Developing Trends in Mg-alloys for Biomedical Implant Applications: A Short Review

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***Abstract*–Magnesium based alloys are biocompatible and safe for the manufacture of temporary implantable medical devices. Specifically, Mg-Zn-Ca alloys have received much attention as a biodegradable implant material due to superior mechanical properties. Various alloying and processing techniques have been adopted to simultaneously improve their mechanical properties and degradation behaviors. Extrusion, amongst other processing techniques offers these desired properties, and in addition to effective alloy design can be used in tuning magnesium alloys for various implant applications. With reference to current research progress, future directions should explore the development of alloys that incorporate elements such as Zn and Li that enhance the strength and ductility without promoting localized degradation.**

***Keywords*—biodegradable alloys, magnesium alloys, Mg-Zn-Ca, magnesium processing, uniform degradation.**

I. Introduction

Magnesium based biodegradable alloys are the most desirable choice for devices requiring temporary implantation compared to their zinc and iron counterparts because of the human body's tolerance for Mg (310 – 420 mg) [1], [2]. With its light weight and a modulus close to that of bone (~45 GPa versus 10 - 27 GPa) [3], stress shielding is obviated for prosthetic devices. Furthermore, they can be tailored for short- or medium-term degradation depending on the application. However, controlled and uniform degradation as well as sustained mechanical integrity over the duration of therapeutic use have been primary challenges of these alloys [4]. To this end, numerous investigations are being carried out on magnesium-based alloys. When alloying elements are added to magnesium, a variety of unique behaviours have been observed resulting from diverse microstructures and intermetallic phases [4]. For biomedical applications, alloying elements that can be safely resorbed within the human body include calcium - Ca, zinc - Zn, manganese - Mn, zirconia - Zr, lithium -Li, copper -Cu, strontium - Sr and rare earth metals such as yttrium -Y, gadolinium -Gd, neodymium -Nd, erbium- Er, and cerium – Ce.

This paper focuses on the biocompatibility of magnesium alloyed with zinc and calcium, elements that are inexpensive, abundant, and essential for the human metabolism. They are also non-toxic provided dissolution occurs at a controlled rate within the threshold where the body can effectively manage their bye-products. For example, calcium ions are beneficial for bone solidification [5] while zinc ions have been reported to specifically promote vascular cell viability [6]. The addition of both elements enhances grain refinement, solid solution strengthening, precipitation strengthening and grain boundary strengthening. Furthermore, degradation rate of the alloy also depends on composition, type of precipitates, cathodic reactions of secondary phases, and surface film stability. Post-alloying treatment has been adopted to produce various surface coatings to retard degradation kinetics of underlying magnesium. Unfortunately, rapid degradation kicks in whenever the surface barrier is compromised [7]. For this reason, great attention is placed on selecting the appropriate alloying elements so that adequate mechanical and degradation properties are attained. A significant improvement in properties have been realized from research on a variety of compositions, post-fabrication heat treatments, and coatings. However, this discussion focuses on the properties and behaviours of alloys of various fabrication and thermomechanical processes but not on coatings.

II. Properties of Biodegradable Alloys

Alloys for temporary implantation are required to have certain properties to ensure optimal performance for a given application (cardiovascular, orthopaedic, or dental). They should be completely degradable within the human body without posing any toxicity or deleterious effects to surrounding tissues and retain mechanical integrity during the time for which they are employed for reconstruction. To achieve these desired characteristics, alloys must be designed and fine-tuned by way of chemical, thermal, and mechanical processing. The main goals that have been identified for magnesium alloy design are to improve strengthen by grain refinement, solid solution, or precipitation and to weaken the texture for improved ductility of its hexagonal closed packed structure. For example, grain refinement from addition of calcium has been reported to cause the non-active non-basal slip systems to become activated thereby improving ductility [8]. The micro-alloying of magnesium with about 1 wt.% calcium has been reported [9]–[13] but the mechanical, and degradation properties of the alloy were inferior to those of ternary magnesium zinc calcium (MZC) alloys. Despite the beneficial effect of grain refinement, an increase in calcium content decreases ductility and corrosion resistance of magnesium alloys [6]. This is especially true since calcium is almost insoluble in magnesium.

Alloying with zinc is known to improve age hardening by formation of intermetallic compounds as well as refining the microstructure by decreasing grain size. Fig.1 shows the grain refinement effect of Zn in a Mg-0.5Ca alloy (1. a) and 0.5 – 9 wt. % Zn (1.b – 1.f). Nayak et al. reported improve ductility and formability by the addition of up to 3 wt.% Zn that was

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accompanied by an increases in strength by solid solution strengthening and grain refinement. Above 3 wt.% Zn, ductility decreased due to the formation of intermetallic particles that serve as crack initiation sites [14]. It should be noted that intermetallic phases can negatively impact the corrosion resistance by serving as cathodic sites.

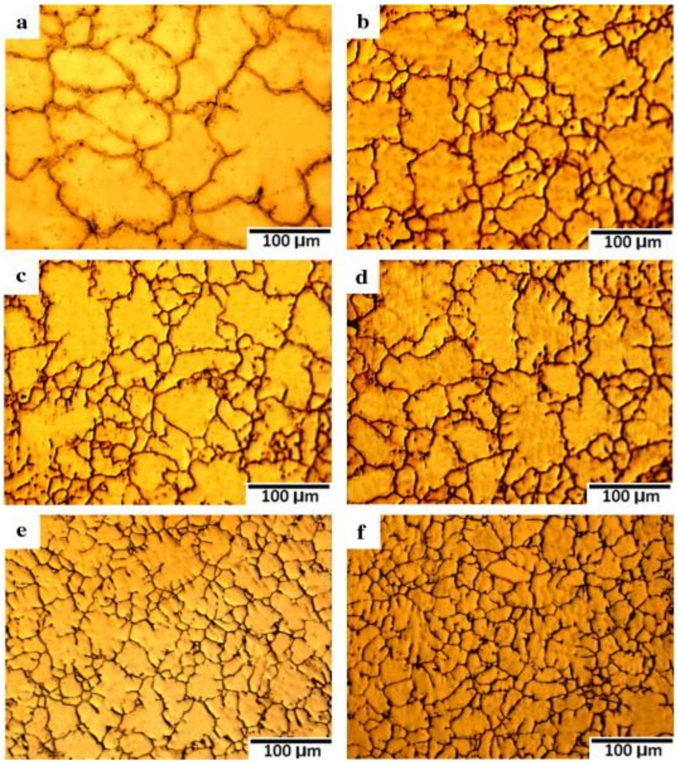

Fig. 1 Grain refining effect of Zn in Mg0.5Ca*X*Zn a) *X=0* b) *X=0.5 c) X=1 d) X=3 e) X=6 and f) X=9 wt.%* [15]

A. *Magnesium-Zinc-Calcium Alloys*

Ternary magnesium alloys incorporating zinc and calcium have received a lot of attention as a choice of biodegradable magnesium alloys for biomedical application. It has shown promise for uniform and controlled degradation behaviour as well as superior mechanical properties by combining inherent properties of magnesium-calcium and magnesium-zinc binary alloys. Microalloying percentages have been reported for alloys containing 0.6 wt.% – 3 wt.% calcium and 0.2 wt.% – 4 wt.% zinc. The most common methods adopted for improving the mechanical performance of these alloys are based on grain refinement and solid solution strengthening mechanisms. The secondary phases associated with ternary alloys are Mg_2Ca and $Ca_2Mg_6Zn_3$ (within an α-magnesium matrix), that serve to strengthen and toughen the alloys. However, they could also adversely affect degradation behaviour. Additionally, excessive amounts of Mg_2Ca reduces ductility and renders the alloy susceptible to localized degradation. Nevertheless, this phase reportedly does not form beyond a Zn/Ca atomic ratio of ~ 1.3 [16], [17], but was detected in an MZC alloy with 1.82 Zn/Ca ratio [10]. The nobler $Ca_2Mg_6Zn_3$ phase on the other hand can act as a temporary barrier to localized corrosion [10]. The effect of Zn/Ca ratio on the microstructure and tensile strength of MZC alloy is shown in Fig .2.

A study on hot extruded Mg-1Zn-XCa reported grain refinement, improved ductility from ~40 – 45 % and a reduction in strength from ~230 – 205 MPa as calcium content increased from 0.2 wt.% up to 0.5 wt.% [8]. Another study on extruded Mg-1Zn-0.3Ca alloys by Hofstetter et al. [18] showed that extrusion modes, whether direct or indirect, can significantly affect mechanical properties. In direct extrusion mode, the billet is forced through a die whereas in the indirect mode, the die is forced through the billet. The differentiating feature of the indirect extrusion mode is the absence of friction, resulting in lower processing pressure. The higher processing pressure of the direct extrusion produced a high defect density in uncrystallized regions, whereas indirect extrusion produced a highly recrystallized microstructure with reduced anisotropy. Hofstetter et al. found that indirect extrusion (at 300 – 325 °C) obtained elongation to fracture above 30 % while direct extrusion method (400 °C) produced an alloy with 25 % elongation. However, similar ultimate tensile strengths of 265 and 268 MPa were achieved with indirect extrusion at 300 °C and direct extrusion at 325 °C respectively. Bian et al. [9] reported an elongation of 24.4% with a corresponding strength of 211MPa for Mg-2Zn-0.2Ca when compared to high purity Mg and Mg-1Ca after hot extrusion.

Cast Mg-3Zn-0.2Ca alloy wires were extruded, cold drawn and annealed by Zheng et al. [19]. A significant decrease (> 60%) in elongation is recorded from the extruded to the extruded and cold drawn wire, whereas an increase from ~300 – 350 MPa was recorded for their tensile strength. Annealing after cold drawing provided more than 2X increase in the elongation but this was accompanied by a decrease (~100 MPa) in strength of the wire. Overall, extruded alloys seem to provide the maximum strength-ductility performance whereas cold drawing introduced vacancies, dislocation tangle and pileups, detrimental to both ductility and uniform degradation. Electrochemical and hydrogen evolution tests showed that annealing was beneficial for improving corrosion resistance of the cold drawn alloy wire.

Solution treatment was used to process alloys of Mg-1.2Zn-0.5Ca followed by age hardening at different temperatures. A reported maximum tensile strength of ~ 150 MPa and ductility of ~ 4.9% was recorded after 3 hours. This was attributed to dissolution of secondary phases and reduction in the cracking tendency after 3 hours of aging. Furthermore, the alloy also exhibited better corrosion resistance caused by the absence of large secondary phase regions that could promote galvanic corrosion and pitting [20]. In another study, a grain size decreased (from ~ 450 to 20 μm) was recorded for solution treated and extruded Mg-3Zn-0.2Ca alloy [21]. The tensile properties varied with extrusion temperature (25 – 300 °C) with ~228 - 242 MPa and ~21 – 37 %. The maximum ductility of 36.7 % was achieved at 300 °C extrusion temperature with a corresponding strength of 240.1 MPa. Grain refinement and solid solution strengthening were identified as the predominant mechanisms responsible for the improved strength of the extruded alloys. Grain refinement was also reported for as-extruded Mg-4Zn-0.2Ca with grain sizes below 12 μm [22].

Lee et al. [23] showed that both hot rolled and hot rolled and annealed sheets of Mg-Zn-Ca possessed higher tensile strength and elongation compared to their Mg-Al-Zn in all directions. This was attributed to the higher crystallization kinetics and twinning, which played a major role to enhance the formability of the alloy.

Another cast alloy of Mg-4Zn-0.1Ca was reportedly annealed and subjected to two isothermal equal channel angular pressing (ECAP) passes at 350 °C. A ten-fold grain size reduction was achieved from 220μm to ~ 20 - 30 μm. Post ECAP rotary swaging successfully increased the ultimate tensile strength of the alloy from 245 to 381 MPa, however this resulted in a reduction in ductility from about 28 – 5 % elongation [16].

The mechanical properties of MZC alloy are summarized in Table I these properties can be tailored by alloying percentages and thermomechanical processing to achieve the desired application properties. In the case of biodegradable stents, a tensile strength of >300 MPa and elongation >18% is required amongst other properties [24].

TABLE I
MECHANICAL PROPERTIES OF MZC ALLOYS

Alloy	Processing	Strength (MPa)	Elongation (%)	Ref.
Mg1Zn0.3Ca	Indirect extrusion @ 300 °C	265	31	[18]
Mg1Zn0.3Ca	Indirect extrusion @ 325 °C	240	32	[18]
Mg1Zn0.3Ca	Direct extrusion @ 325 °C	268	20	[18]
Mg1Zn0.2Ca	Extrusion	240	36 ± 3.0	[8]
Mg1Zn0.5Ca	Extrusion	210	44 ± 5.0	[8]
Mg1.2Zn0.5Ca	As-cast	121 ± 5.2	3.2 ± 0.13	[20]
Mg1.2Zn0.5Ca	Solution treated + age hardened for 3 hrs	150 ± 8.5	4.9 ± 0.24	[20]
Mg2Zn0.2Ca	Extruded	211 ± 11	24 ± 1.4	[9]
Mg3Zn0.2Ca	Extruded + cold drawn	356 ± 7.1	4.1 ± 0.6	[19]
Mg3Zn0.2Ca	Extruded + cold drawn + annealed	253 ± 8.5	9.2 ± 0.9	[19]
Mg3Zn0.2Ca	Extruded @ 150 °C	242	28.3	[21]
Mg3Zn0.2Ca	Extruded @ 300 °C	240	36.7	[21]
Mg3Zn0.2Ca	Extruded	336	16.4	[25]
Mg3Zn0.2Ca	Extruded + aging	273	18.5	[26]
Mg4Zn0.2Ca	Extruded + aging	295	18	[26]

While it is important to use alloying and thermomechanical processes to tune the mechanical properties of biodegradable alloys, it is imperative to ensure that uniform degradation is also achieved. Localized degradation can adversely deteriorate the mechanical properties of biomedical implant causing them to fail prematurely. The degradation rates of MZC alloys of various microalloying content and processing techniques are represented in Table II.

Bakhsheshi et al. [15] reported that corrosion resistance of MZC is increased with the addition of Zn up to 1 wt.% beyond which an increase in degradation rate of the alloy is observed. Immersion tests also showed that excess addition of Zn leads to increased precipitation of degradation products on the alloy surface. Generally, increasing Ca alloying content is detrimental to the degradation rate of MZC alloys. Zander and Zumdick [10] showed that increasing Ca content of Mg-0.8Zn from 0.6 – 1.6 wt.% increased degradation rate from 0.11 – 0.21 mm/yr in Hank's solution. On the contrary, an increase in Zn content of Mg-0.6Ca from 1 – 2 wt.% decreased degradation rate from ~3.9 – 2.2 mm/yr [11]. Further increase in the Zn content can become detrimental to degradation kinetics as reported by Li et al. [26] where an increase from 3 – 4 wt.% of Zn in Mg-0.2Ca resulted in an increase in degradation rate from 0.75 – 0.85 mm/yr. It is important to note that microalloying content should be kept within certain threshold to maintain higher corrosion resistance.

TABLE II
DEGRADATION PROPERTIES OF MZC ALLOYS

Alloy	Processing	i_{corr} (μA/cm^3)	CR-immersion (mm/yr)	Ref.
Mg0.5Zn0.5Ca	As-cast	0.004	-	[7]
Mg1Zn0.5Ca	Extruded	-	2	[27]
Mg1Zn0.6Ca	As-cast	3.2	3.91	[11]
Mg2Zn0.6Ca	As-cast	1.9	2.16	[11]
Mg2.5Zn1.5Ca	As-cast	2.8	5.46	[11]
Mg1.2Zn0.5Ca	As-cast	695	8.2	[20]
Mg1.2Zn0.5Ca	Solution treated + age hardened	507	4.6	[20]
Mg0.8Zn0.6Ca	As-cast	3.5	0.11	[10]
Mg0.8Zn1.6Ca	As-cast	5.0	0.21	[10]
Mg1.8Zn0.6Ca	As-cast	1.0	0.12	[10]
Mg1.8Zn1.6Ca	As-cast	1.5	0.16	[10]
Mg3Zn0.2Ca	Extruded + cold drawn	97.6	-	[19]
Mg3Zn0.2Ca	Extruded + cold drawn + annealed	48.2	-	[19]
Mg3Zn0.2Ca	Extruded	-	3	[25]
Mg3Zn0.2Ca	Extruded + aging	-	0.75	[26]
Mg4Zn0.2Ca	Extruded + aging	-	0.85	[26]

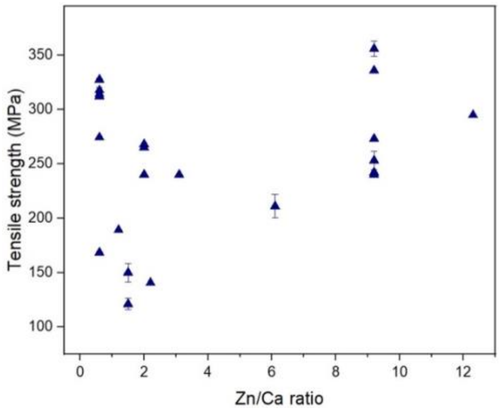

Fig.2 Ultimate tensile strengths as a function of Zn/Ca ratio for select MZC alloys.

B. *Quaternary Composition with Zinc and Calcium*

Addition of manganese, zirconia, and rare earth metals to the MZC alloys have been studied as quaternary magnesium alloys for biomedical implants. An extruded manganese containing alloy Mg-1Zn-1Ca-0.5Mn [5] provided reduced grain size (40.1% reduction compared to cast MZC alloy), promoted ellipsoidal second phase of $Ca_2Mg_6Zn_3$ but decreased the volume fraction of the Mg_2Ca phase. The alloy showed increase in yield and tensile strengths but decrease in ductility. It also possessed a thicker passivation film and exhibited slower degradation rates compared to other compositions with 0.3, 0.7, and 0.9 wt.% Mn. An increase in ultimate tensile strength, hardness, and elongation, was reported for another alloy of Mg-2Ca-0.5Mn-2Zn as compared to binary Mg-Ca alloys, even when zinc content was increased up to 4 wt.%. It also showed the highest compressive strength after immersion testing in comparison to pure magnesium and magnesium calcium alloys. This was due to uniform distribution of secondary phases within the refined microstructure, which served as obstacles to electron transfer from α-magnesium to other phases. This electron transfer resistance reduces the effective driving force for galvanic corrosion [17].

The study on the effect of heat treatment (300 – 500 °C) on cast Mg-Zn-Mn-Ca alloy showed improved hardness, tensile strength and elongation, as well as improved degradation resistance [28]. The alloy heat treated at 420 °C for 24 hrs possessed the highest hardness, tensile strength, and degradation resistance. This was attributed to the dissolution of secondary phases into the matrix which both pinned dislocation movement from lattice distortion and weakened micro galvanic couple effect by a reduction in secondary phase volume.

Addition of Zr to MZC promotes grain refinement. In a study of Mg-0.5Zn-0.5Ca and Mg-0.5Zn-0.5Ca-0.2Zr, ultrasonicated was able to achieve grain refinement of the MZC comparable to the zirconium containing alloy. Ultrasonication treatment was very effective for reducing grain size of the dilute alloy, increasing number of nucleation sites which can be activated and reducing effect of composition on grain size. The ultrasonicated MZC alloy also showed decrease in degradation rate after 4 weeks of in vivo implantation probably due to formation of complex corrosion layers of calcium phosphates, magnesium oxides and hydroxides or growth and encapsulation of implants by surrounding tissues[29].

Some Mg-Zn-Ca-Gd alloys were reported to have low tensile strengths below 100 MPa [30].

C. *Other Compositions with Zinc or Calcium*

Liu et al. studied the degradation rates of magnesium alloys via mass loss, volume loss and hydrogen evolution [27]. The alloys containing Zn, Zr and RE had an increased mass loss when compared to the MZC alloy. Furthermore, addition of RE to the MZC had no significant effect on the degradation rate of the alloy.

A study of four Mg-Zn-Gd alloys showed that the maximum strength recorded at room temperature corresponded to the highest Zn/Gd ratio content whereas the elongation was significantly reduced with an increase in alloying content of Gd from 2 wt.% to 10 wt.% [31]. However, this increase in alloying content also increased secondary phases which caused a drop in the corrosion resistance of the alloys. Luo et al. [32] also reported the microalloying of Mg-2Zn with Gd and found that increasing the Gd content from 0.1 - 0.3 wt.% resulted to a gain in strength and loss in elongation of hot rolled sheets. Another study was carried out by Chen et al. [33] to investigate the effect of Gd addition to Mg-Zn-Zr alloy. It was found that increasing Gd content up to 2 wt.% increased both strength and elongation due to second phase strengthening and grain refinement. However, this promoted galvanic corrosion which decreased the degradation resistance.

Bhattacharjee et al. [34] reported that twin roll cast and hot rolled Mg-6.2Zn-0.5Zr-0.2Ca alloy provided good formability and tensile strength of 300 MPa which improve to 321 MPa with peak aging. Further addition of Ag to the alloys only showed a slight increase in strength but with no significant improvement to elongation or formability of the alloy.

Some magnesium-lithium based alloys have been investigated for biomedical use. A solid solution Mg-4Li alloy with the α-magnesium phase also showed improvement in ductility and this was attributed to the influence of lithium on dislocation mechanism and stacking fault energy of the crystals. It was reported that the activation energy for prismatic slipping was reduced and there was dynamic recrystallization mostly at grain boundaries and triple points, making twinning less important [35]. Single phase Mg-14Li alloy was also reported to show uniform degradation and no pitting, the Li_2CO_3 film formed a protective coating for the alloy [7].

The addition of 8 wt.% Li to Mg-1Ca alloy was reported to produce a dual phase alloy and resulted in improved ductility and strength of the alloy after extrusion. The alloy was also found to have a four-layer natural oxide film and there was improved overall corrosion resistance of the magnesium alloy [36]. Investigations carried out on cast Mg-4Li-Ca showed that rolled and annealed alloys possessed higher corrosion resistance in SBF owing to a more homogenous twin-free microstructure [37].

Extruded Mg-Li-Zn alloys were also studied by Liu et al. [38] as potential biodegradable stent materials. They reported that the mechanical properties for Mg-3.5Li-2Zn was superior to those of previously researched Mg-Li based alloys. In addition, low degradation rates <0.3 mm/yr were reported for all alloys owing to the protective $Li_2CO_3/MgCO_3$ formed on their surfaces. Zn shows the best strengthening effect for bio-alloys and as such is effective for achieving good balance between strength and ductility. The degradation rates of the extruded alloys were close to those of the requirements for biodegradable stent [39].

III. Discussions

Alloys and processing techniques that provide solid solution strengthening mechanisms and grain refinement are important for uniform degradation behaviour. This is both dependent on the solid solubility limit and thermodynamic activation energy for the formation of secondary phases. For biomedical applications, the desired performance property of biodegradable alloys requires improved mechanical properties without promoting localized degradation resulting from micro galvanic pairs.

The most popular fabrication techniques that have proven to be effective for improving the strength, ductility, and degradation behaviors of biodegradable magnesium are alloying, extrusion, solution treatment and ageing. Solution treatment is useful for improving both the mechanical and degradation properties when followed by ageing. This can find very useful application as heat treatment process of post shaped materials where extrusion is not feasible such as in 3D printing [20]. Other hot working techniques also improve the mechanical properties of Mg alloys. Multidirectional impact forging was reported to provide over 10% increase in the ultimate tensile strength and elongation of Mg-Zn-Zr alloys in different forging directions [40].

Extrusion amongst other thermomechanical processes was the most beneficial to both strength and ductility. This is a very useful technique for reducing grain size as well as increasing strength and ductility. Extrusion can be carried out at lower temperatures unlike solution treatment, and most importantly, it can greatly reduce the average grain size of the alloy. This grain size reduction is rarely obtainable with heat treatments such as solution treatment and aging. Other deformation techniques such as rolling has been reported to improve strength and ductility but it is accompanied with a detrimental effect to the degradation behavior of the alloy [14] and as such is not a recommended material processing step for biomedical implant applications. The mechanical properties of alloys can also dependent highly on the extrusion mode and extrusion temperature [18].

Alloying is the most popular approach for improving the service properties of magnesium. For biomedical applications, the goal is to design a material with small amounts of alloying elements (microalloying) that can prove effective for bone fixation or stents. This microalloying technique is important because it can tailor the microstructure to reduce secondary phase volume depending on the solubility limit of the element. This plays a very important role in degradation kinetics, presence of multiple phases with varying potentials drives electrochemical degradation by micro galvanic corrosion. Alloying with elements such as Li which can induce phase transformation of HCP magnesium to a cubic structure is beneficial for ductility and formability. Room temperature ductility achieved from Mg-Li alloy hcp to bcc phase transformation can be up to 80% increase, higher than any other Mg alloy and this is key for vascular stent application [38]. In addition, Li is also known to provide a protective barrier coating that isolates the alloy from the corrosive environment, thus providing more uniform degradation behaviour. This is illustrated in Fig. 3 for a conventional hcp Mg alloy, dual phase hcp + bcc Mg-Li alloy and a bcc Mg-Li alloy.

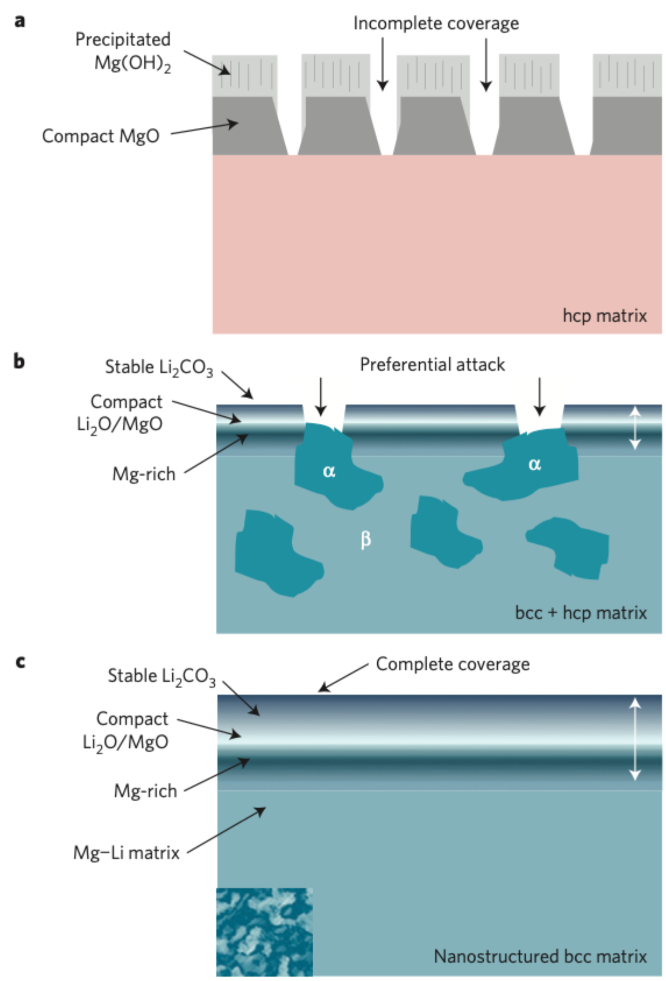

Fig. 3 Surface layer formation on hcp Mg and bcc Mg-Li after exposure to atmospheric conditions [41]

behavior is needed. Selection of processing techniques should be such that both biocompatibility and mechanical performance are simultaneously optimized. Alloying with elements such as Zn and Li is promising for both improved mechanical and degradation performance.

Generally alloying with Zn is more beneficial to corrosion resistance than alloying with Ca. This was evident for both binary alloy systems of Mg-Ca vs Mg-Zn as well as for ternary alloy systems of Mg-Li-Ca vs Mg-Li-Zn as shown in Fig. 4. This can also be attributed to the microstructure evolution of the alloys and the development of secondary phases. Since Ca has a very low solubility in Mg compared to Zn, the development of secondary phases are always present even in microalloying content <1 wt.%. The Ca intermetallic particles form micro galvanic couples with the α-magnesium matrix and speeds up the electrochemical degradation because of their potential differences. The development of secondary phases is dependent on several factors such as solid solubility limit and thermodynamics of formation. From phase diagrams, it can be observed that the solute elements have varying solubility limit in magnesium, for example, Zn has a solubility limit of ~2.4 wt.% while calcium has a solubility limit of ~0.8 wt.%. This is indicative of the amount of each solute element which can go into a super saturated Mg and that which is available for secondary phase formation. Therefore, the chemical composition affects phase formation and ultimately impacts the strengthening mechanism within the alloy.

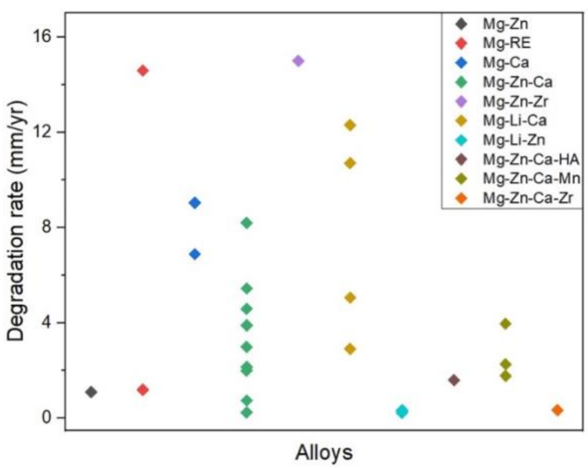

Fig. 4 Degradation rates of alloy systems studied for biomedical applications.

IV. CONCLUSIONS

The progress toward simultaneously improving the strength and degradation resistance of biomedical implant alloys is crucial for their clinical adoption. This work has summarized the development and characterization of magnesium alloys with zinc and calcium solute elements. In the past two decades, these alloys have been fabricated and processed in numerous ways with the intentions to tune their mechanical properties and biocompatibility behavior as biodegradable implant materials. Mechanical tensile strengths > 300 MPa and elongation > 30% have been recorded. Slow degradation rates have been achieved but uniform degradation

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