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Evaluation of the Degradation Rates and Biocompatibility of Magnesium Pins with Different Compositions, and Processing Techniques for Oral Staplers *In Vivo* and *In Vitro*

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ABSTRACT

Oral sutures are common and in high demand for oral treatments, and invariably increase physicians' workload. Herein, we examined the degradation of magnesium alloy pins with different elemental compositions and processing technologies both *in vivo* and *in vitro*, and analyzed their cytocompatibilities to verify the feasibility of their use as oral tissue suture materials. The results showed that Mg–Zn–Ca–4Ag, which completely degraded in less than a week *in vitro*, exhibited large areas of corrosion, local fractures within two weeks, and degraded almost completely within a period of four weeks *in vivo*. The other magnesium alloy pins studied herein showed no distinct degradation even after two months, with small amounts of pitting corrosions found on the surface. The cytocompatibility test revealed that Mg–Zn–Ca–4Ag showed good biocompatibility and promoted cell growth when the Mg concentration was 50 μg/mL. Therefore, Mg–Zn–Ca–4Ag can be biocompatible, while degrading within a month. Therefore, by further optimizing the processing technology and composition, magnesium alloys are expected to emerge as new materials for oral sutures. Moreover, staplers are expected to emerge as a new method for oral, soft-tissue suturing.[a]

KEYWORDS: Magnesium Pin, Composition, Degradation Topography, Cytocompatibility.

1. INTRODUCTION

Suturing is the last step in surgery. An ideal suturing method should be economical, convenient, time-saving, and aesthetically beautiful, and should cause minimal scarring and pain.[1] Suturing methods may use absorbable, nonabsorbable, special materials, staplers, etc. The choice of suturing method and material is based on many factors, including the type and site of wound, tension size, healing time, surgical method, and patient age and health.[2]

The simple, rapid, and efficient stapler suturing method is used on the skin[3] or for gastrointestinal sutures.[4,5] Hulbek et al. showed that the skin stapling method did not increase the likelihood of infection and other complications compared to the traditional suturing technique.[3] At the same time, the stapler has a high tensile strength and can be used in high-tension tissues. Levi et al. measured the resistance of different suturing methods to wound cracking. The adhesions of zipper wound closure, suturing, and anastomotic staplers are equal to 9.7 ± 3.1, 0.8 ± 0.5, and 12.5 ± 4.8 pounds (4.4 ± 1.4, 0.4 ± 0.2, and 5.7 ± 2.2 kg), respectively. There is no statistically significant difference between a zipper wound closure device and anastomotic stapler. This implies that the zipper wound closure device and anastomotic stapler have significantly higher tensile strengths than stitches.[6]

Given that the nonabsorbable stapler technique requires the eventual removal of the pins, it is relatively painful and likely to cause scarring. There have been a few reports on the use of polymers as stapler pins. According to these,

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[a]ANOVA: One-way analysis of variance; AoSMC: Human aortic smooth muscle cells; CCK-8: Cell counting kit-8; DMEM: Dulbecco's modified eagle medium; DMSO: Dimethyl sulfoxide; DNA: Deoxyribonucleic acid; EDS: Energy-dispersive spectroscopy; SEM: Scanning electronic microscope; HAEC: Human aortic endothelial cells; hDF: Human dermal fibroblasts; MMP: Metalloproteinases; SD: Spraque Dawley; SD: Standard deviation; SPF: Specific-pathogen free.

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the commonly used ones include copolymers of l-lactide and ethyl lactide, poly(lactic acid), and polyethanol.[7,8] However, the mechanical properties of polymer absorbable staplers are poorer and the operation time for their placements is longer than those of metal staplers.[7] At the same time, biodegradable polymer materials and their products can cause skin irritation and wound infection.

The study of biodegradable metals has emerged as one of the most interesting subfields in the field of biomaterials since the beginning of the 21st century when it was first proposed. The development of a biodegradable Mg stapler has many advantages. First, the use of a biodegradable Mg matrix eliminates the need for stitch removal and reduces secondary pain for patients. Second, biodegradable metals have sufficient biocompatibility, mechanical properties, and corrosion stability, and can be applied in various clinical fields. Finally, the stitching process is simple and quick.

Fe plays an important role in the body's metabolism, for instance oxygen transport, deoxyribonucleic acid (DNA) synthesis, electronic transport in the respiratory chain, and in other important processes. Fe and its alloys are potential biomaterials with high strength, good plasticity, and degradability. Stainless steel has been extensively used in cardiovascular stents[9] and implants.[10] Many studies have shown that Fe implants do not cause significant local or systemic inflammation or toxicity in human tissue. For example, Hermawan et al. demonstrated that Fe–Mn alloys (Mn content = 20–35%) degrade at the rate of 520 μm per year with low inhibition to fibroblasts.[11] Mokhamad et al. proved that the iron–bioceramic composite is biologically active and has good wound healing properties.[10] Though its biodegradation rate is low, the biocompatibility of the corroded products has been a controversial topic.[12] It has been reported that the production of large amounts of iron oxide in the human body can cause inflammation.[13] Kraus et al. reported that an iron-based material was implanted in Spraque Dawley (SD) rats for one year, and showed that there was no significant volume reduction. Fagali et al. demonstrated that high Fe^{3+} concentration could inhibit mitochondrial activity and cause cell damage.[14] Therefore, the application of Fe in bone synthesis may be associated with some limitations, and its feasibility remains to be verified.[15]

Zinc is potentially biocompatible and possesses a degradation capacity. Chen et al. prepared pure zinc and zinc alloys discs, embedded them in dorsal locations in rats for 24 weeks, and proved their good biocompatibility.[16] Pure zinc has been rarely studied because of its disadvantages, such as its low-corrosion rate in the body, poor mechanical properties, brittle nature, and low strength. Shearier et al. directly exposed HAEC, AoSMC, and hDF to the zinc surface. This initially led to cell adhesion and to subsequent rapid cell necrosis. After zinc surface coating with a layer of gelatin that mimics a protein layer, cells could adhere and proliferate on the zinc surface *in vivo*. The effection of zinc concentration on cell proliferation and differentiation was dose-dependent, thus indicating that free Zn^{2+} may hinder cell adhesion and migration.[17] The most studied zinc products are magnesium, iron, and calcium alloys, which possess improved mechanical and degradation properties.[18] However, zinc-based alloys have disadvantages such as nonuniform stress shielding effects.[19]

Magnesium is abundant and easily obtained from seawater. It acts as an enzyme activator. The human body needs to ingest 350–500 mg of magnesium every day to maintain bodily functions. Mg is involved in neuromotor functions, emotion regulation, and in the control of vasoconstriction and endothelialization.[20] Lin et al. reported that magnesium could affect signal channels and promote cell proliferation, transformation factor, and other cytokines. Additionally, Mg-based materials have low densities and exhibit good biocompatibility[21,22] and biodegradability,[23] along with increased strength and a modulus of elasticity that is similar to that of bone.[24] Finally, Mg degradation is harmless to the body and does not cause metabolic disorders.[21,23] Thus, it stands out among biodegradable metals. Mg implant studies have been evaluated the effect of magnesium implants in human bone with fracture,[25] gastrointestinal anastomosis,[26] biliary anastomosis,[27] cardiovascular stents,[28] vocal sutures,[29] nerve repairs,[30] and in other diseases. However, only a few studies on the suture of the skin and oral mucosa using magnesium alloy staplers exist.

Therefore, our research group developed five magnesium alloy pins with different compositions and processing techniques. The objective of the study was to research and develop a suitable magnesium alloy pin that degrades within a short period and has good cytobiocompatibility. This helped us evaluate whether the magnesium alloys are promising candidates as soft-tissue suture materials for use in oral wound staplers.

2. MATERIALS AND METHODS

2.1. Material and Animal Sources

Five different alloy materials were acquired from the materials laboratory of the Beijing University of Science and Technology (China) (Table I). The pin length was set at

Table I. Properties of the five studied magnesium alloys.

Group	Composition	Tensile strength (MPa)	Elongation rate (%)
1	Mg–Zn–Ca–0.2Mn	282	14.29
2	Mg–Zn–Ca–4Ag	334	8.67
3	Mg–Zn–Ca–Ag*	327	7.4
4	Mg–Zn–Ca–Ag*	305	12.94
5	Mg–Zn–Ca–Ag*	302	10.95

Note: *Groups 3, 4, and 5, were subjected to different heat treatment processes.

20 mm. The SD male rats were obtained from the Peking University Health Science Center (China) and had weights in the range of 180 to 220 g.

2.2. Ethical Approval

The experimental scheme involving animals has been approved by the biomedical ethics committee of Peking University (protocol No. LA2017281). All animals reproduce under standard conditions and were treated in accordance with the NIH guidelines for the care and use of laboratory animals.

2.3. *In Vitro* Degradation Observations

The magnesium alloy pins were soaked in artificial saliva (Nanjing xinfan Biological Technology Co., Ltd., China) and were put in a CO_2 thermostat (WCI-40, INFORS Biotechnology Co., Ltd., China) at 37 °C, which simulated degradation conditions of magnesium alloy pins exposed to the saliva environment after the oral suture. The materials were excised after 1, 2, 3, and 4 weeks to observe the *in vitro* degradation rate and macroscopic morphology.

2.4. Animal Division and Operations

Nine male specific-pathogen free (SPF) SD rats with body weights in the range of 180 to 220 g were selected. Five new magnesium alloy pins were washed and disinfected with ultrasound for 15 min. Before animal experiments, pins were subjected again to high-temperature (121 °C) and high-pressure (0.1 MPa) sterilization for 15 min using hot air sterilizer (HAS-T50, Biobase Co. Ltd., China). The SD male rats were injected intraperitoneally with chloral hydrate and anesthetized. After the incision was disinfected with iodide, 1 mm micro-incisions were made in both legs. Five groups of magnesium pins with different compositions were inserted into five different sites within the leg muscles, and 4–0 absorbable sutures were used to seal the wounds. Three rats were sacrificed randomly at specific times and the Mg pins were extracted from the body after 1 week, 2 weeks, and 4 weeks postoperatively for observations. The experiments were repeated three times for each group.

2.5. *In Vivo* Surface Morphology Assessment

The pins were treated with acetone, ethanol, and distilled water ultrasonically. A 200 g/L CrO_3 solution was used

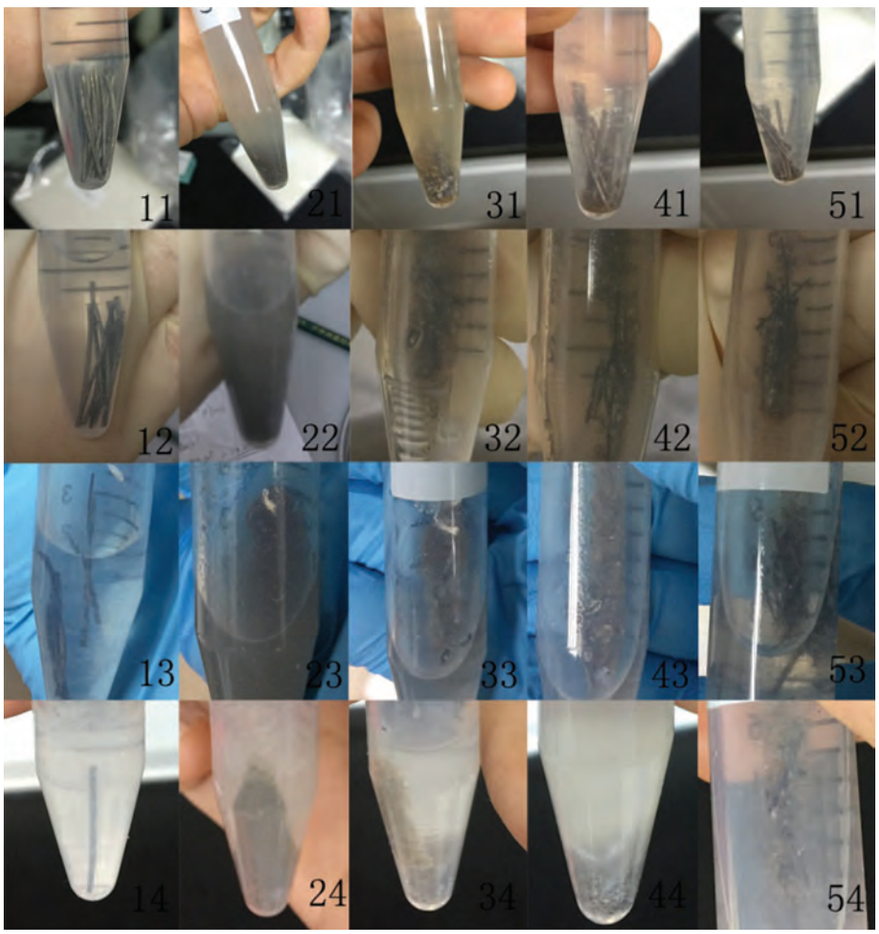

Fig. 1. Macroscopic degradation changes near the artificial saliva within a period of 1–4 weeks *in vitro*.

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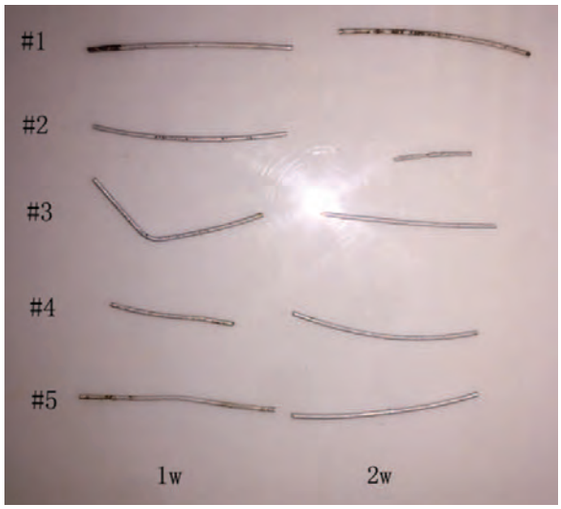

Fig. 2. Macroscopic degradation in Mg alloy pins after 1–2 weeks *in vivo*.

to clean away the corrosion products. Degradation surface morphologies were evaluated using SEM (Phenom XL, Phenom-world BV, Netherlands) before and after removal of corrosion products 1, 2, 3, and 4 weeks after the operations. Samples were also imaged and analyzed using EDS (Phenom XL, Phenom-world BV, Netherlands) to obtain elemental compositions before corrosion products removed.

2.6. Cytocompatibility of Mg–Zn–Ca–4Ag

The biocompatibility of the new magnesium alloys has not been verified. The degradation rate of the magnesium alloy from group 2, viz. Mg–Zn–Ca–4Ag, was the best among the five recorded degradation rates. Therefore, a cytobiocompatibility experiment was to verify biosafety of Mg–Zn–Ca–4Ag.

Effects of the magnesium alloy extract on cell compatibility were detected using CCK-8 (Dojindo, Japan). The magnesium pins were swabbed with alcohol and washed with double-steaming water. The pins were then soaked in a plate, which contained cell culture solution, after it had been disinfected with ultraviolet light. The rate of the material surface area to cell culture medium was 1.25 cm^2:1 ml. Based on calculations, 5 ml of liquid was added for every set of eight magnesium alloy pins. After 24 h, the leaching liquid was extracted from the magnesium alloy pins and diluted into 50% and 10% material leaching liquids. The magnesium ion concentration and the pH of the solution in each treatment group and control group were measured.

A stable cell line of gingival fibroblasts was selected from newborn SD rats. Passage 48 h∼72 h vigorous cells, digest with 0.25% trypsin, collect, centrifuge, then add fresh medium to make cell suspension. Cell suspensions (100 μl/well) were inoculated in three 96-well plates with 30000 cells/well. After cells were adhered to the wall, each 96-well plate contained five culture solutions with different components: original material leaching solution, 50% material leaching solution, 10% material leaching solution, conventional cell culture solution (positive control), and 10% dimethyl sulfoxide (DMSO) cell culture solution (negative control). The culture plates were placed in the incubator for preculturing.

CCK-8 detection was performed on days 1, 3, and 5. The medium was changed and a 1:10 ratio of CCK-8 solution to the cell culture medium was prepared. A 100 μL cell culture solution containing CCK-8 was added to each well to avoid bubble formation. It took 2 hours that the culture plate was put in incubator, a 90 μL supernatant aliquot was absorbed, and a microplate analyzer was used to measure the cell proliferation was measured by absorbance at 450 nm.

2.7. Statistical Analyses

SPSS software (Version 19.0, SPSS Inc., USA) was used to perform statistical analyses. The experimental values are displayed as SD. ANOVA was performed to determine the differences between groups for each evaluated parameter at each point in time. Nonparametric tests were performed when equal variances were not assumed in one-way ANOVA. The level of significance was defined as $p < 0.05$.

Fig. 3. Macroscopic morphology of Mg alloy pins of group 2 after 0, 1, 2, and 4 weeks *in vivo*.

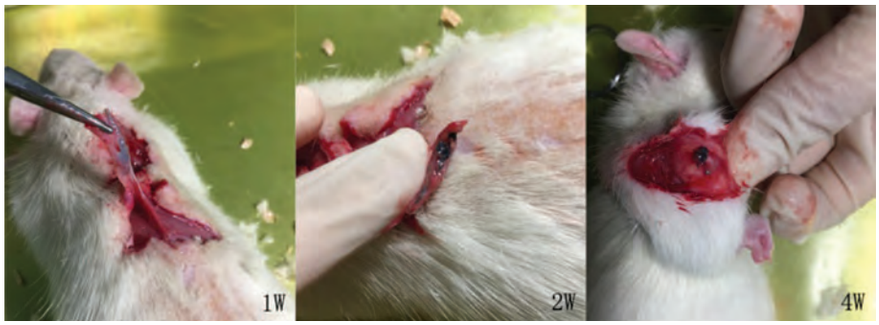

Fig. 4. Degradation of the Mg alloy pins of group 2 *in vivo* after 1, 2, and 4 weeks. It is noted that Mg alloy pins exhibited significant degradation after 4 weeks.

3. RESULTS

3.1. Degradation Rate *In Vitro*

In vitro experiments were performed using artificial saliva, and samples were obtained every week. The degradation rank was 2, 3, 4, 5, 1, as shown in Figure 1.

3.2. General Condition of Experimental Animals

All the rats had a normal diet, exhibited normal growth, and performed regular activities. The rats exhibited no signs of infection, bleeding or swelling, and no diseases were observed throughout the experimental period.

3.3. *In Vivo* Degradation Rate and Surface Topography

Five Mg alloy pins with different compositions were embedded in the rat muscles for 1, 2, and 4 weeks, which were then removed. Macroscopic observations revealed that the tissue exhibited no inflammation or reaction to foreign bodies, such as redness, swelling, and maturation. There was no distinct boundary between Mg alloy pins and muscle soft tissue, and a few bubbles were discovered on the surface of a few Mg alloy pins. There was significantly different among Mg alloys synthesized

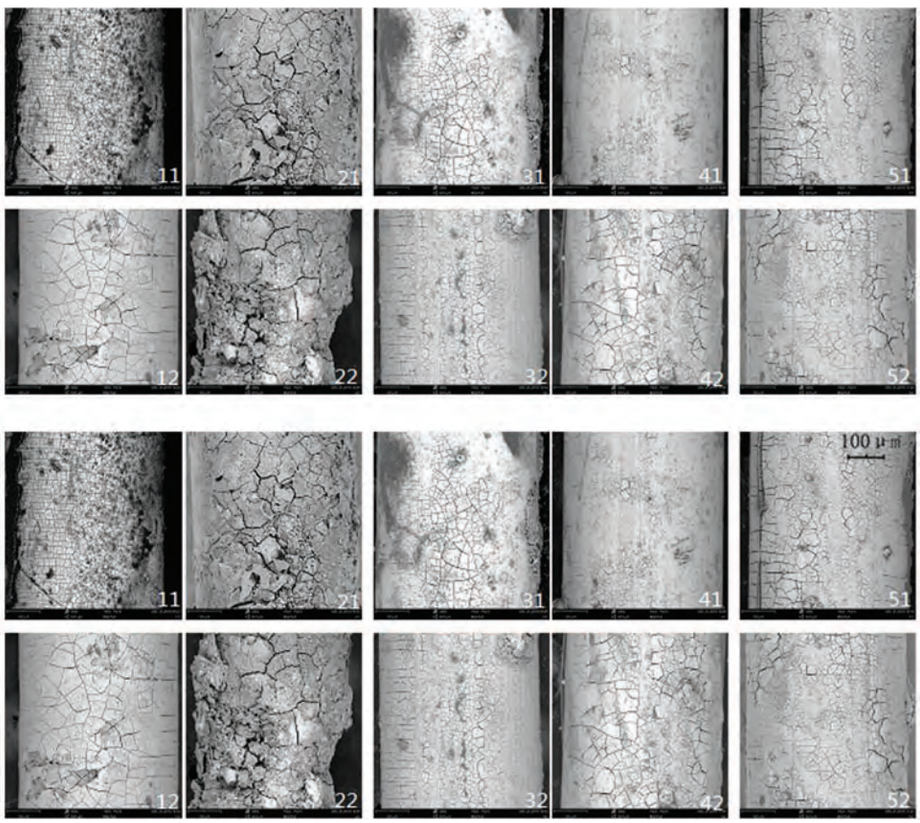

Fig. 5. Surface topography of Mg pins after 1–2 weeks *in vivo* observed with energy-dispersive spectroscopy (EDS) before corrosion removal.

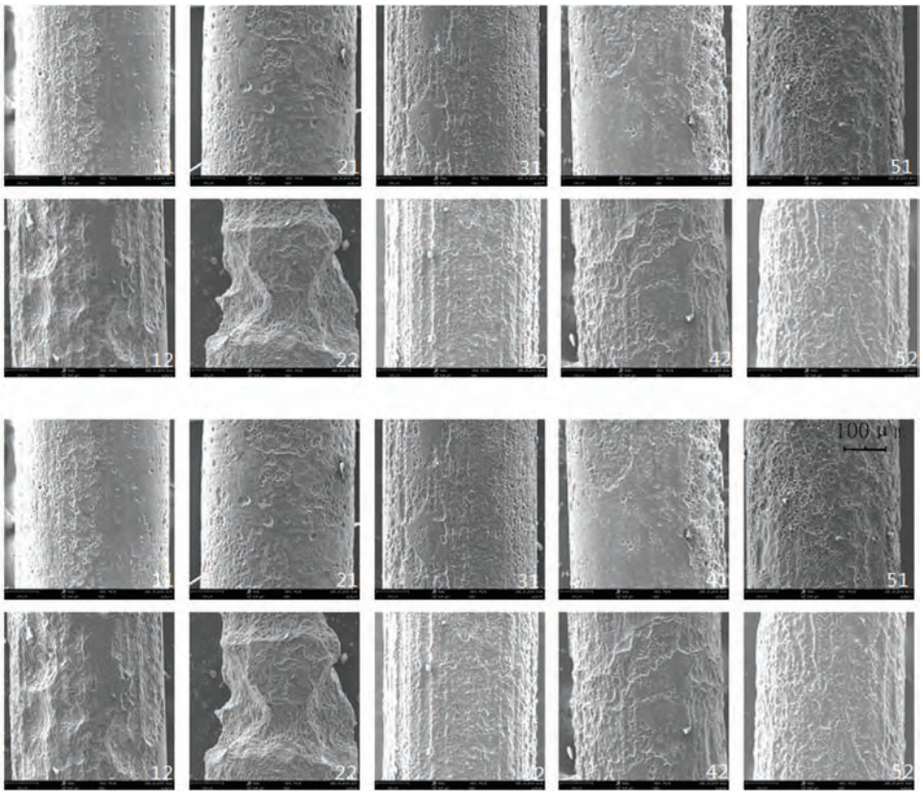

Fig. 6. Surface topography of Mg pins after 1−2 weeks *in vivo* observed by SEM after corrosion removal.

with different components and processes, and the order of degradation rate was 2, 1, 4, 5, and 3. The macroscopic degradation of each group after removal from the body after 1–2 weeks is shown in Figure 2. The Mg alloy pins from group 2 yielded the highest degradation rate (Fig. 3). The Mg alloy pins deformed and eventually broke into several pieces. A large area of degradation was observed after 2 weeks, which formed a large number of corrosion pits and broke into pieces after 4 weeks (Fig. 4). However, the Mg pins from other groups showed no significant changes even after 8 weeks, and they were still intact. Corrosion was observed on a small area of the surface. Numerous surface cracks were observed by electron microscopy before corrosion. The Mg alloy pins from group 2 had a loose surface and the largest number of surface cracks, followed by the Mg alloy from group 1 (Fig. 5). The ratios of the elements were different in different sites, but the elements were mostly Ca, P, K, Na, C, O, Fe, except the elements from the alloy, which were the by-products of reaction with blood or body fluids. The corrosion products

Table II. Concentration of Mg ions and pH value of Mg alloy leaching solution with different concentrations.

Group	Mg ion concentration (μg/mL)	pH
Mg alloy leaching solution (100%)	510.0	9.46
Mg alloy leaching solution (50%)	255.0	8.93
Mg alloy leaching solution (10%)	51.0	7.60
DMEM cell culture medium	15.8	7.40

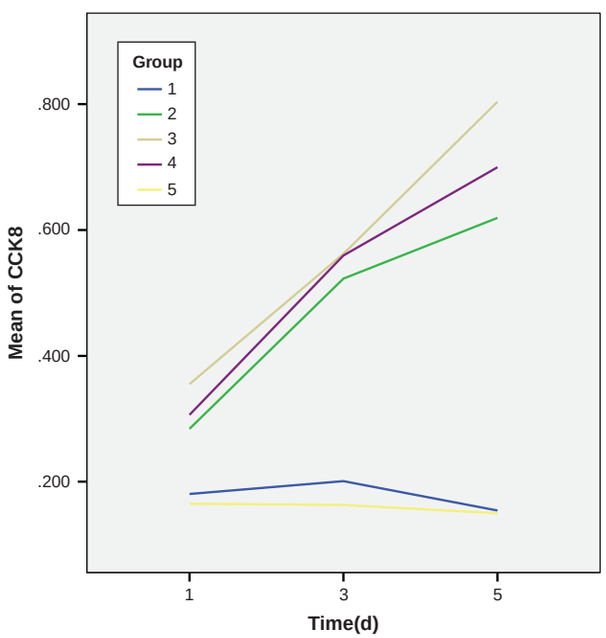

Fig. 7. Broken line chart of cell activity on days 1, 3, and 5.

on the surface were removed via reaction with a complex acid. The surface corrosion increased with time (Fig. 6). The degradation rates of Mg alloy pins in group 2 were the most ideal. These pins were fully degraded within 2–4 weeks, and did not affect the functional activities of the tissue, did not induce adverse reactions in the body, and met the guidelines pertaining to the degradation rates of absorbable suture materials in soft tissue.

3.4. Cytocompatibility of Mg–Zn–Ca–4Ag

The concentration of Mg^{2+} and pH values between different groups are listed in Table II. The CCK-8 method was used to test the activity of gingival fibroblasts in the rats with different concentrations of Mg alloy leaching solutions. The broken line graph of cell activity at days 1, 3, and 5, reflects the growth trend of each group of cells over time (Fig. 7). The histogram reflects the confidence intervals and differences among the different groups during the same period (Fig. 8).

The experiments proved that although the original solution of this new Mg alloy pin inhibited the growth of gingival fibroblasts in the rats, there was no statistical difference between 50% concentration group, which was maintained in natural culture medium. A concentration of 10% may even promote the growth of fibroblasts.

Two-factor ANOVA showed that although the mean value of group 1 was higher than that of group 5, there was no significantly statistical difference between the two groups. However, there were significantly statistical differences among groups 1 and 5 and the remaining groups. In addition, the fourth and third groups also exhibited statistically significant differences, such that the mean value of group 3 was higher than that of group 4. The CCK-8 of group 2 was slightly lower than that of group 3, and there was a statistically significant difference between the two groups ($p < 0.05$). However, there was no statistically significant difference between the second and fourth groups at a concentration of 10% (the concentration of Mg ion was 51 g/mL). A concentration of 50% (the concentration of Mg ion was 255 g/mL) had no effect on cell activity, while a concentration of 100% (the concentration of Mg ion was 510 g/mL) inhibited cell activity. Regulating the concentration of the Mg alloy within an appropriate range will not only affect cell activity but will also alter cell proliferation, thus promoting wound healing.

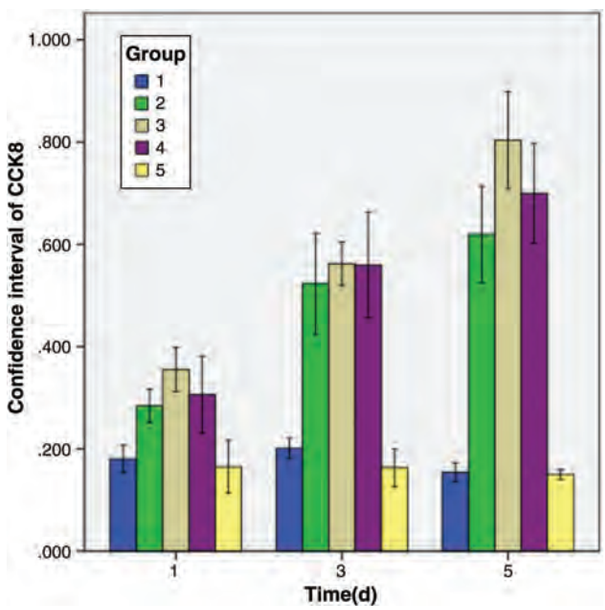

Fig. 8. Histogram of cell activity at days 1, 3, and 5 reflects the cell viability differences among different groups at the same time period.

4. DISCUSSION

This study analyzed degradation processes of Mg alloys *in vivo* and *vitro*. Artificial saliva was selected *in vitro* to emulate the degradation of Mg alloys in oral saliva. The degradation of five Mg alloy pins in artificial saliva was faster than that found *in vivo*. This indicated that the results of the *in vivo* and vitro experiments were significantly different. The order of degradation rates of Mg alloy pins with five different components or heat treatments *in vitro* were 2, 3, 4, 5, and 1, and 2, 1, 4, 5, and 3, *in vivo*. The Mg alloy pins of group 2 (Mg–Zn–Ca–4Ag) degraded significantly faster than the remaining four Mg alloys, and had the highest Ag content (but less than 5% mass percentage). As the composition of the alloy became more complex, the number of precipitated phases formed became larger. The potential difference between precipitated phases and Mg matrix triggered galvanic corrosion, thus accelerating degradation. The content of Ag is directly proportional to degradation rate. Liu et al. proved that as content of Ag increases, degradation rate of the Mg–Ag alloy increases. In addition, Mg–Ag alloys have good antibacterial properties and have the same cellular compatibility with pure Mg.[31] All the five materials tested herein were completely degraded *in vitro* within 4 weeks, and the overall degradation rate *in vivo* was lower than that *in vitro*. This could be because chemical reactions of materials were different in different liquid environments.

Degradation rate *in vivo* and *vitro* will be of great significance for the design and placement of Mg alloys in the future. For example, if these alloys are used for oral mucosal sutures, the degradation rates *in vivo* and *in vitro* should be considered when some Mg alloys are exposed to oral saliva, while only the degradation rate *in vivo* needs to be considered when Mg alloys are buried in the submucosal muscularis.

The degradation of Mg releases hydrogen, which can permeate through the cuticle, capillaries, or lymph nodes. If the bubble is too large, it will cause the wound to swell and deform. The release of hydrogen can be controlled by changing the composition. Bruno et al. reported an obvious decrease in the hydrogen evolution in Mg–Zn–Ca glasses

with Zn-rich.[32] The bubbles will also gradually disappear over time. Mirua et al. proved that the size of the air cavity decreased significantly after 4 weeks of implantation of the Mg alloy plates.[33] In rat muscle tissue, hydrogen can be carried away though the surrounding voids or by blood vessels.[23] There were small bubbles around some of the Mg pins, but no serious effect was observed on wound healing. Recent basic and clinical studies have found that moderate amounts of hydrogen play a positive role in the maintenance of the normal functioning of the central nervous, respiratory, and digestive systems. Rich hydroxides and hydrogen-induced pH changes may cause tissues to become alkaline and possibly damage other surrounding tissues.[34] However, no distinct inflammation or systemic adverse reactions were observed in this study.

Corrosion deposits are rich in Ca and P, which is a sign of good biocompatibility.[35] Navarro et al. showed that the release of calcium could stimulate MMP, collagen synthesis, and cytokine expression.[36] Thus, the calcium on Mg alloy pin surface might improve wound healing. Paital et al. showed that a textured calcium-phosphate-based bioceramic coating improved bioactivity *in vitro* and biocompatibility *in vitro*.[37] After the removal of corrosion, porous pits of different sizes were identified. The pits were attributed to the crystal corrosion that started from the Mg matrix, while the large pits may have been caused by the corrosion at the boundaries of some crystalline phases, such as the Mg–Zn phase, which spreads to deeper or surrounding areas, thus breaking large pieces of material. We can compare the degradation rate of different groups by observing the number and size of pits. Circular corrosion was also observed, which may be attributed to the manufacturing or process error, and local strength concentration. These narrow corrosion sites are the first to break. This decreases the interference on local movement when the wound has healed.

Controlling the degradation rate of the suture material is important in wound healing. If the degradation rate is too high, there might be high alkalinity and inflammation in the local wound, which will make it difficult to sustain the wound in a closed state. However, a low degradation rate will cause discomfort to patients, especially around muscle areas or tissues that move. In addition, long-term foreign body residues may induce allergies or inflammations. The degradation rate is influenced by many factors, such as movement of rats, body environment—such as serum proteins[38]—residual stress of materials resulting from operational or process errors,[39] surface oxidation layer, material composition, and processing. Manufacturing and processing can artificially control the degradation of Mg, and these methods include the selection of appropriate alloying elements, processing technology—such as heat treatment—refinement of microstructures,[40] and surface modifications.[41]

The cellular compatibilities of the materials were determined by analyzing the gingival fibroblasts of rats. The results of CCK-8 indicated that cell growth was inhibited when the concentration of Mg ion was 510 g/mL. When the concentration of Mg ion was 255 g/mL, significant difference was not detected between the growth status of cells and the cells grown in ordinary DMEM statistically. When the concentration of Mg in the third group was 51 g/mL, cell growth was even better than that of the control group with an ordinary DMEM medium, and promoted cell growth. The degradation rate of materials affects pH and Mg ion concentration, both of which affect cellular activity. This phenomenon is consistent with the results reported in a large number of other studies. For example, Okawachi et al. have shown that Mg may facilitate fiber cell adhesion to the surface and promote cell vitality and activity.[42] Zhen et al. demonstrated that Mg had minor effects on cells even when the concentration of Mg was 100 g/mL. High concentrations of Mg ions (>300 g/mL) induced cell death in L929 cells.[43] In this study, the wounds showed no distinct signs of inflammatory reactions, and the normal daily activities of the rats proved that the material was biocompatible.

5. CONCLUSIONS

In conclusion, the degradation rates of different pins were studied *in vivo* and vitro. This met requirement of wound healing duration and led to good cytobiocompatibility. We proved that Mg alloy pins are likely to be promising candidates as stapler pins for oral, soft-tissue wound closures. We will further improve Mg alloys properties and cooperate with specific oral tissue suture staplers to realize easy and fast oral tissue suturing.

Ethical Approval

The protocols which involved animals were approved by the Biomedical Ethics Committee of Peking University (protocol no. LA2017281). All procedures adhered to the applicable international, national, and/or institutional guidelines for the care and use of animals.

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