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A snapshot of remarkable potential of mg-based materials as implants

Abstract

Magnesium is one of the most required nutritional metallic elements required by human body for multiple health benefits. Its non-toxicity makes it a potential non-permanent implant material in human body. However, magnesium is also one of the most susceptible elements to wet corrosion. Its reaction with simulated bio fluids leads to localized increase in magnesium ions, pH, formation of hydrogen bubbles and formation of Ca-P layer. In view of corrosion susceptibility and its effects on the neighboring environment, the potential of Mg-based materials as implants is presented in brevity keeping the interest of a broad spectrum of researchers in mind.

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Introduction

Metallic materials are commonly used as permanent and non-permanent implants in human body for more than a century.[1,2] This stems from their ability to exhibit good strength, ductility and fracture toughness which holistically remain beyond the capabilities of polymers and ceramics. For permanent implant applications such as knee and hip replacements, we need the materials to be inert means targeting the ones with minimum or extremely low corrosion rates and high wear resistance. Moreover, the corrosion products have to be non-toxic and the metal ions/debris that is generated should also lead to appropriate host response. Titanium and steels are commonly used as implant materials for such purposes. Titanium is more stable in body but is expensive while steels are cheaper but remains comparatively more reactive when compared to titanium. Co-Cr alloys were also attempted but led to adverse host response and acute toxicity and are being currently avoided by research community.[3–5] A list of commonly used metallic materials as implants is shown in Table 1.[6]

Table 1 Most common metallic implants used in human body

Material	Application	Form	Comments
Steels	Fixation Devices	Pins, screws, plates, wires and rods	**Advantages:** Affordability, availability, low cost, biocompatibility.
			Disadvantages: Can create stress-shielding effects. It can show toxicity effects after long-term use.
Co-Cr alloys[7–12]	Permanent Implants such as Knee and Hip joint replacement	Ball and socket joints	Implant loosening reported due to high levels of Co and Cr in serum. Inflammatory response near implant. Carcinogenic.
Titanium/ alloys	Permanent implants in orthopedic and dental applications	Nails, screws, nuts and plates	**Advantages:** Corrosion resistance and biocompatibility.
			Disadvantages: Expensive and can create stress shielding effect. In long term use, Al and V can reach out and are linked to Alzheimer and neuropathy.[13,14]
Ni-Ti Alloys	Orthopedic applications		Elastic modulus is similar to bone and exhibit good ductility and fatigue resistance. Toxicity of Ni is leading to its elimination.
Ta/alloys	Orthopedic applications	Hip and Knee replacements	Used in porous form with good response in early bone development.[15]

Potential of magnesium

Magnesium is the lightest and one of the most abundant metallic materials with a density (1.74g/cc) and elastic modulus (40-45GPa) closest to bone.[1,16] This translates to almost no stress shielding effect. The compressive and tensile strengths of magnesium and its alloys can easily be tailored to exceed that of bone and its ductility in both compression and tension remains higher than bone making it a mechanically suitable material for implant applications. Human body needs about 250-400mg of magnesium per day as magnesium is the fourth most prevalent ion in human body and assists in bone health, multiple metabolic processes in body and exhibit antibacterial properties against *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*.[17] As magnesium is biocompatible and biodegradable, its use as non-permanent biodegradable implant in human body ensures:

a. No revision surgery.

b. Reduced patient trauma.

c. Reduced medical cost.

d. Reduced doctor's time.

Moreover, excess magnesium can easily be excreted through urine thus preventing any side effects that may arise due to excess magnesium.

Corrosion of magnesium

As magnesium is currently targeted as biodegradable implant, it is important to understand its corrosion behavior as the degradation of magnesium-based implants has to be controlled and tuned with the bone healing time such as in orthopedic applications. Moreover, an understanding of the impact of dissolution on the surrounding tissues has to be clear. The corrosion of magnesium in aqueous medium can be expressed as:

Anodic Reaction: $Mg \rightarrow Mg^{2+} + 2e^{-}$

Cathodic Reaction: $2H_2O + 2e^{-} \rightarrow 2OH^{-} + H_2$

Investigating these equations reveal that following will happen locally as a result of corrosion of magnesium implant in the body:

a. Increase in Mg ion concentration.

b. Increase in pH.

c. H_2 bubble Formation.

d. Formation of Ca-P layer.

The effects of each of these events are described in Figure 1.

The positive effects of magnesium ion concentration are described in.[18,19] The positive effects of pH increase are reported in.[20] The benefits of hydrogen formation are indicated in.[21] Finally, the Ca-P layer that is formed on magnesium implant and its positive effects are reported in reference 18 based on in vivo studies. Overall, it can be seen that magnesium corrosion in human body is beneficial provided its rate can be controlled to avoid undue surges. More study is also required to establish the upper limit of pH that can be tolerated by human tissues. A list of metallic ions in the body is presented in Table 2. The information indicates that magnesium and iron are two possible choices as implant materials which are a significant part of human body systems. Trace elements can be used as alloying elements only and not as main elements as they can lead to toxicity as observed in the case of Co-Cr implants.

Magnesium based compositional systems that have been investigated in recent past for bio-applications are listed in Table 3.[1] More details on these systems can be found from.[1] The alloys/composites shown in Table 3 exhibit different properties and corrosion rates. Accordingly, they can be used as implants depending on healing time required by body to heal an injury which is not a constant and depends on the age of individual and type of fracture. For example, while certain fractures can heal in 3 weeks in young kids, it may take 6 weeks to heal in teens. In addition, based on the type of bone fractured (e.g. tibia or phalanges) the average healing time may vary from 3-12 weeks.[22] The required lifetime thus has to be based on worst case scenario which is about 12 weeks. In yet another research finding, researchers in Kobe University, Japan developed Mg-based surgical clips that can be exit the body in about a year. Monitoring was done for about 12 weeks suggesting yet again that typical healing period is benchmarked at 12 weeks for most the cases.[23]

Table 2 Elements that can be used as main metallic implant or as an alloying element in metallic implants in the human body

Element	% of body	Functional significance
Calcium	1.2	A building block of bones and teeth; its ionic form is essential in muscle contraction, impulse conduction in nerves, and blood clotting. It cannot be used as the main material for implant fabrication.
Potassium	0.4	Necessary for conduction of nerve impulses and muscle contraction. It cannot be used as the main material for implant fabrication.
Sodium	0.2	Assists in muscle contraction and nerve cell transmission. It cannot be used as the main material for implant fabrication.
Magnesium	0.1	Found in bone and assists in many metabolic functions. Its mechanical properties can be matched more closely to the bone.
Iron	0.1	Basic building block of the haemoglobin molecule which is a major transporter of oxygen in body. It is used as an implant material. Can cause stress shielding effect and is very heavy compared to bone.
The following elements are trace elements and are required in very minute amounts. They are important elements and found as part of enzymes or are required for enzyme activation.		
Chromium		Promotes glucose metabolism; helps regulate blood sugar.
Cobalt		Promotes normal red-blood cell formation.
Copper		Promotes normal red-blood cell formation. Acts as a catalyst in storage and release of iron to form hemoglobin. Promotes connective tissue formation and central nervous system function.
Manganese		Promotes normal growth and development. Promotes cell function. Helps many body enzymes generate energy.
Molybedenum		Promotes normal growth and development and cell function.
Selenium		Complements Vitamin E to act as an efficient anti-oxidant.
Vanadium		Plays role in metabolism of bones and teeth.
Zinc		Maintains normal taste and smell. Aids in wound healing. Helps to synthesize DNA and RNA.

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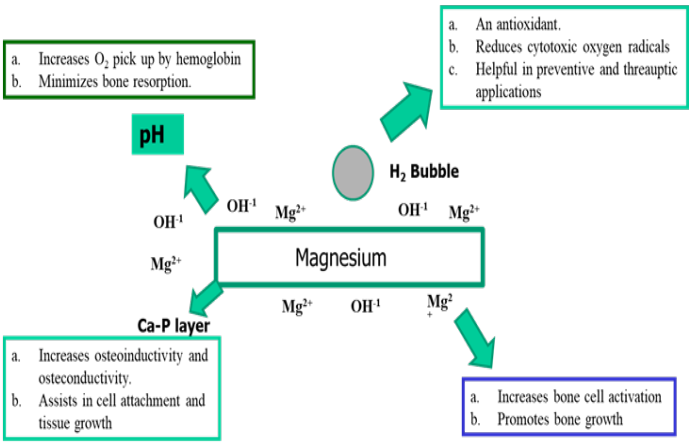

Figure 1 Beneficial effects of corrosion of magnesium in bio-applications.

Table 3 Magnesium Based monolithic and composite formulations investigated for bio-applications

Mg-Sr	Mg-Zn-Sr	Mg-Ca	Mg-Zn-Ca
Mg-Mn	Mg-Zn-Mn	Mg-Ca-Zn	Mg-Nd
Mg-Zr	Mg-Zr-Sr	ZK30*	Mg-Y
Mg-Zn	Mg-Si	ZK40*	Mg-Gd
Mg-Nd-Zn-Zr	Mg-Y-Zn	ZK60*	Mg-Y-Er-Zn
Mg-Mn-Ca-Zn	Mg-Y-Zn-Zr	WE43*	Mg-Ag
Mg-In	Mg-Ti-GNP+	Mg-HAP+	Mg-TiO_2+
Mg- ZrO_2+	Mg-ZnO+	Mg-TiC+	Mg-TiN+
Mg- TiB_2+	Mg-CNT+	Mg-Al_2O_3+	Mg-Ti+

*Commercially available alloys.
+ Composite materials.

In-Vivo Vs *in-Vitro* studies

In-vitro and *in-vivo* studies correspond to the studies conducted outside and inside body environment. *In-vitro* studies are less expensive and are used to qualify/shortlist the potential materials for implant applications. *In-vivo* studies are conducted in humans or animals and at times challenges the research ethics. However, as long as the intention of researchers is to bring comfort and to improve the quality of life of patients the rule utilitarian and duty ethics are satisfied. Researchers are always attempting to correlate *in-vitro* results with *in-vivo* results so as to speed up the qualification time of implants. It may be noted that as the complexity of living system cannot be duplicated in *in-vitro* studies, not all the time the results can be correlated. Targeting magnesium, the fundamental differences in *in-vitro* and *in-vivo* studies are indicated in Table 4.[24]

Besides the differences in the two types of studies, some research work also showed similar outcome of the two types of studies.[25] For example, researchers reported the ability of Ca-P layer generated on magnesium implant to promote tissue growth during biodegradation in both *in-vitro* and *in-vivo*.[26,27] In yet another study, investigators indicated that *in-vitro* tests can be translated to *in-vivo* behavior provided a proper test bed is created and due considerations are given to simulate the actual conditions and function of implant in the body.[28]

Table 4 *In-vitro* vs *in-vivo* studies

***In-Vitro* studies**	***In-Vivo* studies**
No formation of H_2 gas pockets.	Formation of H_2 gas pockets trapped by local tissues.
Cell adhesion indicates biocompatibility.	Biocompatibility is more dynamic and depends on Ca-P layer formed, increase in local pH and rate of H_2 evolution.
Biological response can be indicated but not accurately predicted.	Biological response depends on the function and nature of implant.
Only one corrosion rate in one medium/ condition.	Corrosion rate can change with the location of implant.[23]

Unknowns and challenges

The main challenge faced by researchers in their pursuit to use magnesium based implants is to control their corrosion/degradation rate within the human body. This requires a well planned *in-vitro* testing followed by *in-vivo* testing. The main variables *in-vivo* that may have complex interactions and can significantly affect the corrosion rate is:[28]

a. Location of implant.

b. Stress levels on implant.

For example, stresses can trigger stress corrosion cracking and corrosion fatigue and if they are not targeted in *in-vitro* testing than the results of *in-vitro* testing will be misleading. Additionally, there are still unknowns in the use of larger implants in animals/humans in terms of how much pH rise and increase in magnesium ion concentrations locally can be tolerated by the surrounding tissues. Further research is warranted in this area.

Conclusion

Magnesium based materials have emerged as potential biomaterials and both animal and human studies have been conducted successfully on patented/protected compositions. Choice of magnesium based materials as biomaterials is still limited for materials selectors and its portfolio needs significant enhancement to go from smaller implants (pins, clips and screws) to larger implants (such as plates) and as scaffolds. The key challenge is to control the degradation rate at different levels depending on the function of implant and its required lifetime in human body. Further, it has to be ensured by material scientists that the inherent composition of the implant does not release ions or corrosion products that can create local or systemic toxicity. As the magnesium based implants avoids the revision surgery and comes with related benefits, advancement in this area has the potential to create a multi-billion dollar market with noble cause of alleviating human discomfort.

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Conflict of interest

The author declares no conflict of interest.

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