone contact (%)	Systemic toxicity	Ref.
TiNbTaZr	Rabbit	Femur (intramedullary)	12 weeks	Minimal (Grade 1)	Good	68–75	None detected	[153]
TiNbTaZr	Rat	Tibia (cortical)	8 weeks	Minimal (Grade 0–1)	Excellent	72–78	None detected	[154]
TiNbZr	Rabbit	Femur (cortical)	16 weeks	Minimal (Grade 1)	Good	65–72	None detected	[153]
TiNbTa	Rat	Calvaria (flat bone)	12 weeks	Minimal (Grade 0–1)	Good	70–76	None detected	[154]
Ti-6Al-4V	Rabbit	Femur (intramedullary)	12 weeks	Mild (Grade 1–2)	Good	65–70	Detected in organs	[153]

Notes:

- Inflammatory response grading: Grade 0 = none, Grade 1 = minimal, Grade 2 = mild
- Bone-implant contact (BIC) measured by histomorphometry
- Most studies show comparable or improved performance vs. Ti-6Al-4V
- Critical limitation: Very limited number of in vivo studies (only 4–5 independent studies identified)
- Longest duration = 16 weeks (insufficient for long-term assessment)
- No large animal models or load-bearing functional studies reported
- Systemic biodistribution and organ accumulation rarely assessed comprehensively

6.4. Comparison with conventional titanium alloys

Vanadium-free Ti-based HEA/MEAs tend to have better in vitro biocompatibility, especially in terms of cell adhesion and proliferation, than Ti-6Al-4V when benchmarked [120,155]. Such improvements can often be attributed to more stable passive films of chemicals and lower ion release. However, it is important to emphasize that similarity in in vitro performance does not necessarily imply clinical outcome improvement [156].

Although vanadium-free HEAs/MEAs remain in their infancy during biomedical validation, Ti-6Al-4V has decades of clinical experience and regulatory acceptance. Thus, instead of solitary laboratory-scale experiments, assertions of superiority should be based on long-term studies of biology on a systematic basis [157,158].

6.5. Critical assessment and research gaps

Despite promising preliminary results, the biological assessment of vanadium-free Ti-based HEAs has several limitations. There is a lack of long-term in vivo research on systemic effects, overreliance on short-term in vitro tests, and inadequate recognition of ion release under realistic service conditions [107,159].

For coherent experiments, future studies should employ integrated testing methods that combine corrosion, ion release, mechanical loading, and biological testing. Such practices play an important role in building credible relationships between structure, corrosion, and biocompatibility and in developing vanadium-free HEAs/MEAs for safe and effective clinical applications.

Although most investigations showed favorable results in terms of cytocompatibility of vanadium-free HEAs/MEAs, it is important to note that most of the investigations conducted on these alloys were short-term in vitro investigations. In addition, variations in experimental protocols, cell types, and exposure durations of studies add complexity to the interpretation of biological performance and underscore the necessity of standardized testing methodologies.

7. Additive manufacturing and clinical translation challenges

7.1. Opportunities offered by additive manufacturing for biomedical HEAs/MEAs

Additive manufacturing (AM) allows the use of vanadium-free Ti-based HEA/MEAs in load-bearing biomedical implants. Directed energy deposition (DED) and selective laser melting (SLM) allow the creation of patient-specific geometries, complex internal structures, and adjustable porosity, which are difficult or impossible to achieve using conventional fabrication methods [24,94,160]. The main difference between DED and SLM is their processing principles. In DED, a metal powder or wire is fed continuously into a focused energy source, such as a laser beam or an electron beam, which then melts and is deposited onto a substrate. On the other hand, SLM is a powder bed fusion process in which a high-power laser is used to fuse metal powder laid out in a thin layer on a substrate. Compared with DED, SLM is more accurate in terms of dimension and microstructure; however, DED is more appropriate for building larger structures or repairing existing ones. These capabilities are particularly attractive for orthopedic and dental implants, where implant geometry and surface characteristics play a critical role in load transfer and osseointegration [94].

Another significant advantage of AM is that it offers near-net-shape processing, which can reduce material loss during processing. This is another significant advantage of AM, which is important in the context of vanadium-free Ti-based HEAs/MEAs because they contain expensive alloying elements such as Nb, Ta, Zr, and Hf. Thus, AM processes can be beneficial for improving cost efficiency during the production of advanced biomedical alloys [24,160]. However, such benefits can be attained when the processing parameters are carefully optimized to consider the thermophysical properties and complexity of the composition of multi-principal element alloys [25].

7.2. Processing–microstructure–property relationships in AM HEAs/MEAs

The successful implementation of AM on vanadium-free Ti-based HEAs/MEAs requires a proper understanding of the relationship between processing parameters, microstructural development, and functional properties. High cooling rates and sharp thermal gradients typically generate elemental segregation, residual stresses, and fine cellular or columnar microstructures during AM processes [24,161,162]. Segregation and chemical inhomogeneity can adversely affect corrosion resistance and biocompatibility, as discussed in the previous sections, although strengthening can be enhanced by grain refinement, as observed in Figure 6. Among the most important parameters that affect microstructure development in Ti-based HEAs/MEAs are laser power and scanning speed. An increase in laser power is known to increase melt pool depths and metallurgical bonding between layers, thus reducing the lack of fusion defects and increasing RD values. Nevertheless, it is also possible that when high laser powers are applied, keyhole porosity and evaporation of alloying elements may occur, particularly at different vapor pressures. Scanning speed is also a key parameter that determines the cooling rates and grain structures in Ti-based HEAs/MEAs. An increase in scanning speed is known to increase cooling rates and develop finer cellular or columnar structures, thus increasing mechanical properties through grain refinement. Nevertheless, it is also possible that when insufficient energy is supplied owing to the increased scanning speeds, a lack of fusion and porosity may occur, thus compromising the mechanical and corrosion properties.

Moreover, compositional control in AM processing is complicated by differences in the melting temperature, vapor pressure, and diffusion behavior between the constituent elements. Alterations in the desired alloy composition may occur owing to partial mixing or preferential evaporation, particularly for elements that have high melting points, such as Ta or Mo [163]. Rather than simply modifying the AM parameters with those of conventional titanium alloys, these effects underscore the necessity of integrating the process, structure, and property optimization.

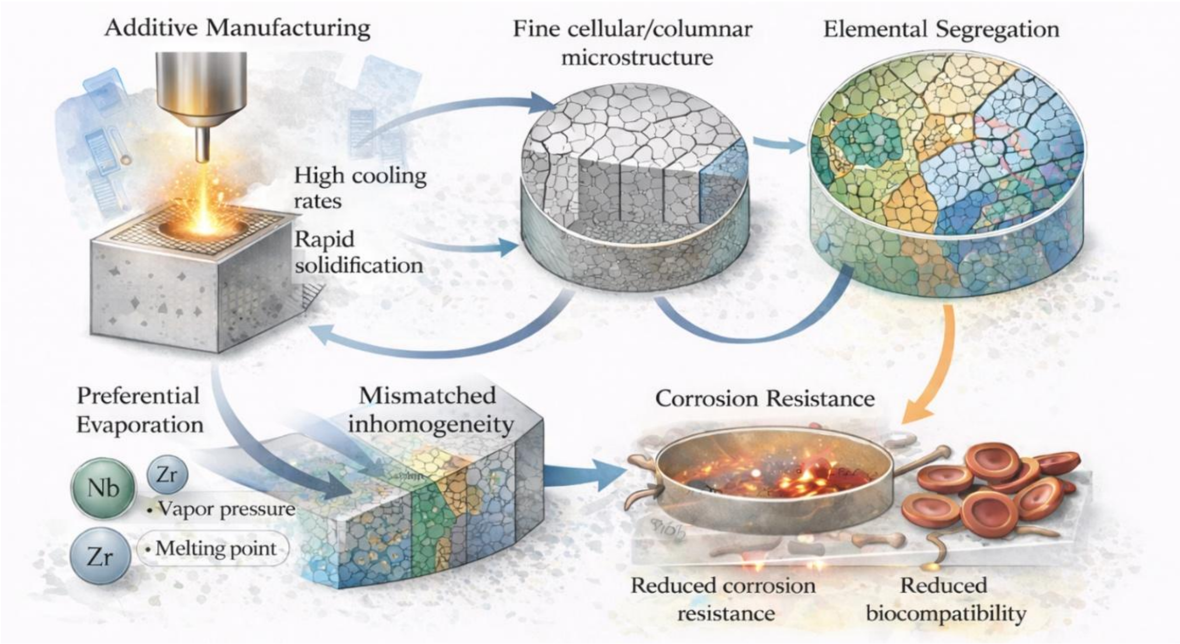

Figure 6. Correlation between the processing, microstructure, and properties of additively manufactured Ti-based HEAs/MEAs without vanadium. During AM, high cooling rates and thermal gradients help in grain refinement, although they may also lead to elemental segregation and leftover stresses, which influence mechanical strength, corrosion resilience, and biocompatibility.

7.3. Defects, post-processing, and their biomedical implications

AM-made HEAs/MEAs may have process-induced defects, such as porosity, lack-of-fusion flaws, and differences in surface roughness. Such imperfections may result in localized cellular corrosion and undesirable biological responses and/or undermine mechanical integrity [105,164]. To prepare qualities that can be used in biomedical applications, post-processing steps, including surface finishing, heat treatment, and hot isostatic pressing (HIP), are often required.

Although post-processing can significantly increase the density and homogenize the microstructure, it may also alter the phase stability and grain structure, potentially raise the elastic modulus or lower the corrosion resistance unless it is closely controlled [116]. Thus, the productivity of post-processing methods for vanadium-free HEAs/MEAs remains a research problem, particularly in terms of determining the compromise between biological safety and mechanical performance.

Although additive manufacturing is known for its benefits in making intricate biomedical implants, the effect of processing parameters on the homogeneity of the microstructure and defect formation in Ti-based HEAs/MEAs is not well understood and requires further investigation for better processing conditions.

7.4. Regulatory and standardization challenges

In addition to technical concerns, substantial regulatory and standardization challenges exist regarding the clinical use of vanadium-free Ti-based HEAs/MEAs produced by AM. The existing measurements of the metallic biomedical implants are mainly geared toward ordinary alloys such as Ti-6Al-4V and Co-Cr and cannot readily accommodate the processing variation and compositional intricacy of the HEAs/MEAs [165].

Regulatory approval requires extensive evidence of material consistency, the regulated release of ions, long-term corrosion resistance, and biological safety under clinically relevant conditions. It is also complicated by the fact that there are no standardized testing procedures for AM HEAs/MEAs, which highlights the need to seek harmonious collaboration between regulatory agencies, standards organizations, and researchers to develop appropriate qualification pathways [166].

7.5. Outlook for clinical translation

Even though Ti-based HEAs/MEAs (vanadium-free) demonstrate tremendous promise as next-generation material types for load-bearing implants, it is essential to address several related problems to achieve their successful clinical implementation. These include the generation of long-term in vivo data to enable claims of safety and efficacy, good structure–property–biocompatibility relations, and reproducible AM processing.

In future studies, the use of multidisciplinary approaches with a combination of alloy design, optimization of additive manufacturing, testing of corrosion and ion release, and bioassessment using harmonious experimental models should be prioritized. Such strategies are essential to achieve the maximum clinical capabilities of vanadium-free HEAs/MEAs and go beyond proof-of-concept investigations.

8. Conclusions and future outlook

Vanadium-free Ti-based high- and medium-entropy alloys (HEAs/MEAs) are emerging as a new generation of metallic materials with promising applications in load-bearing biomedical implants that provide a powerful alternative to conventional titanium alloys. These alloys enhance the flexibility of compositions and deal with long-term ion release and biosafety concerns by replacing biocompatible β-stabilizing elements such as Nb, Ta, Mo, and Zr with vanadium.

This critical review highlights the interdependent relationships among alloy design, microstructural evolution, corrosion behavior, ion release, and biological response in vanadium-free Ti-based HEAs/MEAs. This analysis indicates that compositional balance, processing route, and microstructural homogeneity are very sensitive to such performance in the face of the fact that most of the reported systems have been characterized by good mechanical compatibility, enhanced corrosion resistance, and promising in vitro cytocompatibility. In particular, the notion that high configurational entropy per se guarantees higher performance is disproved; rather, it is essential to carefully combine thermodynamic design principles with biomedical principles.

Another issue noted in this review is that there is still insufficient biological evidence to make a solid clinical translation. Most studies performed short-term in vitro tests without much in vivo testing, leading to no standard testing protocol for biological testing, ion release, and corrosion. Although additive manufacturing introduces new challenges associated with microstructural heterogeneity, defect control, and regulatory qualification, there are also new opportunities in patient-specific implant fabrication with the help of additive manufacturing.

The following areas should be of interest in future studies:

1. Development of uniform testing protocols for ion release, corrosion, and biocompatibility testing.
2. Long in vivo studies to determine the effects of loads on the system and bone under load-bearing conditions.
3. A comprehensive system of AM-produced alloys that considers process, structure, property, and biocompatibility.
4. Development of regulatory frameworks considering the peculiarities of HEAs/MEAs.

A solution to these problems will be necessary to transition vanadium-free Ti-based HEAs/MEAs from laboratory-scale research to safe, reliable, and clinically approved implant materials. One of the avenues that can lead to the full utilization of these new biomaterials for next-generation orthopedic and dental applications is the combination of computational material design, advanced manufacturing, and extensive biological testing.

Use of AI tools declaration

The authors declare that they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization, Mohammed Abdulrehman and Khairunisak Abdul Razak; methodology, Mohammed Abdulrehman, Ahmed Abbas, and Khairunisak Abdul Razak; literature survey and data curation, Nada Hamad, Rusul Ghadban, Ahmed Mohammed, Ali Flayyih, and Ali Salman; formal analysis and critical interpretation, Mohammed Abdulrehman, Ahmed Abbas, and Khairunisak Abdul Razak; visualization and figure preparation, Ali Flayyih, Rusul Ghadban and Ahmed Mohammed; writing—original draft preparation, Nada Hamad and Mohammed Abdulrehman; writing—review and editing, Mohammed Abdulrehman, Ahmed Abbas, Khairunisak Abdul Razak, and Ali Salman; supervision, Mohammed Abdulrehman and Khairunisak Abdul Razak; project administration, Mohammed Abdulrehman. All authors have read and agreed to the published version of the manuscript.

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