DEVELOPMENT OF NEW BIODEGRADABLE ALLOYS FOR MEDICAL APPLICATIONS

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Abstract

In surgery, besides the joint replacements that need permanent prosthesis implantation in the human body, there are many other clinical cases, such as bone fracture, cardiovascular diseases, in which the temporary implant materials are needed. The fixation or mechanical support are there temporarily needed during the healing process of the injured or pathological tissue, and after that, the implants accomplish their mission have no longer function in human body. In this case, biodegradable materials are the optimal choice as these materials do their job while healing and a new tissue forming occur and degrade in the human body thereafter. Amorphous alloys based on magnesium and calcium are nowadays a very perspective group of metallic glasses. We have developed composition series of completely new (not published) ternary Ca-Mg-Au biodegradable alloys with attractive properties in terms of possible future applications (density and elastic modulus comparable to human bones, wide supercooled liquid region etc.). Although the rate of their degradation in physiological solutions is still too fast, these ternary alloys will serve as precursors for design of future highly alloyed systems with tuned dissociation rate in human body.

Keywords: Biodegradable alloys, X-ray diffraction, nanoindentation, alloy dissolution

1. INTRODUCTION

The progressive ageing of the world's population has increased the need for improved and longer-lasting materials for use in biomedical devices. The majority of current medical devices are either made of ceramics or metallic alloys composed mainly of titanium, which is known for its reliable biocompatibility. However, the most well known of these common titanium alloys, Ti-6Al-4V, contain vanadium and aluminium. The latter element has been identified as potentially toxic. The design of a new alloy that provides reliable mechanical characteristics without negative effects on the human body is a current challenge for the biomedical sector. Another issue associated with today used materials for orthopaedic implants are that the existing hard tissue biomaterials are employed as permanent fixation devices which are used primarily in load-bearing applications. Examples include bone plates, staples, suture anchors, screws and pins to secure fractures, along with dental implants. However, most fracture fixation devices are removed after healing, requiring invasive procedures and additional costs. In case of load-bearing, fracture fixation devices, such as intramedullary rods or bone plates, stress shielding (bone becomes weaker due to transfer of normal stresses to stiffer implant) is another challenge associated with their permanent in-vivo presence [1,2]. There exist clinical cases such as cardiovascular diseases or bone fracture where only temporary implant materials are needed. For such cases the fixation or mechanical support are needed for just the healing process, and after it the implants should

dissolve in the human body and feed surrounding local tissue. For these reasons, interest in bioresorbable metallic vascular scaffolds and orthopaedic fracture fixation devices has increased in the last decade [3]. Biodegradable or bioresorbable materials based on Mg and Ca elements are the optimal choice as those materials consist of elements pre-existing in the human body to which the organism has an inherent tolerance. Implants in these cases will do their job while healing and new tissue forming occurs and degrades in the human body thereafter. To achieve the ultimate orthopaedic resorbable tissue implant, a series of general conditions need to be fulfilled before the material can be used clinically [4]:

- cell response: encourage new bone formation through both osteoblast and osteoclast attachment and proliferation, but also avoid fibrous capsule formation [5]
- mechanical integrity: > 6 months
- yield strength and ultimate tensile strength: > 230MPa and > 300MPa
- elongation to failure: > 15-18 %
- elastic modulus: close to cortical bone to avoid stress-shielding (10-20 GPa)
- fatigue strength at 10^7 cycles (MPa): :256
- hydrogen evolution: < 10 µL/cm^2/day

This work reports our development of a brand new fully biocompatible bulk metallic glass based on Mg, Ca and Au. Our alloys development is based on machine learning prediction described in the article [6].

2.   MATERIAL SELECTION

The alloys selection was based on the condition that the elements that will be used are exclusively biocompatible. The choice of the chemical composition of alloys that could form metal glass is based on the new machine learning prediction approach described in the article F. Ren et al. [6]. The result of this prediction is shown on the Mg-Ca-Au ternary alloy as probabilistic colour map where the most probable compositions to form metallic glass are in red colour, see **Figure 1**. We decided to experimentally verify compositions laying on concentration of Au up to 10 at.%. Our selections are marked in the figure by squares and circles.
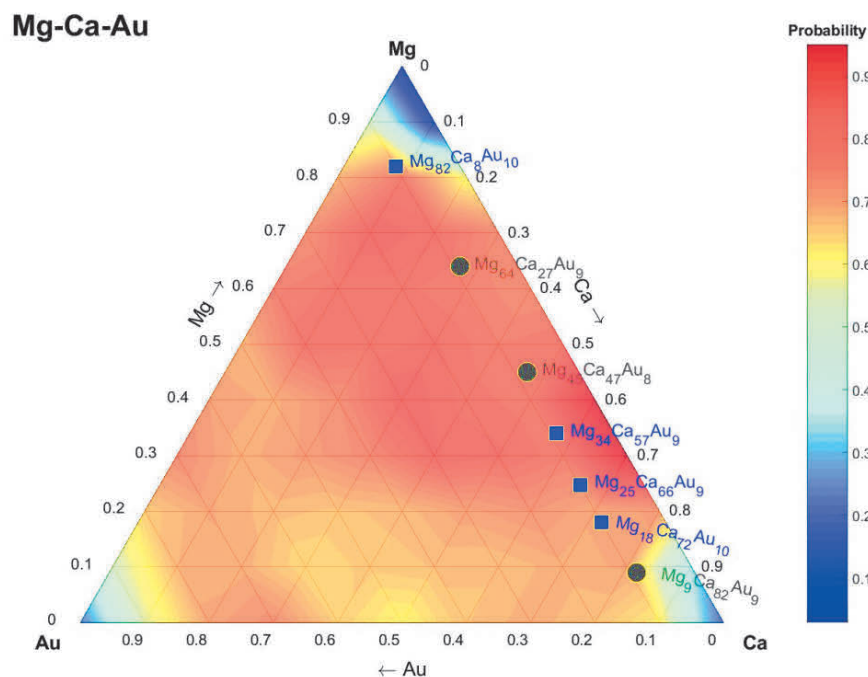

Figure 1 Mg-Ca-Au ternary diagram showing in colour map prediction of glass forming probability calculated by machine learning algorithm, the alloys which were tested experimentally are marked by squares and circles

3.   MATERIAL

3.1.   Preparation

The Mg-Ca-Au alloys of different compositions were fabricated by induction melting of the pure constituent elements (Ca 99.5 wt% Mg 99.98 wt% and Au 99.99 wt%) in a BN coated quartz tube under a high vacuum (better than 3.0×10^{-3} Pa) at 1000 °C. Ribbons of maximum thickness of 40 µm, width ~4 mm and length below 70 mm were prepared by the single-roller melt-spinning method.

3.2.   Characterization

The density of the alloys was measured at room temperature applying Archimedean principle using a analytical balance Kern ABT 120-4M with special density determination kit ABT-A01. Measurements were performed in oil of density 0.882 g/cm^3.

Elastic modulus of the alloys was determined by nanoindentation experiment conducted using the NHT, CSM nanoindenter instruments calibrated on pure fused silica. The indenter tip was a diamond Berkovich indenter (three sided pyramid) and the results were evaluated using the Oliver-Pharr method. Indentation was performed in single load mode to loads as high as 50 mN using the loading rate 1 mN/s, with dwell time 10 s.

Thermal stability of the alloys was ascertained by Perkin Elmer power-compensated differential scanning calorimeter (DSC 8000) at scan rate of 10 $K.min^{-1}$. Measurement was carried out in graphite sample pans under pure argon atmosphere. The temperature and the enthalpy were calibrated by using pure In and Zn. Each measurement was followed by a second run to determine baseline of the measurement.

To determine phase composition a hard X-ray diffraction experiment was performed at the beamline I15-1 located at the Diamond Light Source (electron storage ring operating at an energy of 3 GeV with beam current ~300mA operating in top-up mode). During the experiment, monochromatic synchrotron radiation of photon energy 76.69 keV (λ = 0.016166 nm) was applied. The following setup was applied: transmission (Debye-Scherrer) geometry; monochromatized high energy X-ray beam of photon energy 76.69 keV (λ = 0.016166 nm) to obtain high quality diffraction patterns up to the magnitude of the scattering vector $Q_{max}=4\pi \sin(\theta)/\lambda=2$ nm^{-1}; beam cross-section on the sample was ~ 0.7 mm × 0.15 mm (h x v); fast 2D image plate detector Perkin Elmer XRD 4343 CT (2880 pixels × 2880 pixels, size of a pixel: 150 µm × 150 µm) to record diffracted X-rays. After corrections for the background, polarization, absorption and Compton scattering the scattering intensity was converted to the X-ray total structure factor using the PdfGetX2 software [7].

We have investigated also degradation behaviour of the alloys by immersion the alloys to the Hanks' balanced salt solution (H6648) and documented their degradation by photographing the alloy at regular time intervals.

4.   RESULTS AND DISCUSSION

Figure 2a shows X-ray structure factors calculated from the X-ray diffraction measurement. From this figure it is evident that the alloys of the composition $Mg_{64}Ca_{27}Au_9$, $Mg_{45}Ca_{47}Au_8$ and $Mg_9Ca_{82}Au_9$ are crystalline, (marked by grey circles on the **Figure 1**), while the $Mg_{82}Ca_8Au_{10}$, $Mg_{34}Ca_{57}Au_9$, $Mg_{25}Ca_{66}Au_9$ and $Mg_{18}Ca_{72}Au_{10}$ alloys were prepared in fully amorphous state (squares). **Figure 2b** shows reduced atomic pair distribution functions $D(r)$ of the corresponding $S(Q)'s$. Since we have prepared a series of different compositions, it is interesting to see changes in first coordination shell, by altering the Mg - Ca ratio. Individual atomic pairs with indicated X-ray weights are shown for one particular amorphous alloy in the **Figure 2c**.

Chemical composition determined by the EDX analysis, phase composition, elastic modulus, nanohardness as well as the characteristic phase transformation temperatures of the Mg-Ca-Au alloys are listed in **Table 1**. By comparing the results we can formulate the following conclusions:

- with increase of calcium content, the modulus of elasticity in the alloy decreases. The $Mg_{25}Ca_{66}Au_{10}$ has the lowest E_{IT} value which is close to a value typical for cortical bone.

- nanohardness of the amorphous alloys is in the range of 2.4 - 2.7 GPa, whereas for crystal samples the values varies considerably more.

- super-cooled liquid region (important technological parameter for thermoplastic forming of the material) is in the case of Mg$_{34}$Ca$_{57}$Au$_9$ extraordinarily wide 80°C. This parameter also confirms that the Mg$_{34}$Ca$_{57}$Au$_9$ composition is close to deep eutectic of this ternary system. Such observation is in good agreement with the machine learning prediction.

- As expected, the alloy density decreases with increasing Ca content at the expense of Mg. The lowest measured density 2.04 g.cm^{-3} is close the value reported for of non-porous cortical bones 1.9 g.cm^{-3}.
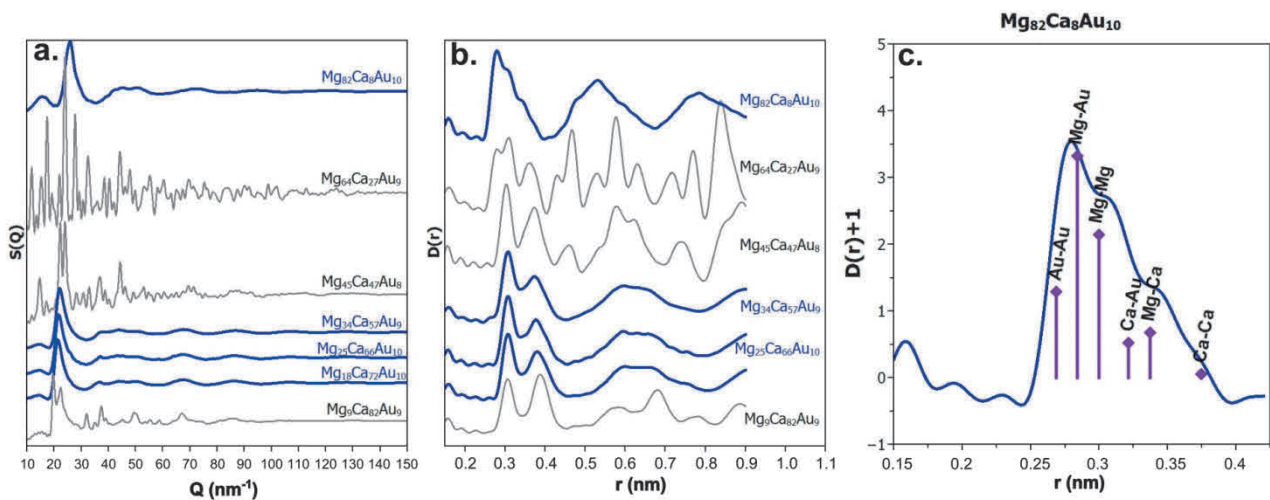

Figure 2 a. The total X-ray structure factors, **b.** corresponding reduced atomic pair distribution functions $D(r)$, **c.** $D(r)$ of the Mg$_{82}$Ca$_8$Au$_{10}$ corresponding to the first coordination shell shown together with interatomic metallic (Goldschmidt) bond lengths and X-ray weights of the Mg-Mg, Mg-Ca, Mg-Au, Ca-Ca, Ca-Au and Au-Au atomic pairs

The degradation of the sample in physiological solution is shown in **Figure 3** where the upper row presents photographs of the alloys prior to immersion into the saline. The lower row of **Figure 3** shows the same alloys but after 6 minutes of exposure in the Hank's salt solution. From this photo documentation it is obvious that all the alloys are dissolving in the saline but with different rate. We have estimated rate of the samples dissolution 6 minutes after immersion and our estimations are listed in the last column of **Table 1**.

Table 1 Properties of the Mg-Ca-Au alloys, from left to right EDX determined chemical composition, phase composition (A - amorphous C - crystalline phase), E_{IT}- elastic modulus H_{IT} - hardness both determined by nanoindentation, T_g - glass transition temperature, $T_{x1\ onset}$ - onset of the 1th crystallisation temperature, ΔT - supercooled liquid region, ρ - density and cr - corrosion rate estimated 6 minutes after immersion alloys into the Hank's salt solution

Alloy	Phase	E_{IT} (GPa)	H_{IT} (GPa)	T_g (°C)	$T_{x1\ onset}$ (°C)	ΔT (°C)	ρ (g.cm^{-3})	cr x10^{-4} (mm/s)
Mg$_{82}$Ca$_8$Au$_{10}$	A	44± 1	2.65 ± 0.06	99	139	40	2.75	5.4
Mg$_{64}$Ca$_{27}$Au$_9$	C	34±7	4.9±0.3				2.63	6.4
Mg$_{45}$Ca$_{47}$Au$_8$	C	34.9±0.4	3.72±0.06				2.57	0.5
Mg$_{34}$Ca$_{57}$Au$_9$	A	37.9 ± 0.6	2.64 ± 0.08	74	154	80	2.45	2.1
Mg$_{25}$Ca$_{66}$Au$_9$	A	20±1	2.39±0.04	78	120	42	2.41	1.2
Mg$_{18}$Ca$_{72}$Au$_{10}$	A	27± 1	2.4 ± 0.2	83	107	24	2.40	5.8
Mg$_9$Ca$_{82}$Au$_9$	C	23±2	1.8 ±0.2				2.04	10.7

Figure 3 upper row: photographs of the alloys prior to immersion to physiological solution, lower row: the same alloys after 6 minutes exposure in the Hank's salt solution

5.   CONCLUSION

In this paper we report our development of a brand new fully biocompatible bulk metallic glass based on Mg, Ca and Au elements. Design of the alloys was based on machine learning prediction described in the work of F. Ren et al. [6]. In the range of gold concentrations up to 10 at.% we have identified compositional areas that can be prepared to fully amorphous state by rapid quenching method with critical cooling rate ~10^5 K^{-1}., see **Figure 1**. The amorphous alloys have hardness ranging from 2.4 to 2.7 GPa and elastic modulus between 27 to 44 GPa. The alloy $Mg_{34}Ca_{57}Au_9$ exhibits extraordinarily wide 80°C super-cooled liquid region. The corrosion/degradation rate of these alloys has been estimated 6 minutes after immersion into the Hank's salt solution, see **Table 1** and **Figure 3**.

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