STRUCTURAL, MECHANICAL, AND BIOACTIVITY PROPERTIES OF CALCIUM FLUOROALUMINOSILICATE BIOGLASS-CERAMICS FROM WASTE FOR BIOMEDICAL APPLICATIONS

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirement for the Degree of Doctor of Philosophy

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This study explores a significant advancement in glass-ceramics through the development of bioglass-ceramics derived from waste materials, aiming to enhance the mechanical properties of calcium fluoraluminosilicate (CFAS) based bioactive glass-ceramics for biomedical applications. While the 45S5 bioglass is known for its tissue bonding capability, its poor mechanical strength remains a drawback. To addresses this, CFAS bioglass-ceramics were synthesized from waste materials, specifically soda lime silica (SLS) glass and eggshells (ES), with an investigation into the effect of varying Al_2O_3 composition and sintering temperatures on the 44wt%SLS-24wt%CaO-(20-x)wt%Na_2CO_3-6wt%P_2O_5-6wt%CaF_2-(x)wt%Al_2O_3 system, where x = 0,3,6, and 9 wt%. The bioactivity was evaluated by immersing the ceramics in PBS solution to assess their ability to form a hydroxyl apatite (HA) layer. Cytotoxicity was determined using the MTT assay, indicating their suitability for biomedical use. Structural and microstructural properties were analyzed using X-ray Diffraction (XRD) and Scanning Electron Microscopy (SEM), with density measured by the

Archimedes' method and chemical bonds identified by Fourier Transform Infrared Spectroscopy (FTIR). Results showed that bioglass-ceramics with 9 wt% Al_2O_3 which sintered at 950 °C exhibited excellent properties, a density of 2.734 g/cm^3, increased crystallization of anorthite, fluorapatite and nacaphite and an optimal compressive strength of 136.58 MPa. The bioactivity test showed the formation of HA layer on the surface of the sample, which 28 days of immersion showed the thickest HA layer formation. Cell viability above 70% at concentrations $\leq 2.5\ wt\%$, and a pH of 10.17. Additionally, the mechanical properties after immersion included a compressive strength of 130.81 MPa, a microhardness of 4.874 GPa, and a fracture toughness of 5.709 MPa. These enhanced properties combined with their bioactivity and biocompatibility, suggest that CFAS bioglass-ceramics derived from waste materials show great promise for biomedical applications due to their improved performance.

Keywords: Bioglass-ceramics, compressive strength, fluorapatite, in vitro, melt-quench

SDG: GOAL 3: Good Health and Well-Being, GOAL 9: Industry Innovation and Infrastructure, GOAL 12: Responsible Consumption and Production

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENYIASATAN SIFAT STRUKTUR, MEKANIKAL, DAN BIOAKTIVITI KALSIUMFLOROALUMINOSILIKAT (CFAS) BIOKACA-SERAMIK UNTUK APLIKASI BIOMEDIKAL

Oleh

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Kajian ini meneroka kemajuan signifikan dalam kaca-seramik melalui pembangunan biokaca-seramik yang diperoleh daripada bahan buangan untuk meningkatkan sifat mekanikal kaca-seramik bioaktif berasaskan kalsium fluoaluminosilikat (CFAS) untuk aplikasi bioperubatan. Walaupun biokaca 45S5 terkenal dengan keupayaannya untuk mengikat tisu, kekuatan mekanikalnya yang lemah adalah kekurangan utama. Untuk menangani masalah ini, kaca-seramik bio CFAS disintesis daripada bahan buangan khususnya kaca soda lime silika (SLS) dan kulit telur (ES), dengan penyiasatan terhadap kesan komposisi Al_2O_3 yang berbeza dan suhu pensinteran pada system 44SLS-24CaO-(20-x) Na_2CO_3-6P_2O_5-6CaF_2-xAl_2O_3, di mana x=0, 3, 6, dan 9wt%. Bioaktiviti dinilai dengan merendam kaca-seramik dalam larutan PBS untuk menilai keupayaannya membentuk lapisan hidroksiapatit (HA), sementara ketoksikan ditentukan menggunakan ujian MTT, yang menunjukkan kesesuaiannya untuk kegunaan bioperubatan. Sifat struktur dan mikrostruktur dianalisis menggunakan pembelauan Sinar –X (XRD) dan Mikroskopi Elektron Imbasan (SEM), dengan ketumpatan diukur menggunakan kaedah Archimedes dan ikatan kimia dikenalpasti melalui Spektroskopi Inframerah Transformasi Fourier (FTIR). Hasil kajian menunjukkan bahawa kaca-seramik dengan 9 wt% Al_2O_3 disinter pada suhu 950 ˚C, mempamerkan sifat yang sangat baik termasuk ketumpatan 2.734 g/cm3, peningkatan penghabluran anorthite,fluorapatite, dan nacaphit, serta kekuatan mampatan optimum 136.58 MPa.Keputusan terbaik diperhatikan selepas 28 hari perendaman, yang dicirikan oleh pembentukan lapisan HA yang lebih tebal, daya hidup sel melebihi 70% pada kepekatan ≤2.5 wt% dan pH 10.17. Selain itu, sifat mekanikal selepas perendaman termasuk kekuatan mampatan sebanyak 130.81 MPa, kekerasan mikro sebanyak 4.874 GPa dan ketangguhan patah sebanyak 5.709 MPa. Sifat-sifat yang dipertingkatkan ini digabungkan dengan bioaktiviti dan biokeserasian mereka menunjukkan bahawa CFAS bioglass-ceramics yang berasal daripada bahan buangan mempunyai potensi besar untuk aplikasi bioperubatan kerana prestasi mereka yang lebih baik.

Kata Kunci: Biokaca-seramik, kekuatan mampatan, fluorapatit, in vitro, cair-pelindapkejutan

SDG: Matlamat 3: Kesihatan dan Kesejahteraan yang Baik, Matlamat 9: Industri, Inovasi dan Infrastruktur, Matlamat 12: Penggunaan dan Penghasilan yang Bertanggungjawab

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LIST OF ABBREVIATIONS

ES	Eggshells
SLS	Soda lime silica
HA	Hydroxyapatite
FA	Fluorapatite
$CaCO_3$	Calcium carbonate
CaO	Calcium oxide
$Ca(OH)_2$	Calcium hydroxide
SiO_2	Silicon dioxide
CaF_2	Calcium fluoride
Al_2O_3	Aluminium oxide
P_2O_5	Phosphorus pentoxide
Na_2O	Sodium oxide
MgO	Magnesium oxide
K_2O	Potassium oxide
$CaAl_2Si_2O_8$	Anorthite
$Ca_5(PO_4)_3(OH)$	Hydroxyapatite
$Ca_5(PO_4)_3F$	Fluorapatite
CFAS	Calcium fluoroaluminosilicate
PBS	Phosphate buffer saline
HBS	Hank's balanced salt
CaP	Calcium phosphate
wt	Weight
wt.%	Weight percentage

a.u.	Arbitrary unit
ppm	Parts per million
ACP	Amorphous calcium phosphate
μm	Micrometer
V_m	Molar volume
MPa	Megapascal
kgf	Kilogram force
F	Force
ρ	Density
H_v	Vickers hardness
XRF	X-ray fluorescence
XRD	X-ray diffraction
FTIR	Fourier transforms infrared
FESEM	Field emission scanning electron microscopy
EDX	Energy dispersive X-ray
ISO	International Organization for Standardization

CHAPTER 1

INTRODUCTION

1.1 Introduction

This chapter presents the introduction of research background of the biomaterials, the first bioactive glass invented. The introduce of the calcium fluoroaluminosilicate (CFAS) based bioglass ceramics. Besides, the problem statement and research objectives why this research is conduct also stated in this chapter.

1.2 Research Background

Biomaterial is substance that is engineered to interact with biological material. Biomaterials can be classified into two main groups: natural and synthetic biomaterials. Natural biomaterials are any material derived from plants or animals that are utilized to enhance, replace, or repair organs and tissues in the body. Natural biomaterials can be categorized into two distinct group: those based on protein-based biomaterials (collagen, gelatin, silk) and those based on polysaccharide-based biomaterials (cellulose, chitosan, glucose). However, a disadvantages of natural biomaterials like chitosan is that it can lead to rapid bone regeneration in its early stages. The process of bone formation after implanting these matrices occurs gradually over an extended period as reported by Garg et al. in 2011. The common drawbacks of natural biomaterials are brittle and poor mechanical properties (Liu et al., 2023). Synthetic biomaterials are biomaterials that are prepared by a process and not from the natural sources. The common types of synthetic biomaterials can be classified into four: metals, polymers, ceramics, and composites. Figure 1.1 shows the classes of synthetic biomaterials and each of them has its own unique benefits and limitations for its application.

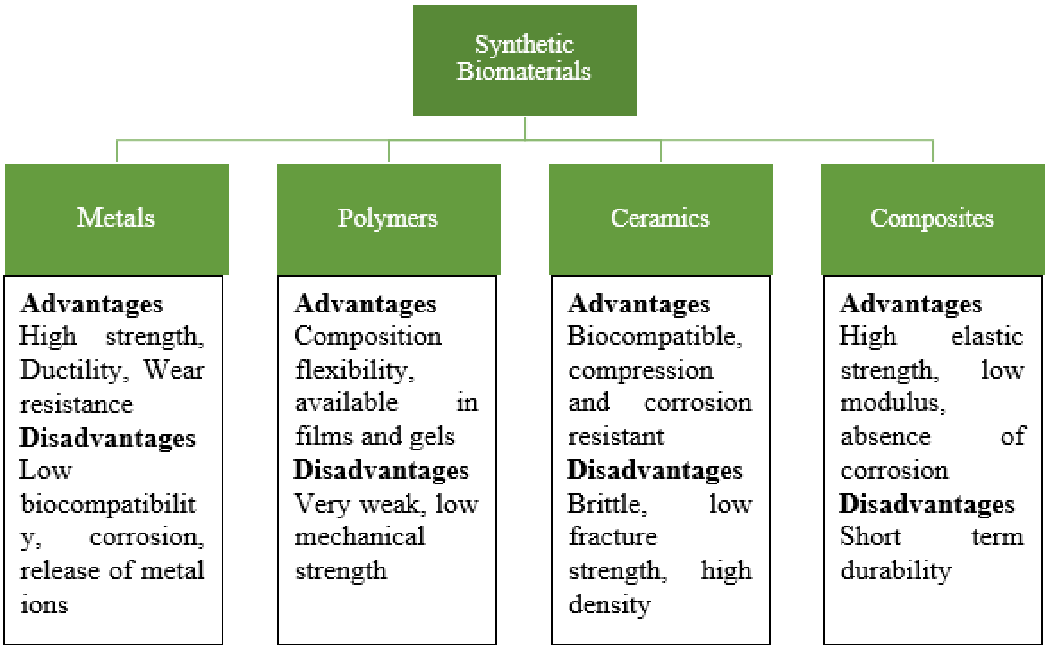

Figure 1.1: **Synthetic biomaterials classification and their properties** (Kaur et al., 2014).

Due to technological advancements in the 20th century, bioceramics now used in the medical field (Rieger W, 2001; Emmanuel et al., 2024). Bioceramics are a class of biomaterials used as a reinforcing material, cementing substance, and as an implant to treat, repair, or replace the diseased or damaged hard tissue of the body. Usually, the hard tissue of the muscular system such as bone and teeth. There are also use in optical, energy and electronic. These materials are applied primarily due to their biocompatibility, moderate degradation, and high mechanical strength. Moreover, ceramics are having properties like low heat conductance, high melting temperatures and resistance to plastic deformation. These characteristics make bioceramics a suitable substitute that is well-tolerated by the body. The success of these ceramic materials relies on their bio-functionality and biocompatibility (Kumar et al., 2018). The biocompatibility of a device or material is its ability to achieve that before it can be used in the human body as implants. The bioceramics mainly classified into three subclasses as shown in Figure 1.2: bioinert, bioactive, and biodegradable ceramics.

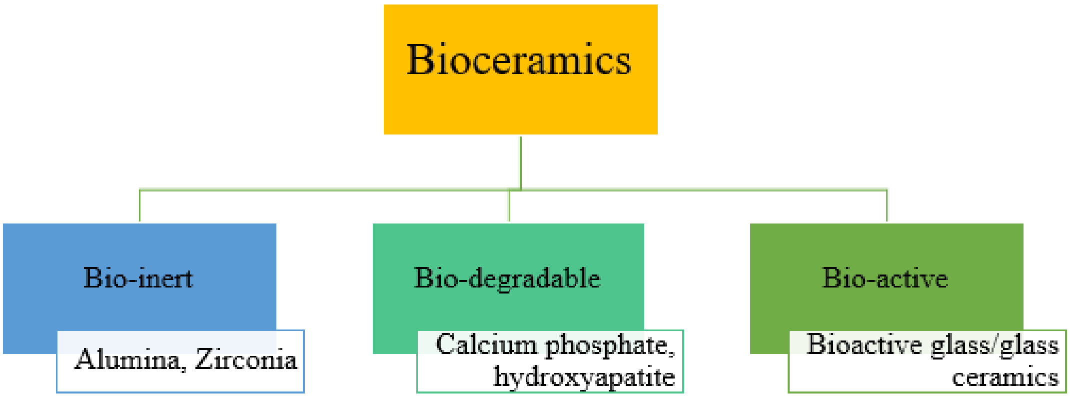

Figure 1.2: **The classification of bio-ceramics**

Bioinert materials such as alumina, zirconia was having stable physiochemical properties and makes good compatibility with the hard tissues (Kumar et al., 2018). In other words, the body will not react and reject by the body tissue when they are implant into the body. As a result, they are commonly used in orthopaedic surgery today. Their advantages have excellent mechanical strength such as high hardness and low friction. This makes them good strength to resist fracture which can be applied as a structural-support implant such as bone screw and bone plates. However, they have many drawbacks such as release of metal ions to surrounding tissues, failure of metalwork resulting to need for subsequent surgery, and distortion of imaging modalities (Godavitarne et al., 2017). These drawbacks have led to the development of biodegradable alternatives.

Biodegradable materials are materials that degrade over a long time following how long it implant in the body. The biodegradable has many names or terms have been used to describe them including resorbable, absorbable, and degradable. This biodegradable is not just overcome the disadvantages of bio-inert materials, but they also can be degraded or replaced by host tissue over a given time. Godavitarne et al (2017) states that they are a lot of advantages of biodegradable materials. These advantages include the absence of any potential to induce inflammatory or toxic reactions upon implantation, the possession of suitable mechanical properties for specific application, and non-toxic degradation products that can be metabolized and safely eliminated from the body, and others. Biodegradable material such as calcium phosphate and hydroxyapatite always use for tooth and bone. However, they sometime are fragile. Due to this, bioactive materials such as bioglass are considered as the most promising biomaterials, due to the show positive effect on living tissues.

Bioactive glass or also known as 45S5 bioglass were discovered by Larry Hench in the late 1960s (Hench, 2006). The idea for the material came to him during a bus ride in 1967. He started discussing his research with Colonel Klinker, a fellow bus traveller who had recently returned to the United States after serving in Vietnam as an Army medical supplier officer. Klinker then explained the amputations he had seen in Vietnam, arising from the rejection of metal and plastic implants by the body.

Once Hench came after the conference to Florida, he sent a proposal to the U.S Command of Army Medical Research and Design. In 1968, he obtained funding, and Hench started his synthesize of small rectangles of what he named 45S5 glass in November 1969. At the VA Hospital in Gainesville, Ted Greenlee, an assistant professor of orthopaedic surgery at the University of Florida, successfully inserted them in rat femurs (Hench, 2006). With this successful experiment, bioglass was born and the first compositions studied. The first discovery of bioglass specifically consist of 45 wt% SiO_2, 24.5 wt% CaO, 24.5 wt% Na_2O and 6.0 wt% P_2O_5 (Jones, 2008; Fernandes et al., 2018; Araujo et al., 2020).

These elements play a crucial role in the composition of bioglass and contribute to its unique properties. SiO_2 act as a network former in bioglass (Fernandes et al., 2018) and it helps in the formation of bioactive glass network. CaO is an important composition in bioglass as it promotes the formation of hydroxyapatite which when bioglass comes in contact with body fluids hydroxyapatite is formed and allowing the bioglass to bond with bone tissue and promote bone regeneration (Filip et al., 2022). Na_2O is added to bioglass to adjust its properties such decrease the glass melting temperature and thermal expansion coefficient (Fernandes et al., 2018). Besides, it also can enhance the bioactivity of the bioglass by promoting the release of Na^+ which can stimulate cellular responses and aid in the formation of new bone tissue. P_2O_5 is an essential element for bone formation and mineralization, and it enhances its bioactivity and promotes the bonding of the bioglass with bone tissue (Adam et al., 2021).

The initial idea of Larry Hench was to combine elements that are commonly found in the human body, in proportions that promote the fast dissolution of alkalis from the glass surface in water-based solutions. This solution is then followed by the formation of a calcium (Ca)-rich and phosphorus (P)-rich layer within the inner alkali-depleted silica layer (Hench, 1975). In fact, the first discovery of bioglass is when bioglass immersed in biological fluids, it undergoes a process where a layer resembling the mineral phase of bone, known as hydroxyapatite (HA) is developed on the surface of the glass. They have the bone-bonding ability which is similar to the mineral apatite phase found in the bone tissue. Due to this, bioactive glass was widely used in medical applications due to their unique interaction with human body tissue. However, the main drawbacks of bioglass are their mechanical performance and brittleness which significantly limit them unsuitable for load bearing applications.

Crystallization of bioactive glasses may be the best way to improve their mechanical properties. Bioactive glass-ceramics materials have higher strength and improved mechanical properties as compared to bioactive glasses. The crystallization behavior can be cause by the compositional changes and the sintering process. It has been reported that bioglass-ceramics in the SiO_2-CaO-Na_2O-P_2O_5 with Al_2O_3 addition containing apatite have a good mechanical property (Mohamad et al., 2016). Besides, glass-ceramics material is prone to crystallize at certain sintering temperature (Bellucci et al., 2010; Montazerian et al., 2024). Most of literature on bioactive glass only discuss in detail on the effect of reformulation of original composition on mechanical properties of the bioactive glass.

In this study, the addition of a network former oxide like Al_2O_3 reduces the glass dissolution. This lower dissolution and the lower release in aluminium lead to the formation of the Si, O, Al layer (Mihardi & Mehdikhani, 2012). On the other hand, addition of network former could significantly reduce the bioactivity of the material. Calcium fluoride (CaF_2) was added in the bioglass-ceramics system to induce the apatite formation and improve the bioactivity of bioglass-ceramics. The focus of this research is to study the effect of Na_2O replacement by Al_2O_3 on the physical, structural, and mechanical properties of the bioglass-ceramics. Other than that, the effect of sintering temperature on physical, structural, and mechanical properties of the bioglass-ceramics also been investigated. Therefore, the calcium fluoraluminosilicate (CFAS) was formulated with containing composition of SiO_2-CaO-Na_2CO_3 -P_2O_5-CaF_2-Al_2O_3.

Bioactivity and biocompatibility of CFAS also been conducted in this study. Bioactivity test is to confirm the formation of HA on the CFAS bioglass-ceramics surface after immersed in the phosphate buffer saline (PBS) solution. The formation of HA on the surface of CFAS bioglass-ceramics indicates its ability to support bone growth. This is because HA is the main component of bone and plays an important role in bone regeneration. To assess the biocompatibility, mechanical stability, and the safety it must undergo extensive investigation on the cytotoxicity test on newly developed material as an ideal for implant. cytotoxicity test is conducted outside of a living organism by using cell cultures. The test is to assesses the effect of CFAS bioglass-ceramics on cell-viability.

The utilization of waste materials such as soda lime silica (SLS) glass and eggshell (ES) were introduced in this study to minimize the usage of pure materials such as silicon dioxide (SiO_2) and calcium oxide (CaO). Besides reduce the cost of fabrication, the use of SLS glass and ES in synthesizing the CFAS bioglass-ceramics directly can overcome the dumping problem of glass and eggshells every year (Efa et al., 2024).

1.3 Problem Statement

Over the years, the production costs for orthopedic applications have significantly risen due to various factors, including the increasing expenses associated with raw materials, manufacturing processes, and research and development. The first composition of bioglass is 45 wt% SiO_2, 24.5 wt% CaO, 24.5 wt% Na_2O and 6.0 wt% P_2O_5. Due to the high-cost production of bioglass-ceramics especially for CFAS bioglass, the compound of SiO_2 can be replaced by alternative potential sources to utilize the waste materials as one way of recycling. The pure SiO_2 is very expensive, and it has high melting point. Thus, by considering the SLS glass, it consists high composition of SiO_2 with low cost of raw materials and provide low melting point compared to pure SiO_2 (Khiri et al., 2020). This reduces the cost especially cost assumption melting process.

Eggshells (ES) are always discarded even though they have many benefits. ES waste can cause harm to environment. Based on the previous research, the percentage of $CaCO_3$ in ES are usually 94-97 wt% (Rovinaru et al., 2020; Saparuddin et al., 2020). CaO can be obtained by calcination the ES high contain in $CaCO_3$ at 900 °C for 2 hours. The use of ES as a source of CaO can be a great help in reducing the disposal problem and reduce the cost of material fabrication.

Bioglass have amorphous structure and low mechanical strength. The development of bioactive-glass ceramics offers the potential to enhance mechanical performance, making them suitable for load bearing applications. CaF_2 and Al_2O_3 can formed fluoarapatite and anorthite phases which have higher potential for application in medical due to the antibacterial effect of its F^- ions (Hill et al., 2006) and increase the strength and improve the mechanical properties (Harabi et al., 2017). Previous study varies Na_2CO_3/Al_2O_3 ratio with increase Al_2O_3 from 0 to 4 wt% on the mechanical properties and shows it can improve in the composition (Mohamad et al., 2016). While other study uses 12.5 wt% shows it still improve the mechanical properties but suppress the bioactivity (Dimitriadis et al., 2021). In this project, varied the composition of Al_2O_3 from 0 to 9 wt% to improve the mechanical properties and retain the bioactivity. The study of CFAS based bioglass-ceramics sintered at various temperatures is needed to find the optimum temperature of the bioglass-ceramics. Sintering temperature is a parameter that plays an important role to increase the crystallinity structure. Mirza et al (2017) states that the sintering temperature influence the densification process and rise in temperature resulting in densified morphology, reduction of pores, and greater mechanical strength (Mirza et al., 2017).

Basically, bioactive glass has excellent bioactive properties, but the major disadvantages of bioglass is low mechanical strength. Bioglass shows impressive bioactivity and biocompatibility due to have an ability to develop an active hydroxyapatite layer on their surface which can bond with bone and soft tissues (Ghannam et al., 2005; Fiumme et al., 2018). Several studies on CFAS related to modifying glass to improve the mechanical properties (Mohamad et al., 2016, Loh et al., 2023). The immersion time is an important parameter where gives an effect to the bioactivity properties of CFAS bioglass-ceramics.

In addition, bioactive glasses show attractive properties making them suitable bone substitute materials (Baino et al., 2018). For newly developed CFAS based bioglass-ceramics, it is of certain interest to be compared and referenced to 45S5 bioglass as the well-known standard amongst bioglass to predict and understand their properties. The biocompatibility of bioglass is identified as an excellent potential as primary testing before it can be used in the human body.

1.4 Objectives

The main objective of this study is to fabricate SiO_2-CaO-Na_2O-Al_2O_3-P_2O_5-CaF_2 (CFAS) based bioglass-ceramics and improve their mechanical strength. This study involved the modification of glass composition by refer the 1st bioglass system, using the conventional melt-quenching technique, development of the sintering process to find the optimum temperature, bioactive glass-ceramics to bond to bone rapidly and biocompatible for potential use in medical application.

Based on the problem statement above, the objectives of this study were:

1. To synthesis the CFAS based bioglass-ceramics derived from waste materials.
2. To investigate the effect of Al_2O_3 composition and different sintering temperature on the physical, structural, and mechanical properties of CFAS bioglass-ceramics.
3. To determine the bioactivity of the sample by immersed in phosphate buffer saline (PBS) solution from 7-28 days.
4. To determine the biocompatibility of the CFAS bioglass-ceramics after immersion by using cytotoxicity test.

1.5 Scope of study

Bioglass-ceramics are a type of bioactive material that merges the advantageous features of glasses and ceramics. They have garnered significant attention in the field of biomedical applications due to their unique properties. To achieve the objectives of the study, the scopes of the study as follow:

1) A series of bioglass-ceramics with the composition of 44wt%SiO_2-24wt%CaO-(20-x) wt%Na_2CO_3 -6P_2O_5-6CaF_2-(x)wt%Al_2O_3 where x = 0, 3, 6, and 9 (wt%), has been prepared using SLS glass, CaO, Na_2CO_3, P_2O_5 CaF_2 and Al_2O_3 powders by melt-quenching technique.
2) The study investigates the impact of sintering temperatures ranging from 650 to 950°C on the structural, physical and mechanical properties of the bioglass-ceramics.
3) XRD is utilized for phase analysis, SEM for microstructural examination, and FTIR for analysing elemental bonding.
4) Density measurements assess the compactness of the material, molar volume provides insights into the atomic arrangement within the material, and linear shrinkage is analysed to understand the extent of material shrinkage during sintering.
5) A weight loss test is conducted to understand the elemental composition changes in the bioglass-ceramics, and pH measurements are taken to determine whether the material is acidic or alkaline
6) Compressive strength testing evaluates mechanical robustness, Vickers microhardness testing assesses surface hardness, and fracture toughness testing measures the material’s resistance to crack propagation.

7) The bioactivity of the bioglass-ceramics is evaluated through hydroxyapatite layer formation, and cytotoxicity tests ensure biocompatibility and safety for biomedical applications.

The expected outcomes identification of the optimal aluminium composition for enhanced bioglass-ceramic properties. Furthermore, understanding the influence of sintering temperature on structure, physical and microstructure. Then, improvement of mechanical properties within the range of cortical bone. Other than that, confirmation of bioactivity through hydroxyapatite layer formation. Also, it is non-toxic for used in human body.

1.6 Outline of Thesis

In chapter 1, the thesis begins with research background of biomaterial, bioceramics, and highlighting the bioglass-ceramics for this study. This chapter identify the problem and emphasize the importance of investigating SLS glass as a source of SiO_2 and ES as a source of CaO. Furthermore, the chapter lays out the specific objectives to be addressed. Moving to chapter 2, a comprehensive literature review unfolds, delving into the unique attributes of SLS and ES as raw materials. The discussion broadens to encompass a review of bioglass, culminating in an exploration of bioglass-ceramics through an analysis of previous research. This chapter also review the formation of new phases such as fluorapatite and hydroxyapatite from bioglass-ceramics which is needed for biomedical applications. Chapter 3 elucidates the methodology used, elaborate in detail the sample preparation, in vitro bioactivity and cytotoxicity. The characterization technique used such as XRF, XRD, SEM, FTIR, density, molar volume, linear shrinkage, weight loss, pH changes, compressive strength, Vickers microhardness, and fracture toughness are explained one by one from the fundamental of the equipment until the process how to characterize the sample by using the characterization. Chapter 4 presents the results and discussions of the five objectives, covering the synthesis of bioglass-ceramics, explore of Al_2O_3/Na_2CO_3 ratio, investigation of different sintering temperature from 650°C to 950°C, assessment of bioactivity and evaluation of cytotoxicity. Finally, the Chapter 5 conclude the obtained results and draw the conclusions also recommendations for future research endeavours.

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