

Appropriate Mechanochemical Conditions for Corrosion-Fatigue Testing of Magnesium Alloys for Temporary Bioimplant Applications

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Magnesium (Mg) alloys possess great potential as bioimplants. A temporary implant employed as support for the repair of a fractured bone must possess sufficient strength to maintain their mechanical integrity for the required duration of healing. However, Mg alloys are susceptible to sudden cracking or fracture under the simultaneous action of cyclic loading and the corrosive physiological environment, i.e., corrosion fatigue (CF). Investigations of such fracture should be performed under appropriate mechanochemical conditions that appropriately simulate the actual human body conditions. This article reviews the existing knowledge on CF of Mg alloys in simulated body fluid and describes a relatively more accurate testing procedure developed in the authors' laboratory.

INTRODUCTION

As elaborated in another article in this issue,¹ for the construction of temporary implants (such as plates, screws, pins, and stents), it is highly attractive to identify a material that degrades in the human physiological environment after the healing process is complete. But, at the same time, this material should not cause any harm to the human body. In this respect, magnesium (Mg) and its alloys have attracted great research interest as temporary implants,^{2,3} as they possess one of the best biocompatibilities and their degradation products are not at all harmful to human physiology.^{4,5} Moreover, Mg is essential to human metabolism and any excess Mg is harmlessly excreted with the urine.⁶ For such applications, Mg alloys also possess a good combination of high strength and ductility.

The simultaneous presence of dynamic loading along with corrosive environment can result in corrosion fatigue (CF) and stress-corrosion cracking (SCC), which often occur at stresses considerably below design stresses for the noncorrosive environment. The most fundamental and detrimental feature of CF and SCC is that a ductile material that would have undergone considerable elongation before fracture may suffer embrittlement in the pres-

ence of the corrosive environment, leading to a premature brittle fracture. Because the brittle SCC/CF fractures can be sudden, catastrophic, and premature, they are believed to be the most dangerous forms of corrosion-assisted failures. CF and SCC are particular concerns for devices with sharp contours, such as pins, screws, and stents (because sharp locations are common crack initiation points). There have been several instances of corrosive body-fluid-assisted fracture of implants of traditional alloys (viz., stainless steels, Ti alloys, and Co-Cr alloys^{7,8}). Such catastrophic failures would generally necessitate troublesome removal of fractured devices and painful irritation or inflammation of surrounding tissues. CF and SCC will be a serious concern for implant devices of Mg alloys since (I) common temporary implant devices have sharp contours and (II) Mg alloys readily suffer pitting in chloride solutions,^{9,10} including in human body fluid.^{11–14} As pits are the most common initiators of CF and SCC, Mg alloys can be susceptible to CF and SCC in a chloride environment,¹⁵ such as body fluid.^{11–14,16,17}

It is also important to note that if the fatigue performance of the alloys is to be evaluated using S–N curves, as stated in ASTM standard E466-96, then “care should be taken with respect to the surface preparation to ensure that improper methods of

preparation can greatly bias the test results.”¹⁸ If, on the other hand, the evaluation were to be carried out on the basis of da/dN versus ΔK relationship, then the tests should be performed as per Appendix X3 of ASTM standard E647-13a.¹⁹ Although these aspects of fatigue testing are critically important, the focus of this article is the mechanical loading and chemical condition specific for human body implants.

APPROPRIATE MECHANOCHEMICAL CONDITIONS FOR CORROSION FATIGUE TESTING

CF and SCC studies on Mg alloys for bioimplant applications^{11–14,16} have been carried out by employing common and relatively simplistic approaches to the mechanical loading, test environment, and test alloys. The *in vitro* testing parameters such as frequency and mode of loading, chemistry of the test solutions, and geometry of the specimens in these studies were considerably different from those under actual *in vivo* conditions. An accurate determination of CF and SCC for such applications requires testing under appropriate mechanochemical conditions as discussed next.

Mechanical Loading

The composition of a bone is a matrix of inorganic salts and connective tissue referred to as collagen fibers. The healing ability of a fractured bone depends on biological and mechanical factors. Besides, body implants are subjected to acute and complex loading during service conditions. For example, a common orthopedic implant such as one for femur bone undergoes cyclic bending loading during normal stance. Therefore, for such applications, the mechanical integrity of the Mg alloys in the femoral midshaft gap should be evaluated under the actual loads and loading pattern experienced by implants. However, mechanical testing under cyclic loading of Mg alloys for bioimplant applications^{16,17} have generally been carried out under plain cyclic loading conditions. Although these studies have provided first CF data on Mg alloys and some critical mechanistic insight, the loading patterns employed in these studies are considerably removed from those actually experienced *in vivo*.

In Vivo Testing

The interfragmentary movement under *in vivo* loading, which is the most important biomechanical factor, is influenced by the internal loads at the fracture site and the stiffness of the implants. For example, the knowledge of the internal forces in the rat femur allows adjustment of biomechanical properties. Wehner et al.²⁰ have investigated the musculoskeletal loads during the gait of a rat to estimate the internal load at the fracture site by using an inverse-dynamic musculoskeletal model of the right hindlimb of the rat. They established a rat-

femur midshaft-gap-osteotomy model. To investigate the Mg alloys for this purpose, an intramedullary nail can be machined out of a Mg alloy. A specifically designed treadmill (Clever Sys Inc., Reston, VA) allows recording and analysis of the ground reaction forces of each rat step, which provides an accurate load/cycle profile. Inverse-dynamics simulations of loaded rat femurs allow to determine the forces on the Mg alloy in the midshaft-gap during each step. An intramedullary nail (2–3 mm in diameter) was loaded in a rat femur during the normal rat gait cycle. The greatest internal force in the femur, as shown in Fig. 1, acted in the longitudinal direction (F_x) with the maximum in the midstance phase. These maxima varied from 6.0 of body weight (BW) in the proximal femur to 7.0 BW in the distal femur. Therefore, the greatest internal load that could be applied to the femoral implant in the femoral midshaft gap during gait could be up to six times its bodyweight. This arrangement creates a highly stressed load-bearing part of the cylindrical nail test piece. Using this setup, the effect of implant corrosion and the continuously increasing load on the bone regenerates, and bone healing can be investigated by using biomechanical evaluations as well as histologically. An accurate load cycle per day can be achieved by forcing the rat to walk on a treadmill. A daily fractionated walking time of 4 h (i.e., 18,000 cycles/h, and frequency/gait cycle of 0.5 Hz) for 4–6 weeks simulates the 250,000–500,000 gait cycles that a human would experience over 3–6 months.

In Vitro Testing

For *in vitro* testing under properly simulated conditions, cantilever bending provides combined loading, in which a force offset from the longitudinal axis creates both compression and bending. When femoral head is subjected to compressive forces, cantilever bending occurs in a loaded femur. These forces create a bending moment in diaphyseal bone shaft along with the axial compressive effect. Therefore, to simulate the *in vivo* conditions of body implants, the stiffness of the femoral implant can be evaluated using the bending CF test. The test can be performed in either the three-point or four-point loading configuration. Under three-point bending, the bending moment is observed to increase linearly from zero at the supports to a maximum under the central loading point, whereas the shear force remains consistent along the length of the specimen. While under four-point bending, the bending moment increases linearly from zero at the supports to a maximum at the loading points and continues to be constant between these points. In contradiction to the three-point bending, where failure occurs at the middle point of force application, fractures in four-point bending occur at the weakest point between the two inner forces but not necessarily at the midpoint. Because of the position of the femoral

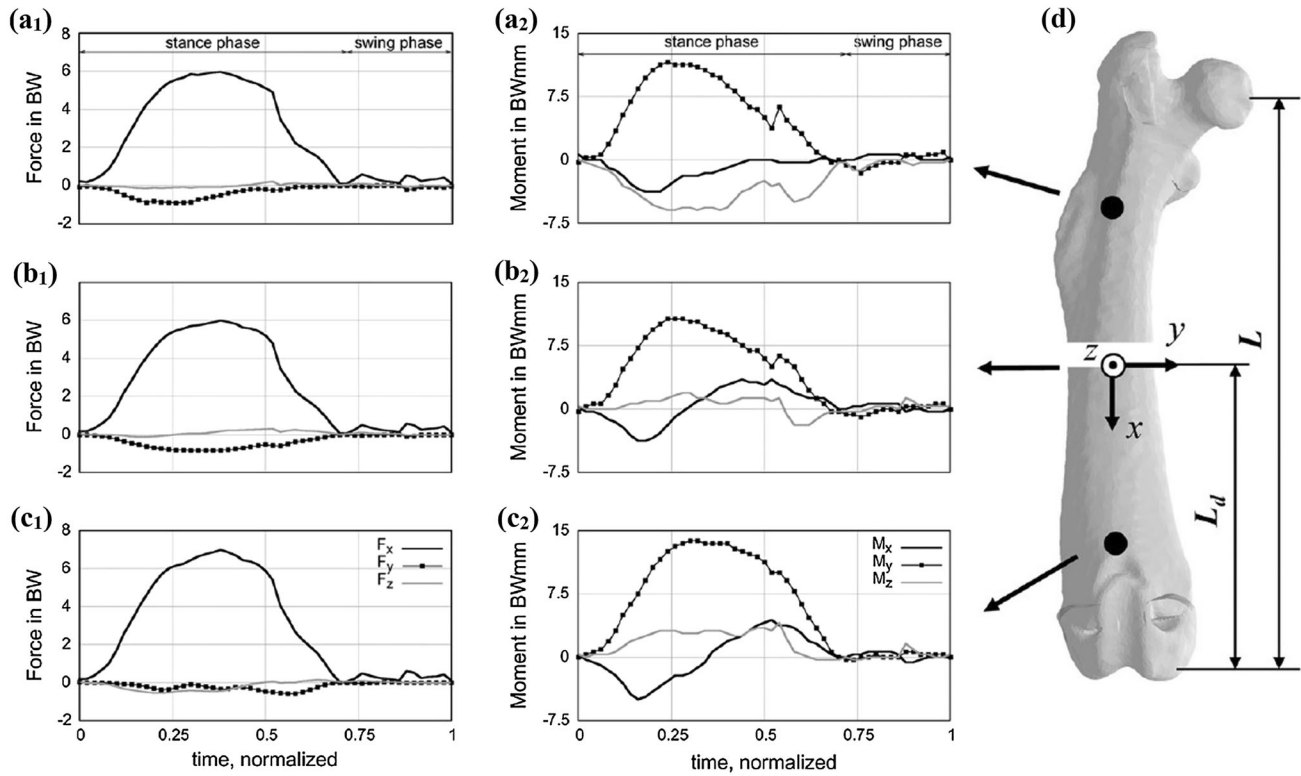


Fig. 1. Internal forces (a₁, b₁, c₁) and moments (a₂, b₂, c₂) at three location along the femoral axis during the whole gait cycle and (d) the femur of the rat. The internal loads in the proximal femur were determined at $L_d = 0.8$ (a₁, a₂), in the femoral mid-shaft at $L_d = 0.5$ (b₁, b₂), in the distal femur at $L_d = 0.2$ (c₁, c₂).²⁰

implant in the midshaft gap, the test alloys undergo three-point cycling bending during the gait cycle.

Bending Fatigue and Bending Corrosion Fatigue Tests

A suitable bending fatigue test can be performed by using a low-capacity servo-hydraulic fatigue machine employing a sinusoidal wave form at frequency of 1 Hz (normal walking frequency in adults) for 1 million cycles, which is considered as the average human activity in a year. For accommodating samples of proper size, a fixture needs to be designed to fit onto the testing machine to perform the three-point bending test. Because bending tests produce both tensile and compression stresses, respectively, on the convex and concave sides of the specimen, an area of shear stress can be created along the midline. To ensure the primary fracture arises predominantly due to tensile or compression stress, the shear stress must be minimized by controlling the span to diameter ratio, which is 16:1 for most materials. Also, the loading nose and supports should have a circular surface to avoid stress concentration in specimens.

For the bending CF test, the authors have developed a bending fixture (Fig. 2). A corrosion chamber made of acrylic was designed. To prevent any leakage of solution from the chamber, two O-rings have been provided to fit the specimens to the chamber. Moreover, to prevent galvanic corrosion during the

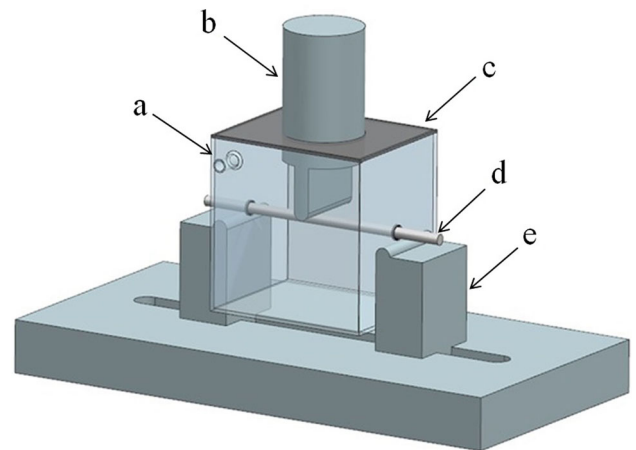


Fig. 2. Schematic diagram of the experimental setup of three-point bending for CF test: (a) solution outlet, (b) loading nose, (c) corrosion chamber, (d) specimen, and (e) support.

tests, the supports of the bending fixture were required to be located out of the corrosion chamber, and loading nose was required to be made of stainless steel coated with a ceramic coating.

Pseudo-physiological Test Solutions

In vitro experiments have employed many types of pseudo-physiological solutions that mimic the composition of body fluids.^{21–23} viz., Hanks' solution,

Table I. Ion concentrations and organic compounds in common solutions²⁴

	Blood						Original				
	Plasma	NaCl	PBS	Hanks'	Ringers'	DMEM	SBF	c-SBF	r-SBF	i-SBF	m-SBF
Na ⁺ (mmol L ⁻¹)	142	125	157	142	130	127.3	142	142	142	142	142
K ⁺ (mmol L ⁻¹)	5	–	4.1	5.9	4	5.3	5	5	5	5	5
Ca ²⁺ (mmol L ⁻¹)	2.5	–	–	1.3	1.4	1.8	2.5	2.5	2.5	1.6	2.5
Mg ²⁺ (mmol L ⁻¹)	1.5	–	–	0.8	–	0.8	1.5	1.5	1.5	1	1.5
HCO ₃ ⁻ (mmol L ⁻¹)	27	–	–	4.2	–	44.1	4.2	4.2	27	27	10
Cl ⁻ (mmol L ⁻¹)	103	125	140	145	109	90.8	148.8	147.8	103	103	103
HPO ₄ ²⁻ (mmol L ⁻¹)	1	–	11.5	0.8	–	0.9	1	1	1	1	1
SO ₄ ²⁻ (mmol L ⁻¹)	0.5	–	–	0.8	–	0.8	0	0.5	0.5	0.5	0.5
Buffer	–	–	–	–	–	HEPES	Tris	Tris	HEPES	HEPES	HEPES
Amino acids (g L ⁻¹)	–	–	–	–	–	1.6	–	–	–	–	–
Glucose (g L ⁻¹)	0.65–1.1	–	–	1	–	4.5	–	–	–	–	–
Albumin (g L ⁻¹)	30–55	–	–	–	–	–	–	–	–	–	–
α-globulins (g L ⁻¹)	5–10	–	–	–	–	–	–	–	–	–	–
β-globulins (g L ⁻¹)	6–12	–	–	–	–	–	–	–	–	–	–
γ-globulins (g L ⁻¹)	6.6–15	–	–	–	–	–	–	–	–	–	–
α ₁ -lipoproteins (g L ⁻¹)	6–12	–	–	–	–	–	–	–	–	–	–
Fibrinogen (g L ⁻¹)	1.7–4.3	–	–	–	–	–	–	–	–	–	–
Total cholesterol (g L ⁻¹)	1.2–2.5	–	–	–	–	–	–	–	–	–	–
Fatty acids (g L ⁻¹)	1.9–4.5	–	–	–	–	–	–	–	–	–	–
Lactate (mmol L ⁻¹)	0.5–2.2	–	–	–	–	–	–	–	–	–	–
Urea (mmol L ⁻¹)	3–7	–	–	–	–	–	–	–	–	–	–

PBS = phosphate buffered solution; DMEM = Dulbecco's modified Eagle's medium; SBF = simulated body fluid; c-SBF = conventional simulated body fluid; r-SBF = revised simulated body fluid; i-SBF = ionized simulated body fluid; m-SBF = modified simulated body fluid; HEPES = hydroxyethyl-piperazine ethanesulfonic acid

Dulbecco's Modified Eagle's medium (DMEM), modified simulated body fluid (m-SBF), and so on. Compositions and ion concentrations of common solutions are listed out in Table I. However, in addition to inorganic ions, physiological environments also contain organic compounds such as proteins, amino acids, and glucose. Yamamoto et al.²⁵ studied the effect of organic components on the corrosion behavior of pure Mg and showed that protein adsorption retarded Mg degradation, whereas amino acids encourage the dissolution of Mg alloys. Thus, the selection of a suitable test medium is identified as one of the primary concerns in performing in vitro studies of biodegradable Mg alloys.

As shown in Table I, albumin, globulin, and fibrinogen are the main proteins present in blood plasma. Approximately 55% of blood proteins are accounted for by serum albumin. The normal concentration of albumins in blood is 30–50 g/L (3.0–5.0 g/dL). Albumin maintains the osmotic that is needed to distribute body fluids between body tissues and blood vessels. Bovine serum albumin (BSA) and human serum albumin (HSA), which are derived from bovine and human blood, respectively, are frequently used in biophysical and biochemical studies. α₁ globulins, α₂ globulins, beta globulins, and gamma globulins are found in plasma, which comprises approximately 38% of plasma proteins. The normal concentration of globulins in the blood plasma is approximately 2.6–4.6 g/dL. Fibrinogen also plays

an important role in blood clotting and accounts for 7% of blood proteins. However, studies on the influence of proteins in corrosion of Mg alloys are limited. Xin et al.²⁶ reported that the formation of a barrier layer, originated by the adsorption of proteins, can improve the corrosion performance of Mg alloys. However, this blocking effect is very short lived as it weakens gradually with exposure time. Hence, it is important to investigate the corrosion and cracking behavior of Mg alloys in an environment that is similar or closer to the physiological environment. More importantly, there has been no study particularly on the effect of proteins of body fluid on CF life of biodegradable Mg alloys.

To compare the effect of proteins on corrosion and CF of Mg alloys, Hanks' balanced salt solution

Table II. Compositions of the Hanks' balanced salt solution

Component	g/L
Sodium chloride (NaCl)	8.00
Potassium chloride (KCl)	0.40
Potassium phosphate (KH ₂ PO ₄)	0.06
Sodium phosphate (Na ₂ HPO ₄ ·2H ₂ O)	0.06
Magnesium sulfate (MgSO ₄ ·7H ₂ O)	0.20
Calcium chloride (CaCl ₂)	0.14
Sodium bicarbonate (NaHCO ₃)	0.35

(HBSS) with three different compositions can be used as follows:

- The Hanks' balanced salt solution without proteins (Table II).
- The Hanks' balanced salt solution with albumin and fibrinogen separately.
- The Hanks' balanced salt solution with combinations of albumin and fibrinogen.

The test medium should be maintained at a temperature of 37°C during the entire test. This can be achieved by using an arrangement consisting of a thermostat and a circulation system. Because the corrosion rate of the Mg alloy can be altered considerably by the buffering agents in the solutions, CO₂ gas can be bubbled at certain partial pressure through the experimental solution for regulating the pH during the test. A CO₂ partial pressure of 0.013 atm maintains a pH of 7.4 for Hank's solution with an initial bicarbonate concentration of 4.2 mmol L⁻¹.²⁷

Suitable Alloys

For implant applications, it is important to identify Mg alloys with alloying elements that confer strength and corrosion resistance in human body fluid without being toxic to the human body, as well as without causing human body fluid-assisted cracking (such as SCC or CF) during their use as temporary implants. Hydrogen generation due to corrosion of Mg-alloys in human body fluid is another traditional problem in using Mg alloys.

Aluminum

Al provides corrosion resistance and strengthening, and it is the major alloying element in the most common Mg alloys (i.e., AZ series). But Al is highly toxic to the human body (as it can cause neurological disorders such as dementia and Alzheimer disease²⁸). Thus, the AZ series Mg alloys are often ruled out as materials for biodegradable implants where the objective is to let the alloy dissolve within the human body after they have fulfilled their temporary function.

Calcium

Ca is a major component in human bones, and Ca-containing Mg alloys quickly develop a surface layer of hydroxy apatite that improves compatibility of the alloy with human body.²⁹ Ca is also essential for chemical signaling in human cytosystem.²⁹ Also, Mg has been found to facilitate Ca addition into bone. Ca refines the Mg-alloy grain size,³⁰ and thereby it improves both their mechanical properties and corrosion resistance. However, at ≥1 wt.%, Ca leads to the precipitation of Mg₂Ca along alloy grain boundaries, causing embrittlement.²⁹

Zinc

The human requirement for Zn is ~15 mg/day.³¹ Alloying with Zn causes solid-solution strengthen-

ing of Mg. However, at ≥6.2 wt.%, Zn starts to form Mg-Zn secondary phases, again causing embrittlement. A few Mg-Ca, Mg-Zn, and Mg-Zn-Ca alloys^{2,29,32} have been investigated in vivo for bioimplant applications, and these alloys were found to meet nontoxicity requirements (as per the cytotoxicity tests).

Rare Earth (RE)

Although the reports on the toxicity, if any, due to REs are inconclusive and insufficient,³³ REs are generally believed to be nontoxic.³³ Mg alloys with sufficient amount of RE can develop a corrosion-resistant surface film. For example, Elektron 21 alloy (having ~2.8% Nd and ~1.3% Gd) forms a film of mixed oxide of Nd and Gd³⁴ that is considerably more stable and robust than the surface films that develop on rare-earth-free alloys (e.g., Mg(OH)₂-type films that develop on pure Mg or common Al-containing Mg alloys^{23,24,35} are easily disrupted in chloride solutions). Furthermore, REs readily form very fine and stable intermetallic precipitates that are very effective in strengthening, even when present in small quantities. But, these intermetallics when present in sufficient size and quantity can cause localized corrosion and embrittlement. However, a few of REs (e.g., Nd, La, Ce, Pr, Sm, and Eu) have much lesser solubility in Mg and, hence, greater tendency to form intermetallic precipitates than others (e.g., Y, Gd, Yb, Tb, Dy, Ho, Er, and Th),³³ thereby, providing a window of opportunity to select one or more REs in their tolerable quantities for alloying with Mg, which will confer the required corrosion resistance while minimizing intermetallic formation. A few recently developed Mg-Zn-Ca alloys with and without Y have shown their specific attributes of harmlessly dissolving away while the fractured bone joined during in vivo tests.³⁵ However, these samples were tested without any mechanical loading. These alloys must demonstrate the desired resistance to fracture due to the synergistic role of mechanical stress and corrosive human body fluid. Recently, author Singh's group has carried out some preliminary studies on a few of RE-containing Mg alloys developed at ETH, Zurich, and they found them susceptible to cracking in a common simulated body fluid.³⁶

CONCLUSION

Potential biodegradable candidates need to fulfill specific requirements including biocompatibility, mechanical properties, and corrosion resistance to be used in temporary implant applications. Magnesium (Mg) alloys are receiving increasing attention for their potential application as temporary bioimplants. However, there is a critical knowledge gap on the CF Mg alloys under properly simulated physiological conditions. For in vitro studies to be more meaningful and realistically comparable with

the in vivo results, the laboratory testing parameters should be selected carefully. Such a comparison will help in optimizing the in vitro test, as well as in reducing the number of relevant animal experiments in the longer term. The authors have developed a bending fixture for appropriate simulation of mechanochemical conditions for bending CF tests.

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