DYNAMIC DEGRADATION OF POROUS MAGNESIUM UNDER SIMULATED ENVIRONMENT OF HUMAN CANCELLOUS BONE

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This present work is specially dedicated to all my family members, *where life begins and loves never ends.*

To my wife, *Noor Faizah Che Ahmad,* who always supports, loves and taking care our childrens, *Wafa' Safiyyah and Alyaa Safiyyah*, while I'm struggling completing this work.

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ABSTRACT

Biodegradable metals have been suggested for bone scaffold applications due to their mechanical properties that are better for load bearing applications. Among biodegradable metals, magnesium and its alloy are the most investigated materials due to their mechanical properties which are closer to the cancellous bone and could prevent complications such as an aseptic loosening of stress shielding effects, and potentially to be used as bone scaffolds. Bone adapts the mechanical loading from the physiological activities that induced the movement of bone marrow passing through the porous structure of cancellous bone due to the pressure differences. The aim of this research is to analyse the degradation behaviour of porous magnesium under dynamic degradation test for bone scaffold applications. Interconnected holes of porous magnesium have been developed with various percentages of porosity (30%, 41% and 55%) and are fabricated using computer numerical control (CNC) machine. Dynamic immersion test rigs are specifically designed to simulate environment of human cancellous bone. There are two types of tests that have been conducted in this study: (1) fluid flow with different flowrates (0.025, 0.4 and 0.8 ml/min) and (2) fluid flow integrated cyclic loading (different cyclic loading (1000, 2000 and 3500 $\mu\varepsilon$) under constant flowrate of 0.025 ml/min). A dynamic immersion test has been conducted for 24, 48 and 72 hours. The results showed that the specimen with a higher percentage of porosity as well as the exposed surface area degrades faster compared to the others. The degradation product formation and clogging pores phenomenon are influenced by the level of flow rates. The effects of different flow rates towards the mechanical integrity of porous magnesium have shown a huge drop of 95% from their original mechanical properties within 3 days, which have deteriorated in both functions; porosity and degradation time. The variation in flowrates used showed that degradation of the material is seven times higher compared to the static immersion test environment. Furthermore, the influenced of integrating fluid flow and cyclic loading have increased the relative weight loss and degradation rate as high as 61.56% and 93.67%, respectively. Additionally, the mechanical properties have improved and increased from 53% to 87% as compared to dynamic immersion test using the mechanical stimulus of fluid flow only. Therefore, the dynamic immersion test with integrated cyclic loading was more reliable and provides realistic environment for degradation assessment compared to static immersion test for bone scaffold application as this study using the boundary of human cancellous bone environment.

ABSTRAK

Logam terbiodegradasi dicadangkan untuk aplikasi penggantian tulang disebabkan oleh sifat-sifat mekanik yang lebih baik bagi penggunaan galas beban. Dikalangan logam terbiodegradasi, magnesium dan paduannya adalah yang paling dikaji kerana sifat mekanikal mereka yang lebih dekat dengan tulang kanselus dan boleh mencegah komplikasi seperti aseptik yang merenggangkan kesan perisaian tekanan, dan ianya berpotensi untuk digunakan sebagai penggantian tulang. Tulang dapat menyesuaikan bebanan mekanikal daripada aktiviti fisiologi yang mengaruhkan pergerakan sum-sum tulang melalui struktur poros tulang kanselus kerana perbezaan tekanan. Tujuan kajian ini adalah untuk menganalisis kelakuan degradasi magnesium berliang di bawah ujian degradasi dinamik untuk aplikasi penggantian tulang. Lubang saling magnesium berliang telah dibangunkan dengan pelbagai peratusan keliangan (30%, 41% dan 55%) dan direka menggunakan mesin kawalan berangka terkomputer (CNC). Pelantar ujian rendaman dinamik direka khusus untuk mensimulasikan persekitaran tulang kanselus manusia. Terdapat dua jenis ujian yang telah dijalankan dalam kajian ini: (1) aliran cecair dengan kadar aliran yang berbeza (0.025, 0.4 dan 0.8 ml/min) dan (2) aliran cecair dipadukan dengan kitaran beban (kitaran beban yang berbeza (1000, 2000 dan 3500 $\mu\varepsilon$) di bawah kadar aliran malar 0.025 ml/min). Ujian rendaman dinamik telah dijalankan untuk 24, 48 dan 72 jam. Keputusan menunjukkan bahawa spesimen dengan peratusan yang lebih tinggi keliangan serta kawasan permukaan yang terdedah lebih cepat degradasi berbanding dengan yang lain. Pembentukan produk degradasi dan fenomena liang tersumbat dipengaruhi oleh tahap kadar aliran. Kesan kadar aliran yang berbeza terhadap keutuhuan mekanikal magnesium berliang telah menunjukkan penurunan yang besar sebanyak 95% dari sifat-sifat mekanikal asalnya dalam tempoh 3 hari, yang telah merosot dalam kedua-dua fungsi; keliangan dan masa degradasi. Variasi kadar aliran yang digunakan menunjukkan bahawa degradasi bahan adalah tujuh kali lebih tinggi berbanding dengan persekitaran ujian rendaman statik. Tambahan pula, dipengaruhi oleh paduan aliran bendalir dan kitaran beban telah meningkat penurunan berat relatif dan kadar degradasi setinggi 61.56% dan 93,67%, masing-masing. Selain itu, sifat-sifat mekanikal telah bertambah baik dan meningkat daripada 53% kepada 87% berbanding dengan ujian rendaman dinamik menggunakan rangsangan mekanikal aliran bendalir sahaja. Oleh itu, ujian rendaman dinamik dipadukan dengan kitaran bebanan adalah lebih dipercayai dengan persekitaran realistik untuk penilaian degradasi berbanding dengan ujian rendaman statik untuk applikasi penggantian tulang kerana kajian ini menggunakan sempadan persekitaran tulang kanselus manusia.

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LIST OF SYMBOLS

P_m	-	Degradation Rate in Units of Penetration
ΔW_m	-	Degradation Rate in Units of Weight Change
ρ	-	Density
W_f	-	Final Weight
W_o	-	Initial Weight
d_h	-	Inner diameter
E_N	-	Secants Modulus
ε	-	Strain
$\Delta\varepsilon$	-	Strain Range
σ	-	Stress
$\Delta\sigma$	-	Stress Range
υ	-	Velocity
μ	-	Viscosity
E	-	Young’s Modulus

LIST OF ABBREVIATIONS

ASTM	-	American Society for Testing and Materials
CO_2	-	Bicarbonate
CP-Mg	-	Commercially pure magnesium
CAGR	-	compound annual growth rate
CAD	-	computer aided design
CNC	-	Computer Numeric Control
DAQ	-	Data Acquisition
DR	-	Degradation rate
DMEM	-	Dulbecco's Modified Eagle Medium
EDS	-	Energy Dispersive Spectrometer
FDHP	-	fibre deposition hot pressing
HP-Mg	-	high purity magnesium
HA	-	hydroxyapatite
IOF	-	International Osteoporosis Foundation
Mg	-	Magnesium
μ-CT	-	micro computed tomography
μm	-	micro-meter
με	-	micro-strain
NDE	-	negative difference effect
RANKL	-	receptor activator of nuclear factor kappa B ligand
Re	-	Reynolds number
SEM	-	Scanning Electron Microscope
SBF	-	Simulated Body Fluid
NaCl	-	Sodium Chloride (Salt)
TSWH	-	titanium wire space holder
XRD	-	X-ray diffractometer

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CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Bone grafting is a medical procedure for bone replacement or repairs. It is the second most highly performed surgical procedures on tissue transplantation after blood transfusion [1]. The usage frequency of bone graft has been paramount every year. The transparency market research has reported that due to the rising demand for bone graft substitutes, its market is expected to expand at a 4.5% compound annual growth rate (CAGR) between 2015 and 2023, and it is estimated to be worth USD 3.48 billion by 2023 [2]. Over two million orthopaedics procedures on bone-graft substitutes have been annually performed worldwide, with over 400,000 and 600,000 procedures recorded in Europe and the United States, respectively [3–6]. Asian Audit 2009 has reported from International Osteoporosis Foundation (IOF) [7] that in China, almost 69.4 million of people over the age of 50 years old suffering from osteoporosis. This huge number includes 0.687 and 1.8 million of hip and vertebral fractures, respectively stirring each year. Hong Kong and Singapore have demonstrated in the past four decades that hip fractures have remarkably increased in number by 300% and 500%, correspondingly. In Japan, 12 million people suffering from osteoporosis and the incidence rate of hip fractures are increasing radically among both men and women of age 75 years old and above.

The amplifying prevalence of bone and joint disorder such as deformities, trauma, tumor, degenerative and aging population have been accompanied by the increase in number of orthopaedics reconstructions. This has driven the high demand on bone graft substitutes. Bone-graft substitutes have been established with different types that are available in the worldwide market. The common types of bone-graft substitutes used are autografts, allografts and xenografts; which the existence depends on their sources. Autografts can be referred to as the gold standard in medical procedure to repair damaged bone or for bone replacement. It provides the best osteo-conductive, osteo-inductive and osteo-genic properties since their sources are from the parts of the patient's body [8]. As for allografts and xenografts, their tissues sources come from different members of the same species and different species respectively. However, those bone-graft substitutes have exhibited a vital concern of donor site morbidity (autografts), and limited supply and possibility of pathogen transmission and immune-rejection (allografts and xenografts) [9,10]. Therefore, researchers have developed the new generation of synthetic bone-grafts substitutes to eliminate susceptibility of the aforementioned drawbacks [11]. Hence, with the advancement of technology in biomaterials engineering, the biodegradable materials have attracted researchers to investigate a lot in favour of obtaining the ideal synthetic bone-grafts substitutes or known as bone scaffolds [12–14].

Biodegradable materials have been acknowledged as an ideal model in biomaterials that has inspired researchers to focus on. These materials serve as a device to provide temporary support for tissue regeneration while bone heals and gradually degrades after fulfilling its function [15]. Among biodegradable materials, polymer can be classified as an excellent material due to its good biodegradability, biocompatibility and easy to fabricate [16,17]. However, the advantages of polymer are retarded due to its low mechanical properties for load bearing applications [18,19]. This has led to the use of biodegradable metal which possesses good mechanical properties [14]. In comparison to iron-based and newly introduced zinc alloys, magnesium and its alloys are the most investigated biodegradable metals for their potential application as biomedical implants [12,14]. They have shown an excellent performance to human bone in terms of mechanical integrity and their mechanical properties (41-45 GPa of Young's Modulus [14,20]) is close to cortical bone (3–23 GPa of Young's Modulus [14,21]) while cancellous bone

(0.01–3.0 GPa of Young's Modulus [22]) and bioactivity of Mg stimulatory effects have induced the growth of new formation of bone-apatite like of hydroxyapatite (HA) crystallization [14,23,24] and are favourable to bone strength [25]. These two factors have favoured the idea of using biodegradable metals to be used as the materials for bone tissue engineering [26–28].

Recent advancements in bone tissues engineering is to develop the multifunctional capabilities of the scaffold to be well-integrated with the biological environment and physiological functions of natural bone [12,29]. Bone scaffolds are typically required to have porous structure to allow nutrient to be transported from the surrounding tissues and releases waste disposal from the regenerated tissues [30,31]. Ideally, this porous structure will have 25-90% porosity and a 10-1000 μm pore size to provide an ideal condition for infiltration of essential nutrients, oxygen, and progenitor cells for cell survivability [32,33]. The porosity of porous structure can be controlled and regulated to a desired form. Though the employment of porous structure reduces the mechanical properties, it is still an advantage in obtaining the scaffold that has the mechanical properties which are well-matched with natural bone. Researchers have investigated the strength of porous scaffolds using polymers, ceramics, composites and metals. It is suggested to use metals due to their mechanical properties that are close to the mechanical properties of bone [34].

Biomechanically, cancellous bone adapts to the mechanical loading from the perpetual motion of physiological activities through the mechanobiological signalling of osteocytes [35,36]. Cancellous bone adapts the compressive strain level of 1000 – 3000 με that is generated from various activities and beyond 3500 με leads to bone fracture [37,38]. Due to the cyclic motion of compressive strain, it causes the bone marrow, which is the home for progenitor cells of osteoblasts and osteoclasts, moves as a fluid medium with a flowrate range of 0.0072-1.67 ml/min [36,39–42]. The interaction between the bone marrow movement and the cancellous bone structure induces mechanical stresses that stimulate the mechanobiological response to the bone quality and bone healing process [36]. The movement of bone marrow through the porous structure of cancellous bone due to pressure differences is generated by continuous cycles of mechanical loading from physiological activities [43]. This cyclic motion of compressive strain and bone marrow movement in the cancellous bone must be considered as an actual boundary for testing the biodegradable materials of bone scaffolds.

1.2 Problem Statements

Bone scaffold were developed by a wide range of the biomaterials. Instead of metallic biomaterials, others than that have been produced is unsuitable for load bearing purposes [44]. By using load bearing bone scaffold, patients will able to speed up in performing their daily lives activities which could also contribute to a better healing process [35]. The metallic biomaterials that already approved and commonly used as biomedical implant are stainless steels, titanium and cobalt chromium based alloys [14]. However, the suitability to be acted as an ideal scaffold for bone was degraded by the possible release of toxic metallic ions and poor stimulation of new bone growth due to elastic moduli mismatch [45,46]. The interest in metallic biomaterials have expanded to biodegradable metal which exhibit the most promising properties and can be used temporarily during bone healing process [13]. In order to be well integrated with host tissue, bone scaffold is required to have characteristics such as porous, mechanical properties, and biocompatibility which are also very important for tissues regenerations [34].

The comprehensive degradation assessment systems of biodegradable metals must be carefully selected towards specific applications [47]. Biodegradable metals have an assorted degradation behaviour and mechanism contingent depending on the environments and types of measurements used [12]. Witte *et al.* have reported that the current ASTM degradation test methods for *in-vitro* test cannot be used to predict the *in-vivo* degradation rates [48]. They reported that the degradation rates of specimen with cylindrical rods in the *in-vitro* test have shown a four magnitude higher compared to the *in-vivo* test. It is crucial for the *in-vitro* test to be precisely mimicked the *in-vivo* conditions, in order to provide more accurate information and to obtain promising implants [49]. In fact, the acceptable degradation rate of the bone scaffold should be 0.02 mm/y [19,50]. However, based on the literature findings, there was none of the studies have obtained the required degradation rate. Thus far, all studies conducted on porous biodegradable metals for potential bone scaffold applications have been done under static immersion tests only [26,51–53]. The static degradation assessment does not represent the actual boundary in human cancellous bone environment. The bone scaffolds made of biodegradable metals will be in contacted with cancellous bone and exposed to the surrounding environment once implanted [35,36]. Therefore, to address the existing gap, in this study, we had integrated a biomechanical condition of cancellous bone for testing porous magnesium specimens under a dynamic immersion condition.

1.3 Objectives

The aim of this study is to analyse the degradation behaviour of porous magnesium under dynamic degradation test for bone scaffold applications. The specific objectives are:

(i) To analyse the influences of different flow rates fluid passing through porous magnesium structure on dynamic immersion test.

(ii) To analyse the effects of different cyclic loading of porous magnesium under a constant flow rate on dynamic immersion test.

1.4 Scopes

A commercially pure magnesium (Mg) rod with a diameter of 25.4 mm and 99.9% purity (Goodfellow Inc., Cambridge, UK) was used for developing porous specimens with three different percentage of porosity (30%, 41% and 55%). The porous structure was fabricated using CNC machine. The specific specimen chamber was developed for both experimental setups of fluid flow and different cyclic loading test. The specimens were cleaned internally and externally using interdental brush to remove any excess materials and chemicals and ground using abrasive paper, respectively. The dynamic immersion test rig has been built, equipped with data acquisition (record the pressure value of the fluid before and after the specimen chamber), water bath (heating the fluids medium to human body temperature) and peristaltic pump (pulsatile flow). The simulated body fluid (SBF) was used as fluid medium in this study. The dynamic immersion test was conducted for 24, 48 and 72 hours. The variation of flow rates and cyclic loading were used as the boundaries in the dynamic immersion test as there were to mimic the condition of fluid pass through cancellous bone structure and compressive strain levels of physiological activities. The universal testing machine (The FastTrack 8874, Instron, Norwood, USA) was used to perform the cyclic loading and to determine the mechanical properties of the specimen. The tested specimen was characterised using X-ray diffractometer (XRD), Scanning Electron Microscope (SEM) and Energy Dispersive Spectrometer (EDS). The weight loss measurement was used as the method to assess the degradation rates of the porous magnesium. Limitations of this study was not included the hydrogen evolution measurement as it required the hydrogen gas trapping system.

1.5 Significance of the Study

This study has assessed the potential of the porous magnesium as bone scaffold using dynamic degradation under simulated environment of human cancellous bone. The implementation boundary of human cancellous bone environment in dynamic immersion integrated cyclic loading had demonstrated significant degradation behaviour and mechanical property changes of the porous magnesium compare with using static immersion test only. Hereby, through this study, the degradation assessment of biodegradable material especially metal is required to use the dynamic immersion test integrated cyclic loading. This will be very beneficial to the community because once bone scaffold implanted, the patients can perform daily routine as usual. Because the use of bone scaffold that has taken into account for load bearing purpose. Thus the more activities are carried out, it could improve the bone healing process and also the health of the patient himself. Not just that, when the process of bone healing occurs in a very good condition, then the failure of the bone scaffold that has happened in the past can be avoided so that patients no longer need a second surgery. This can reduce the costs to be incurred by the patient and the use of bone scaffold causing the patient can continue to perform the desired activity, thus reducing the time the patient gets treatment and contribute to a better living environment.

1.6 Thesis Structure and Organization

Chapter 1 presents an introduction of this research which provides an overview and the needs of bone scaffolds. Background is provided on both mechanobiological of bone and degradation techniques used for biodegradable metal evaluation. Then, research aims, scopes and significance of this study are highlights. Chapter 2 is the literature review which contains reviews on bone remodelling process, the usage of biodegradable metal for bone scaffolds and concept of biodegradation. Chapter 3 explains how the dynamic degradation of porous magnesium were produced, prepared tested and analysed. The results and discussion of the study was presented in three subsequent chapter. Chapter 4 reports the results and discussion of the effects using dynamic immersion test on degradation behaviour of porous magnesium under constant flowrates. Chapter 5 presents the results and discussion of the influences of variation flow rates towards degradation behaviour of porous magnesium in dynamic immersion test. Chapter 6 contains the results and discussion of the influenced integrating the cyclic loading on the dynamic degradation behaviour of porous magnesium under dynamic immersion test using constant flow rate. Finally, chapter 7 concludes the findings attained in this study. The limitations and recommendations also are highlight for future works.

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