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Degradable Biomaterials based on Magnesium Corrosion

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Abstract

Biodegradable metals are breaking the current paradigm in biomaterial science to develop only corrosion resistant metals. In particular, metals which consist of trace elements existing in the human body are promising candidates for temporary implant materials. These implants would be temporarily needed to provide mechanical support during the healing process of the injured or pathological tissue. Magnesium and its alloys have been investigated recently by many authors as a suitable biodegradable biomaterial. In this investigative review we would like to summarize the latest achievements and comment on the selection and use, test methods and the approaches to develop and produce magnesium alloys that are intended to perform clinically with an appropriate host response.

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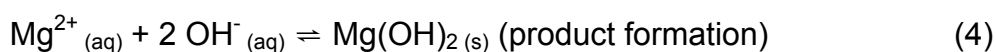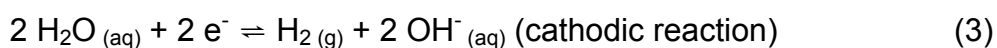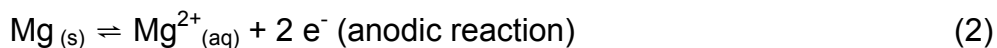4. How to choose the right magnesium alloy?

1 Introduction

Biodegradable metals are breaking the current paradigm in biomaterial science to develop only corrosion resistant metals. In particular, metals which consist of trace elements existing in the human body are promising candidates for this approach. The purpose of biodegradable implants and coatings is to support tissue regeneration and healing in a specific application by material degradation and concurrent implant replacement through the surrounding tissue. Biodegradable metals have an advantage over existing biodegradable materials such as polymers, ceramics or bioactive glasses in load bearing applications that require higher tensile strength and Young`s modulus closer to bone [1] (Table 1).

In this review we will focus on biodegradable magnesium and its alloys. Preliminary and most recent advances will be reviewed. Magnesium and its alloys are generally known to degrade in aqueous environments via an electrochemical reaction (corrosion) which produces magnesium hydroxide and hydrogen gas. Thus, magnesium corrosion is relatively insensitive to various oxygen concentrations in aqueous solutions which occur around implants in different anatomical locations. The overall corrosion reaction of magnesium in aqueous environments is given below:

$$Mg_{(s)} + 2\ H_2O_{(aq)} \rightleftharpoons Mg(OH)_{2\ (s)} + H_{2\ (g)} \tag{1}$$
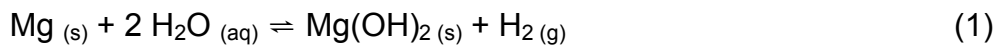
This overall reaction may include the following partial reactions:

$$Mg_{(s)} \rightleftharpoons Mg^{2+}_{(aq)} + 2\ e^- \text{ (anodic reaction)} \tag{2}$$

$$2\ H_2O_{(aq)} + 2\ e^- \rightleftharpoons H_{2\ (g)} + 2\ OH^-_{(aq)} \text{ (cathodic reaction)} \tag{3}$$

$$Mg^{2+}_{(aq)} + 2\ OH^-_{(aq)} \rightleftharpoons Mg(OH)_{2\ (s)} \text{ (product formation)} \tag{4}$$

Magnesium hydroxide accumulates on the underlying magnesium matrix as a corrosion protective layer in water, but when the chloride concentration in the corrosive environment rises above 30 mmol/l [2], magnesium hydroxide starts to convert into highly soluble magnesium chloride. Therefore, severe pitting corrosion can be observed on magnesium alloys *in vivo* where the chloride content of the body fluid is about 150 mmol/l [3-5]. In magnesium and its alloys, elements (impurities) and cathodic sites with low hydrogen overpotential facilitate hydrogen evolution [6], thus causing substantial galvanic corrosion rates and potential local gas cavities *in vivo*. The corrosion morphology of magnesium and its alloys depends on the alloy chemistry and the environmental conditions [4, 6]. Currently investigated magnesium alloys were obtained off-the-shelf, purchasable standard alloys or alloys which can be easily cast.

As discussed in the field of biodegradable materials, there is at least a two-way relationship between the material and the biological host response i.e. the degradation process or the corrosion products can induce local inflammation and the products of inflammation can enhance the degradation process. The complexity of this relationship is generally unknown for biodegradable metals, even though first results have shown that fast corroding magnesium alloys respond with a mild foreign body reaction [7].

1.1 General: Major recent advances

The major recent advances in magnesium alloys as temporary biomaterials have been in understanding the interface and interaction of magnesium alloys and their biological environment. In contrast to previous technical alloy developments aiming on the improvement of mechanical properties, corrosion resistance and production costs, the main focus is shifting to the influence of the alloying elements on the

formation of the corrosion protective interfaces and on the surrounding biological environment *in vitro* and *in vivo*. However, currently available magnesium alloys were investigated in different biomedical applications. Indisputably the most advanced clinical applications are biodegradable cardiovascular magnesium stents which have been successfully investigated in animals [8-10] and first clinical human trials have been conducted [11-13]. Magnesium alloys were also investigated as bone implants [3, 4, 14] and can be applied in various designs e.g. as screws, plates or other fixture devices. Magnesium chips have been investigated for vertebral fusion in spinal surgery of sheep [15] and open-porous scaffolds made of magnesium alloys have been introduced as load bearing biomaterials for tissue engineering [7, 16-18]. However, high extracellular magnesium concentrations have been found beneficial for cartilage tissue engineering [19].

2   Magnesium and its alloys

2.1   Chemical composition and production process of magnesium

2.1.1   Magnesium alloys

The magnesium alloys currently under investigation as implant materials are mostly commercial alloys which have been developed for the needs in transportation industry [20]. The designation system of magnesium alloys is generally following the nomenclature of the American Society for Testing and Materials (ASTM) [21, 22] and uses a typical letter-figure combination (Table 2). The magnesium alloys can be divided into three major groups: pure magnesium (Mg) with traces of other elements, aluminium (Al) containing alloys and those alloys which are free of Al [3-7, 14, 17, 18, 23-36]. Typical Al containing magnesium alloys are AZ91, AZ31, AE21, calcium (Ca)

modified AZ alloys, and LAE442. AZ31 and AZ91 have been used over decades in technical applications [20, 37]. In addition to the given elements Al and zinc (Zn), these alloys also contain a small amount of manganese (Mn) [20, 37]. AE21 consists of Mg, Al, rare earth elements (RE), a small amount of Mn. Furthermore, its composition is very similar to the commercial creep resistant alloy AE42 [20, 37]. LAE442 is based on the alloy AE42 and contains Al, RE, Mn and additionally lithium (Li). LAE442 has been developed recently as a density reduced magnesium alloy with improved ductility and enhanced corrosion properties [38, 39].

Typical Al-free magnesium alloy systems are WE, MZ, WZ, and Mg-Ca alloys. The magnesium alloy WE43 has been developed to improve creep resistance and high temperature stability [20, 37, 40]. This alloy contains yttrium (Y), zirconium (Zr) and RE respectively. Manganese-zinc (MZ) alloys have comparable properties to the alloying system ZM, which is a known system for wrought applications in the transportation industry [20, 37].

However, almost none of the above mentioned alloys have been originally developed to be a biodegradable implant material. Due to the complex alloy composition it is not certain, if the observed *in vivo* degradation can be truly connected to a chemical element, an intermetallic compound or a microstructural effect based on the processing route.

2.1.2   The alloying elements

Alongside pure magnesium, the chemical elements Al, Mn, Zn, Ca, Li, Zr, Y and RE are used in magnesium implant materials [3-7, 14, 17, 18, 23-36]. The detailed metallurgical and metal physical reasons for their use are described in [20, 37, 41]. In general, these elements influence the mechanical and physical properties of magnesium alloys in industrial applications. As long as the alloying elements remain

in solid solution, they can be used for solid solution strengthening. Furthermore, most of the given alloying elements can react with magnesium or among each other to form intermetallic phases. Theses phases contribute to enhance the alloy`s strength by precipitation strengthening. Both solid solution strengthening and precipitation strengthening improve strength, but deteriorate the alloy`s ductility. However, almost any alloying element contributes to some extent to grain refinement which serves as a strengthening mechanism known as grain boundary strengthening or Hall-Petch strengthening. Grain boundary strengthening improves both strength and ductility.

Characteristic impurities in magnesium alloys are iron (Fe), copper (Cu), nickel (Ni), and beryllium (Be). The amount of impurities depends on the alloy`s composition, the technology for production and the progress in alloy development. Typically, Be is limited to 4 ppm. The amount of Cu is limited normally to 100-300 ppm, Fe to 35-50 ppm, and Ni should not exceed 20-50 ppm. Other chemical elements are referred as normal alloying elements and their limits are given together with the nominal contents of alloying elements [42]. For biomedical applications, the amount of these impurities has to be strictly controlled. Although the given impurity concentration are low compared to the physiological range of concentration in the body, elements such as especially beryllium and nickel should be avoided. In general, the amount of impurities should be kept minimal, supporting the aim to obtain more comparable and standardized magnesium alloys. A brief summary for pathophysiological and toxicological characteristics of the alloying elements and the impurities in magnesium alloys are given in Table 3.

2.1.3 The production process

Casting is the predominant process to manufacture magnesium parts and implants. Casting is suitable for the production of small series of near net shape components

as well as for the mass production with high dimensional precision. The limitations of casting are dependent on the casting parameters and could appear as segregations, precipitation shrinkage, micro- and macroporosity, inhomogeneous grain size and grain size distribution during solidification. Additional heat treatment can not be applied to overcome some of these problems [20, 43].

Wrought materials are preheated prior to deformation to dissolve precipitates and to activate additional slide systems in magnesium base materials with a hexagonal close-packed (h.c.p.) crystal structure [20]. Depending on the wrought process and its parameters (i.e. deformation ratio, deformation speed, billet temperature), it is possible to achieve a magnesium alloys with a fine grained, homogeneous microstructure.

The combination of different processing steps, heat treatments and the variety in the alloy composition influences the microstructure – property relationship and can lead to drastic differences in strength, ductility, creep resistance and corrosion performance. Therefore, the process chain has to be determined with regard to the intended application and its requirements.

2.1.4   The effect of alloying elements

Compared to high purity magnesium none of the alloying elements improve the corrosion behavior [37]. Any of the alloying elements in its pure form or intermetallic phase are nobler compared to pure magnesium. Thus, the matrix acts in any case as a cathode and gets dissolved.

Depending on the production process, the grain size and grain size distribution is affected by the process itself and by the selection of alloying elements. Compared to the matrix, a grain boundary is a distorted area with high imperfection and high

internal energy. Any corrosive attack in a pure material attacks therefore normally the grain boundary first. Segregation of the alloying elements towards the grain boundary occurs depending on the present alloying element and the chosen solidification route. Therefore, the composition in the center of the grain will be different from those close to the grain boundary. This fact influences corrosion behaviour and normally the matrix close to the grain boundary shows a more cathodic behavior compared to the center of the grain.

Since the grain boundary is a weak area that promotes early corrosive attacks it could be assumed that coarse grains should be preferred. However, segregations are minimized in small grained magnesium alloys and the corrosion behaviour appears to be more homogeneous.

As an alloying element, Al can provide both solid solution strengthening and precipitation strengthening. Unfortunately the $Mg_{17}Al_{12}$ phase in the Mg-Al system has a low melting point and can not be used to improve high temperature strength. Additionally the increase of the content of Al lowers the temperature of liquidus and solidus lines and enhances the castability of alloys with high Al contents.

Manganese is mainly used to enhance ductility. More important is the formation of Al-Mn intermetallic phases in Al containing magnesium alloys. These phases can pickup iron (Fe) and can therefore be used to control the corrosion of magnesium alloys due to the detrimental effect of Fe on the corrosion behavior.

In smaller amounts, Zn contributes to strength due to solid solution strengthening. It can also improve the castability but in larger amounts (> 2 wt.-%) Zn leads to an embrittlement in combination with Al [37, 44].

Calcium contributes to solid solution strengthening and precipitation strengthening. It also acts to some extent as a grain refining agent and additionally contributes to

grain boundary strengthening. In binary Mg-Ca alloys the Laves phase Mg_2Ca is formed while in Al containing alloys the Laves phase Al_2Ca forms first. Both phases improve creep resistance due to solid solution strengthening, precipitation strengthening and grain boundary pinning. Larger amounts of Ca (> 1 wt.-%) can lead to problems during casting like hot tearing or sticking.

Lithium is the only element known that is able to change the lattice structure from hexagonal close-packed (h.c.p.) to body-centered cubic (b.c.c.) crystal structure in magnesium alloys [45]. Therefore, it can be used to enhance ductility and formability of magnesium alloys but unfortunately it has a negative effect on strength. Zirconium is an effective grain refining agent in Al free magnesium alloys. With regard to the Hall-Petch relationship it contributes to strengthening due to the formation of fine grains (grain boundary strengthening).

Rare earth elements (RE) are introduced into magnesium alloys normally by master alloys such as mischmetal (typically 50% cerium (Ce), 45% lanthanum (La), small amounts of neodymium (Nd) and praseodymium (Pr)), Y-, Ce- or Nd-rich hardeners [20, 37, 40, 46]. These master alloys or hardeners contain one or two RE in larger quantity and almost any other RE in different amounts. In general, the RE can be divided into two groups: the first group contains elements with large solid solubilities in Mg such as Y, gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), and lutetium (Lu) while the second group shows only limited solubility in Mg (Nd, La, Ce, Pr, samarium (Sm), europium (Eu)) [45].

Some amount of the RE is kept in solid solution and therefore RE can strengthen the material by solid solution strengthening. Additionally, all RE can form complex intermetallic phases with Al or Mg. These intermetallic phases act as obstacles for

the dislocation movement at elevated temperatures and cause precipitation strengthening. The RE with limited solubility forms intermetallic phases early during solidification. Thus, RE can arrest grain boundaries at elevated temperatures and contribute to strength mainly by precipitation strengthening. This mechanism increases the service temperature of Mg alloys in transportation industry and improves creep resistance as well as corrosion resistance [47].

2.2 Experimental test systems used in *in vivo* and *in vitro* studies

2.2.1 *In vivo* testing of magnesium alloys

In vivo studies were predominantly performed in small animals, i.e. rats (subcutaneously), guinea pigs and rabbits [3-5, 7, 14, 17]. However, an experimental study in sheep reported about the corrosion of magnesium chips in spinal applications [15] and preclinical experiments for cardiovascular stent applications have been performed in pigs [9, 48, 49]. Since the local blood flow and the water content of the different tissues (local chloride content, hydrogen diffusion coefficient) can be assumed to be different in various animal models (Table 4, 5, 6), the obtained corrosion rates are not directly comparable. Basically, the obtained different local corrosion patterns due to various anatomical locations or different mechanical loading situations might shed light on the underlying corrosion mechanism of the investigated magnesium alloy *in vivo*. Dissolved ions from metal implants are always a concern to induce hypersensitivity and allergy. Magnesium alloys AZ31, AZ91, WE43 and LAE442 have been shown to be non-allergenic in an epicutaneous patch test in accordance with the ISO standard [50]. Various analytical methods have been used to determine the elemental components of biodegradable magnesium alloys (Mg, Al, Li, Zn, rare earth elements) in histological sections, bone, tissue and body fluids

(Table 7). The application of these methods for trace and ultra trace analysis in often small sample volumes is hampered by several problems. The typical concentrations of the elements mentioned above range from < 1 µg/L to about 1 mg/L in serum and from < 1 mg/kg up to about 500 mg/kg for example in liver and bone. Thus, the sensitivity of the method is not sufficient (AES, GD-OES, XRF, SEM-EDX) [51, 52]. Other problems are caused by time consuming sample preparation (AES, OES, ICP-MS), the access to the method (NAA, synchrotron-based methods), the lack of sufficient lateral resolution for solid sample analysis (GD-OES) or difficulties to overcome interferences during the measuring process (AAS, AES, ICP-MS, XRF) [53-55]. Phosphate ions in dissolved bone samples may hamper the accurate determination of trace metal concentrations by AAS due to the formation of very stable phosphate compounds. High concentrations of alkaline and earth alkaline elements cause problems in AES measurements due to their strong influence on the line intensities of other elements. In ICP-MS measurements, signal distortion can occur due to contributions of other ions or molecular ions with the same mass-to-charge (m/z) ratios as the elements which are currently analysed. These effects are known for calcium, phosphorous, iron and zinc. Additionally, oxide formation of rare earth elements could be observed leading to decreased signals and shifts in ICP-MS. Furthermore, X-ray spectra of rare earth element mixtures are characterized by strong signal overlaps when using energy dispersive measurements.

Sensitivity problems could be minimized if the samples are completely dissolved. In this case, ICP-MS, with or without preconcentration of the analyte, will provide good results for most elements of the periodic system. However, locally resolved multi-element analysis of solid samples is still a challenging task. At present, micro-XRF and laser ablation ICP-MS are the most promising methods [56-58], even though their sensitivity is limited.

2.2.2 *In vitro* testing of magnesium alloys

To investigate magnesium corrosion has always been a challenge. Corrosion rates of the same magnesium alloy obtained from various corrosion tests exhibit usually different corrosion rates [41]. Thus, in more complex corrosive solutions which simulate physiological body fluids, the corrosion rate is even more difficult to determine. Therefore, some authors started to measure the volume of hydrogen gas which evolves with ongoing magnesium corrosion. This simple and inexpensive method has some limitations due to atmospheric pressure changes and possible hydrogen leakages from the experimental set-up. Furthermore, the stoichiometry of the redox equation which produces elemental hydrogen is not fully understood and thus the hydrogen gas volume cannot be directly correlated to the production of magnesium ions [59]. The most common methods to determine the corrosion rate *in vitro* are gravimetric measurements and electrochemical measurements (linear polarization, Electrochemical Impedance Spectroscopy). As a non-destructive method microtomography, especially synchrotron-based microtomography, was introduced to obtain general corrosion rates by observing the time-depending change in the metallic volume of the remaining implant. This method was also applied to estimate corrosion rates from explanted samples [5, 60].

The advised guide line for biomaterial testing is the European standard ISO 10993. However, some limitations are conjunct with the use of this standard mainly for testing biodegradable or corroding biomaterials: (i) the recommended cells are cell lines; (ii) for biodegradable materials it is recommended to prepare extracts and apply these to the cells. One major obstacle is the preparation of extracts from magnesium alloys. The resulting solution, regardless of which alloy is used, shows a high osmolarity and pH and hence exposes the investigated cells to an osmotic shock

[61]. By definition, this would classify nearly all magnesium alloys as cytotoxic. For magnesium research, it is reported that other testing methods produce data *in vitro* that are also not well correlated to the obtained *in vivo* data [5].

Following the recommendations of [62] for screening purposes a simple set of tests could be applied, leading to more complex systems for a more rigid selection up to the final *in vivo* experiment. However, for some magnesium alloys, simple test systems such as formazan-based cytotoxcicity tests (i.e. MTT, WST-1, XTT) are restricted by the interference between the corrosion and the test agent (unpublished data). Similar problems are also reported for other biodegradable materials such as polymers and calcium phosphates [63, 64]. Thus, a systematic approach to determine suitable *in vitro* test methods is needed. This *in vitro* test system should be able to simulate the desired implantation site and its local environment.

3 Environmental conditions influencing Mg corrosion – *in vitro* and *in vivo*

3.1 Effect of the solution and organic content

Many authors performed systematic corrosion studies on magnesium alloys with different corrosion media (± proteins) [24, 25, 27]. The composition of the corrosive medium influenced the magnesium corrosion behavior, which was additionally altered by the presence or absence of proteins. Proteins such as albumin have been demonstrated to form a corrosion blocking layer on the magnesium alloys in *in vitro* experiments [24, 27, 36, 65]. This layer is enriched by calcium phosphates *in vitro* [27, 36] and *in vivo* [3, 4, 15] and concomitantly participate in corrosion protection.

More systematic studies have to be performed, until all factors which are influencing the corrosion behavior are fully discovered.

3.2 Effect of flow and temperature

Blood flow and temperature is different in various anatomical sites and especially the flow of the corrosive media has a significant effect on the corrosion rate of magnesium alloys [65], while the effect of temperature in the human physiological range 35.8 – 37.2 °C seem to be less important for magnesium corrosion, it may influence the adsorption of proteins and thus the response of the biological environment.

3.3 Effect of hydrogen diffusion coefficient

The diffusion and solubility coefficient of hydrogen in biological tissues has been widely reviewed [66]. The solubility of hydrogen in tissues is influenced by the content of lipids, proteins and salinity, but in fat and oils, the solubility seems to be approximately independent of temperature in the physiological range [66] (Table 4). Not only viscosity, but also different tissue components and structures like lipids, proteins and glycosaminoglycans influence the numeric value of the hydrogen diffusion coefficient [66] (Table 5). Depending on experimental configuration, the diffusion coefficient may be underestimated in both stagnant and flowing media due to a boundary layer formation, which increases the effective diffusion distance [66]. This finding might be important for intravascular magnesium applications. Correlating the hydrogen diffusion coefficients from various biological media having fractional water contents from about 68% to 100% demonstrated that the diffusion coefficient of hydrogen increases exponentially with the increasing water fraction of the tissue [67]. Table 5 demonstrates that the tissue water content increases from adipose tissue to

skin to bone and to muscles in animals and humans, but is similar for the same tissue regardless of the species. This might explain why different corrosion rates and gas cavities were observed for magnesium alloys in different anatomical implantation sites [3, 4, 7, 15]. In an animal study with rats, it was shown that the adsorption of hydrogen gas from subcutaneous gas pockets was limited by the diffusion coefficient of hydrogen in the tissue; the overall hydrogen adsorption rate was determined as 0.954 ml per hour [68] (Table 6). Thus, the local blood flow and the water content of the tissue surrounding the implant are the most important parameters which should be considered in designing biodegradable magnesium alloys with an appropriate corrosion rate. Concomitantly, it can be assumed that local hydrogen cavities occur when more hydrogen is produced per time interval than it can be dissolved in the surrounding tissue or diffuse from the implant surface into the extracellular medium which is renewed depending on the local blood flow.

This means that magnesium alloys are corroding *in vivo* with an appropriate corrosion rate when no local gas cavities are observed during the implantation period in a specific anatomical site.

4 How to choose the right magnesium alloy?

Current investigated magnesium alloys are used "off-the-shelf" or are known for their properties in technical applications. The empirical approach in biodegradable stent development lead to magnesium alloys containing rare earth elements. This approach seems to be obviously one successful way to obtain usable implant materials [12, 13]. Most rare earth elements show a beneficial effect on magnesium corrosion *in vivo* [4]. However, the rare earth elements are used as mischmetal in alloy hardeners containing various element concentrations. Therefore, a more systematic approach is needed. Currently, aluminium containing magnesium alloys

are investigated by several research groups in biomedical applications. Even though the authors of this review feel that aluminium containing magnesium alloys should not be implanted into humans, a lot of data from various *in vitro* and *in vivo* experiments are available today. Therefore, it is recommended that Mg-Al alloy systems should just be used as experimental alloys to investigate the improvements of processing and surface modification technologies (i.e. coatings) in biomedical applications. For the use in humans the authors of this review recommend to use aluminium free magnesium alloy systems. As indicated in Figure 1, it seems to be of major importance that an interdisciplinary team of researchers is designing the magnesium alloy and the production process according to the intended application and use as well as reviewing available data from literature and the critical analysis of their methods.

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Table 1: Mechanical properties of different normal tissues and requirements in standard stent and orthopaedic implants compared with available data for currently investigated magnesium alloys

Tissue/ Material	Comp. strength (MPa)	Tensile strength (MPa)	E-mod. tensile (GPa)	Apparent density (g/cm³)	Yield strength (MPa)	Elongation (A) at break [%]	Impact strength Charpy V-Notch (J/m^{-2})
Cortical bone [1]	164-240	35-283	5-23	1.8 - 2.0		1.07-2.10	4-70
Cancellous bone [1]		1.5-38	10-1570 (MPa)	1.0 - 1.4			
Arterial wall		0.50-1.72	1 (MPa)				
Titanium (TiAl6V4, cast)		830-1025	114	4.43	760-880	12	19
Titanium (TiAl6V4, wrought)		896-1172	114	4.43	827-1103	10-15	
Stainless steel 316L		480-620	193	8.0	170-310	30-40	
Synthetic Hydrxyapatite	100-900	40-200	70-120	3.05 - 3.15			
Bioactive glass		40 - 60	35 - 35				
DL-PLA		29-35	1.9-2.4			5-6	
AZ91E-F sand cast	97	165	45	1.81	97	2.5	0.79
AZ91E-F HPDC	165	230	45	1.81	150	3	2.7
AZ91E- GAE		457	45	1.81	517	11.1	
AZ31 extruded	83-97	241-260			165-200	12-16	1.78
AZ31 sheet	110-180	255-290			150-220	15-21	1.78
AZ31GAE		445			424	11.5	1.78
LAE442		247			148	18	
WE43A-T6		250		1.84	162	2	
WE43-B	345	220				2	
WE43 extruded		277			198	17	
WE43 tube		260			170	25	
AZ91+2Ca-GAE		452			427	5.4	
AZ91+2Ca		147				1.7	1.3
Mg0.8Ca		428					
Mg(0-4)Ca		210-240					
AM50A-F	113	210		1.80		10	
AM60B-F	130	225		1.80		8	2.8

[1] the range of values are depending on species, age of species, anatomical location and testing conditions

Data were compiled from [1, 32, 37, 65, 69-78].

Table 2: Influence of alloying elements and impurities on properties and processing of Mg alloys at ambient temperatures

Alloying Element/ Impurities	ASTM	Effect of the alloying element / impurity on:									
		UTS	Ductility	UCS	Hardness	Notch Sensitivity	Creep Resistance	High temperature Strength	Corrosion resistance	Grain Refinement	Castability
Aluminium	A	+	+		+					+	+
Calcium	X	+				–	++		–	+	+
RE	E						++	+		+	
Copper	C	–	+	–					– –	–	
Iron	F		+						– –		
Lithium	L	–	+	–					–		
Manganese	M	+	+			+	+		+ [2]	+	
Nickel	N								– –		
Silicon	S		–	+	+		+	+	–		–
Strontium	J	+	+	+			+	+		+	
Yttrium	W	+				–	++	+		+	+
Zinc	Z	+	– [1]								
Zirconium	K	+	+					+		++	

UTS = ultimate tensile stress, UCS = ultimate compressive stress, effect coding: ++ = excellent, + = good, - = bad, -- = detrimental; [1]) at high Zn concentration, [2]) only in combination with Al;

Table 3: A brief summary of the toxicology and pathophysiology of some alloying elements and impurities.

Element	Pathophysiology/Toxicology	Ref.
Magnesium	normal blood serum level 0.73-1.06 mmol/L	[79]
	influences growth factor effectiveness	[80]
	co-regulator of energy metabolism, cell proliferation, protein synthesis, onset of DNA synthesis	[80, 81]
	regulator of more than 350 proteins	[82]
	stabilizer of DNA and RNA	[83]
	long-term influence on cellular reactions	[84]
	cellular up-take via transient receptor potential (TRP) ion channels	[85, 86]
	co-regulator and activator of integrins (cell migration)	[87-89]
Calcium	normal serum level 0.919-0.993 mg/L	[90]
	most abundant mineral in the human body (1-1.1 kg)	[91]
	mainly stored in bone, teeth	[91]
	is tightly regulated by homoestasis of skeletal, renal and intestinal mechanism	[91]
Aluminium	normal blood serum level 2.1-4.8 µg/L	[92]
	established alloying element in titanium implants	[93, 94]
	risk factor in generation of Alzheimer`s disease	[95]
	can cause muscle fiber damage	[96]
	decrease osteoclast viability	[97]
	in magnesium alloys: mild foreign body reactions were observed *in vivo*	[7]
Zinc	normal blood serum level 12.4-17.4 µmol/L	[98]
	trace element	[99]
	essential for the immune system	[99]
	co-factor for specific enzymes in bone and cartilage	[100, 101]
	neurotoxic at higher concentrations	[102]
Manganese	normal blood serum level < 0.8 µg/L	[103]
	essential trace element	[104]
	important role in metabolic cycle of e.g. lipids, amino acids and carbohydrates	[104]
	influences the function of the immune system, bone growth, blood clotting, cellular energy regulation and neurotransmitter synthesis	[104]
	scavenger of free radicals in the manganese superoxide dismutase	[105]
	neurotoxic in higher concentration (manganism)	[106]
Lithium	normal blood serum level 2-4 ng/g	[107]

	compound of drugs for treatment of psychiatric disorders	[108]
	overdosage causes nephrological or lung dysfunctions	[109, 110]
	possible teratogenic effects	[111]
	further reading on lithium intoxication see reference	[107, 112]
Rare Earth elements	many rare earth elements exhibit anticancerogenic properties	[113-116],
Impurities		
Nickel	normal blood serum level 0.05-0.23 µg/L	[117]
	strong allergenic agent which can induce metal sensitivity	[118]
	carcinogenic and genotoxic	[118]
Beryllium	toxic dosage > 2 µg/m^3	[119]
	induces metal sensitivity, highly carcinogenic	[120, 121]
Iron	normal blood serum level 5.0-17.6 g/L	[122, 123]
	essential for life and metabolically regulated and stored	[122, 123]
	generator of age related diseases by reactive oxygen species	[124]
Copper	normal blood serum level 74-131 µmol/L	[125]

Table 4: Ostwald solubility coefficient L (ml gas per ml medium) for hydrogen in biological media at various temperatures (°C) according to Langö et al. [66].

Medium/Tissue	°C	L
Water	37	0.0185
Saline 0.15M	38	0.0178
Plasma, ox	38	0.0175
Red cells, ox	38	0.0166
Whole blood, ox	38	0.0170
Whole blood, man	37	0.018
Skeletal muscle, rat	37	0.0218
Olive oil	25.3	0.036
Lard	25	0.039

Table 5: Fick diffusion coefficient D (10^{-5} cm^2/s), Krogh diffusion coefficient K (10-5 ml gas per ml solvent per atm times cm^2 per second) and $D_{37°C}$ for hydrogen in biological solvents at various temperatures (°C) according to the review of Langö et al. [66].

Medium/Tissue	°C	D	$D_{37°C}$	K
Brain, guinea pig	21	2.2	3.1	-
Blood serum, ox	37	3.9	-	-
Lard	25	1.1	1.4	-
Skeletal muscle, rat	37	2.57	-	0.054
Olive oil	25.3	2.9	3.7	-
Water	25	4.6 ± 0.6	6.0 ± 0.8	-

Table 6: Comparison of tissue water in animals and humans without blood, the residual blood content of rat tissue and the average blood flow of the specific organ.

Tissue	Rat			Rabbit		Human	
	Water content [%]	Residual blood [µl/g]	Blood flow [ml/min/100g]	Water content [%]	Blood flow [ml/min/100g]	Water content [%]	Blood flow [ml/min/100g]
Heart	79.0 ± 0.2	61	39	78.2-79.0	5.0 ± 0.8	71.2-80.3	1000
Muscle	75.6 ± 0.3	7.2	33	76.5-77.0	22.3 ± 2.2	76.0	38
Brain	78.8 ± 0.2	17	0.75 ± 0.09 [1]	74.0-85.0	57.2 ± 5.3	76.0-78.0	560
Liver	70.5 ± 0.7	150	29.4 ± 2.0	70.0-76.0	19.4	72.9-77.3	1000
Spleen	77.1 ± 0.4	311	1.19 ± 0.9 [1]	75.5-78.0	6.35 [1]	76.5-81.1	1200
Intestine	74.9 ± 0.7	12	2.23 ± 0.3	80.6-82.3	149.1 ± 11.3	71.0-72.7	1000
Adipose	18.3 ± 1.7	3.9	9.8 ± 1.3	8.5	87	--	28
Skin	65.1 ± 0.7	7.1	18.9 ± 1.4	54.0-67.8	12.7 ± 1.7	67.8-75.8	120
Bone	44.6 ± 1.7	59	2.3 ± 2.0	39.2-58.1	19.1 ± 1.7	43.9	120

Data were compiled from [126-142]. [1] = mg/min/g

Table 7: Analytical methods used in studying the corrosion rate of magnesium alloys *in vivo* and *in vitro*.

Methods used *in vitro*	Reference
hydrogen evolution method	[28, 29, 143]
electrochemical measurements (linear polarization, EIS)	[24, 25, 27, 28, 143]
volume change of the metallic volume of the remaining sample, microtomography	[5, 60]

Methods used *in vivo*	Reference
atomic absorption spectroscopy (AAS)	[144]
atomic emission spectroscopy (AES)	[145]
mass spectrometry with inductively coupled plasma (ICP-MS)	[144, 146, 147]
laser ablation for solid sampling	[148]
X-ray fluorescence analysis with synchrotron source	[149]
electron beam (SEM-EDX)	[3, 4, 15]
X-ray diffraction (XRD)	[150]
microtomography	[151]
neutron activation analysis (NAA)	[152]
glow-discharge optical emission spectroscopy (GD-OES)	[153]

Figure Captions

Figure 1: Following the steps in this flow chart might help to select the appropriate magnesium alloy for the intended implant.
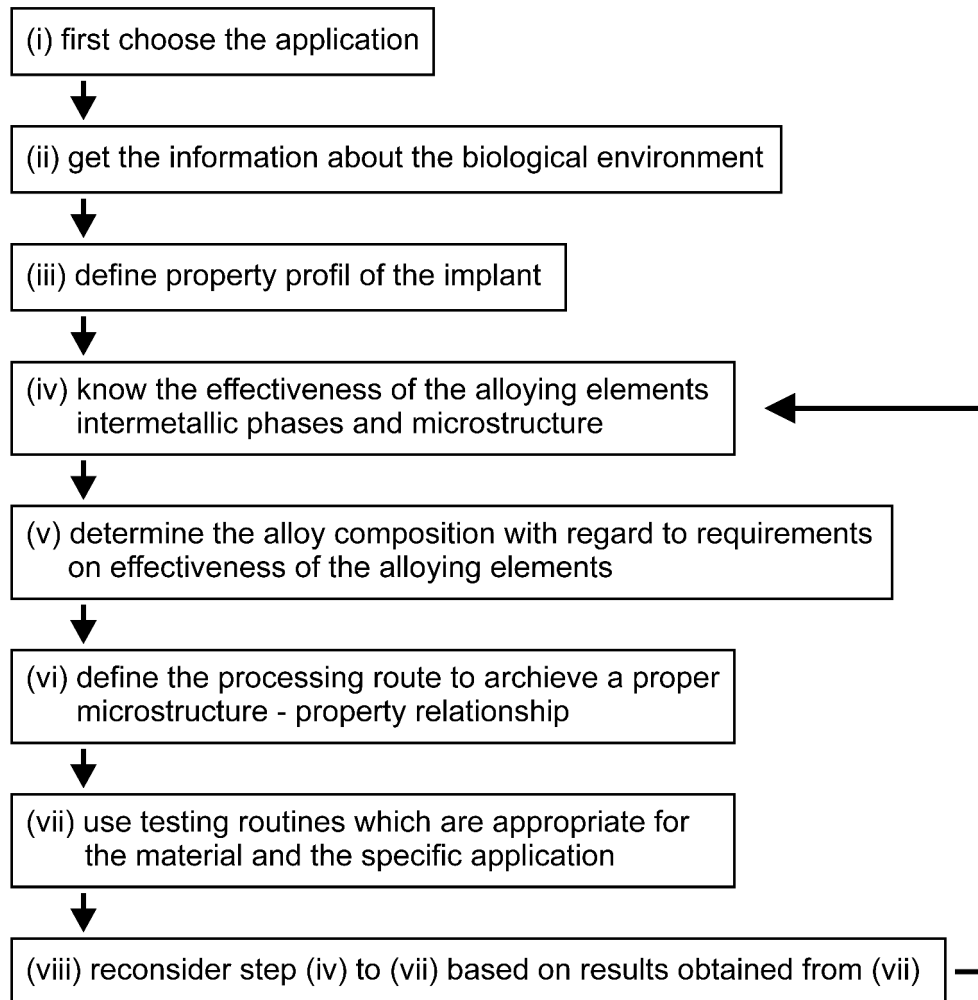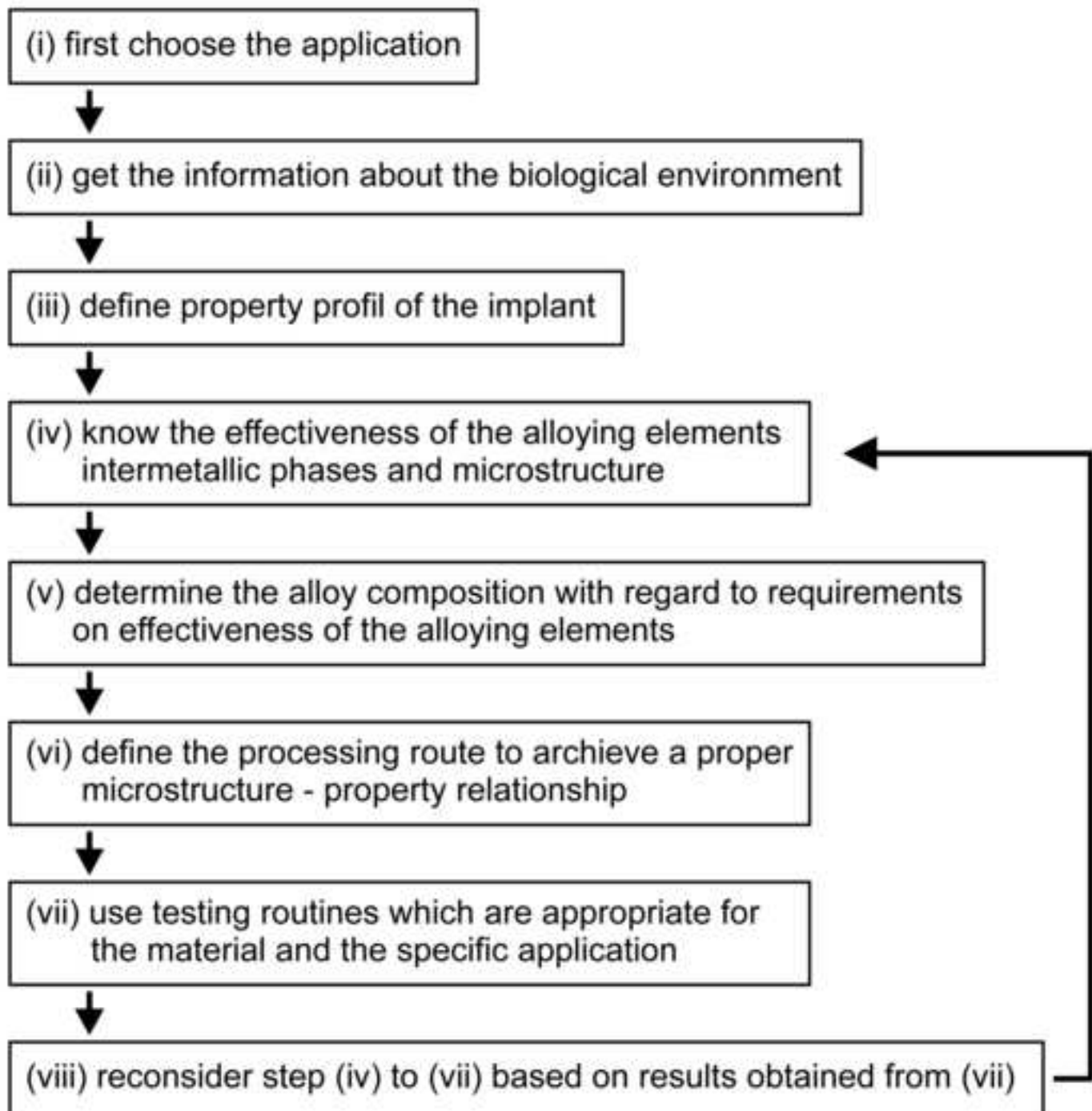
(i) first choose the application

↓

(ii) get the information about the biological environment

↓

(iii) define property profil of the implant

↓

(iv) know the effectiveness of the alloying elements intermetallic phases and microstructure

↓

(v) determine the alloy composition with regard to requirements on effectiveness of the alloying elements

↓

(vi) define the processing route to archieve a proper microstructure - property relationship

↓

(vii) use testing routines which are appropriate for the material and the specific application

↓

(viii) reconsider step (iv) to (vii) based on results obtained from (vii)

Figure 1

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