PREPARATION AND CHARACTERIZATION OF POLYAMIDE 12 COMPOSITES FOR CRANIOFACIAL RECONSTRUCTION UTILIZING ADDITIVE MANUFACTURING

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by

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LIST OF ABBREVIATIONS

3D	Three dimensional
ABS	Acrylonitrile butadiene styrene
AM	Additive manufacturing
Al_2O_3	Alumina
ATR	Attenuated total reflectance
ANOVA	Analysis of varience
ASTM	American Society of the International Association for Testing and Materials
B.C	Before Christ
BPO	Benzoyl peroxide
β-TCP	Beta-Tricalcium phosphate
CAD	Computer aided design
CAE	Computer aided engineering
CP	Cryopreservation
CT	Computed tomography
DMPT	N,N-Dimethyl-p-toluidine
DSC	Differential scanning calorimetry
FDA	Food and Drug Administration
FDM	Fused deposition modelling
FEA	Finite element analysis
FESEM	Field emission scanning electron microscopy
FTIR	Fourier transform infrared spectroscopy
HA	Hydroxyapatite
IPV	Interpersonal violence

MFR	Melt flow rate
MMA	Methyl methacrylate
MMT	Montmorillonite
MRI	Magnetic resonance imaging
MSCs	Mesenchymal stem cells
MVA	Motor vehicle accident
PA	Polyamide
PA 12	Polyamide 12
PCL	Polycaprolactone
PEEK	polyether ether ketone
PLA	Polylactic acid
PMMA	Polymethyl methacrylate
PSI	Patient specific implant
RP	Rapid prototyping
RPM	Rotation per minute
SEM	Scanning electron microscope
SIRIM	Standard and Research Institute of Malaysia
SLA	Stereolitography
SLS	Selective laser sintering
SP	Subcutaneous pockets
SSE	Single screw extruder
STL	Standard tessellation language
TCP	Tricalcium phosphate
TGA	Thermogravimetric analysis
TSE	Twin screw extruder

USM	Universiti Sains Malaysia
USA	United States of America
UTM	Universal testing machine
ZrO_2	Zirconium oxide / zirconia

PENYEDIAAN DAN PENCIRIAN KOMPOSIT POLIAMIDA 12 UNTUK PEMBINAAN SEMULA KRANIOFASIAL MENGGUNAKAN KAEDAH PEMBUATAN ADITIF

ABSTRAK

Kajian ini dijalankan untuk menyediakan dan mencirikan komposit poliamida 12 yang dihasilkan melalui kaedah pembuatan aditif sebagai biobahan yang berpotensi untuk pembinaan semula kraniofasial. Poliamida 12 telah disebatikan dengan bahan pengisi seramik yang terdiri daripada β-TCP (julat antara 5 hingga 25% berat) dan zirconia (ditetapkan pada 15% berat) menggunakan penyemperitan skru berkembar. Pelet yang terhasil digunakan untuk pencirian sifat-sifat terma, kadar aliran leburan dan ikatan kimia komposit tersebut. Baki pelet telah digunakan untuk menyediakan spesimen bagi ujian tegangan, lenturan dan hentaman menggunakan kaedah pengacuanan suntikan dan pencetakan 3D. Sifat-sifat mekanikal komposit poliamida 12 telah dinilai. dan dianalisis secara statistik menggunakan ANOVA sehala dengan tahap signifikan p=0.05. Kadar aliran leburan komposit poliamida 12 menunjukkan perbezaan yang signifikan berbanding poliamida tulen (p<0.01). Sifat-sifat mekanikal dan topologi komposit poliamida 12 yang dihasilkan menggunakan kaedah pengacuanan suntikan menunjukkan percampuran perbezaan yang signifikan dan tidak signifikan berbanding poliamida tulen. Walaubagaimanapun, sifat-sifat mekanikal dan topologi komposit poliamida 12 yang dicetak melalui kaedah pencetakan 3D tidak menunjukkan sebarang perbezaan yang signifikan. Sifat-sifat mekanikal komposit poliamida 12 yang dihasilkan melalui kaedah pembuatan aditif dipengaruhi oleh ikatan antara lapisan yang boleh dipertingkatkan melalui pengoptimuman suhu platform. Dengan sifat mekanikal dan topologi yang boleh dipertingkatkan, komposit poliamida

12 yang dihasilkan melalui kaedah pembuatan aditif adalah berpotensi untuk pembinaan semula kraniofasial.

PREPARATION AND CHARACTERIZATION OF POLYAMIDE 12 COMPOSITES FOR CRANIOFACIAL RECONSTRUCTION UTILIZING ADDITIVE MANUFACTURING

ABSTRACT

This study was carried out to prepare and characterize polyamide 12 composites as potential biomaterial for craniofacial reconstruction utilizing additive manufacturing. Polyamide 12 was compounded with ceramic fillers of β-TCP (ranged from 5 to 25 wt%) and zirconia (fixed at 15 wt%) via twin screw extruder. Obtained pellets were used to characterize the thermal properties, melt flow rate and chemical bonding of the composites. The remaining pellets were used to prepare tensile, flexural and impact specimens via injection molding and 3D printing. The mechanical and topological properties of prepared specimens were evaluated and analyzed using statistical analysis of One-Way ANOVA with significant level of p=0.05. The melt flow rate of the polyamide 12 composites were significantly difference as compared to pure polyamide (p<0.01). Mechanical and topological properties of injection molded polyamide 12 composites showed a mix of significant and insignificant differences as compared to pure polyamide. However, no significant differences were detected in the mechanical and topological properties of 3D printed composites. The mechanical properties of 3D printed polyamide 12 composites was influenced by inter layer bonding which could be boosted further via optimization of bed temperature. Overall, with mechanical and topological properties that could be enhanced, polyamide 12 composites are potential biomaterial for craniofacial reconstruction.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

The increase of accident in Malaysia causes many people left with the trauma. According to Malaysian Automotive Association, vehicle registration has also increased from 536905 in 2009 to 655793 in 2013 (MAA, 2015). Although no specific study has been conducted in coherent relation between vehicle quantity and accident cases, leading causes of craniofacial bone fractures is road accidents (Shankar *et al.*, 2012). Studies at Hospital Universiti Sains Malaysia also gains similar result, where zygomatic, nasal bone as well as orbital floor are the most prominent affected areas after motor vehicle accident (MVA) due to their central position in the face (Pohchi *et al.*, 2013). However, road traffic accident is not the only cause, as infection, tumour or cerebral decompression may also contribute to this physical deformity (Chiarini *et al.*, 2004). In a situation where autologous bone is not available, patient with large craniofacial defect need to undergo surgery utilizing biomaterial implants to correct the craniofacial deformities (Cabraja *et al.*, 2009).

Titanium is a material of choice for implantation as it possesses excellent strength. However, the elastic modulus is moderately higher than bone. Moreover, the cost is also expensive, hence research on alternative material is extensively being carried out in order to find the best material that can suit the application with acceptable cost.

Modern technology that could be utilized to create physical model based on computed tomography (CT) and magnetic resonance imaging (MRI) data is called rapid prototyping (RP) (Starosolski *et al.*, 2014) which was introduced in 1980's. RP allows the building layer by layer in every form of internal and external anatomic structure. Enormous additive processes are being offered. However, the process differ and depend on the method of layer deposition as well as the variety of materials that could be used.

The combination of medical imaging devices, computer-aided design (CAD) and computer-aided engineering (CAE) software in addition to RP technologies, facilitates the cost reduction and time-efficient development of custom-made biomedical devices (Lantada and Morgado, 2012) yet reduce patient waiting time, shortened surgical time, accountable operation risks and produce affordable and accurate implant dimension for craniomaxillofacial surgery use.

This study is conducted together with a bio-modelling project using CAD where the prostheses will be designed based on CT scan data. The designed data will then transfer to a certain extension of the file to be readable by 3D RP machine. The aim of this project is to fabricate the prostheses using RP machine and to characterize the selected material that can suit the craniomaxillofacial surgical application.

1.2 Problem statements

In the modern ages, aluminium was the first metal to be used in craniofacial reconstruction specifically in cranioplasty. However, since many patients suffers from epilepsy and infectious complications, the usage has been vanished (Aydin *et al.*, 2011).

Titanium is currently called a gold standard of alloplastic material for craniofacial reconstruction. It is widely used and well known for its biocompatibility, malleable, inert and radiopaque (Gordon and Blair, 1974). Despite satisfactory cosmetic result after surgical procedure, yet the cost is relatively high. Therefore, alternative material should be provided to make it affordable to all and reach the bottom billions. Current craniofacial implant that is being used by oral maxillofacial surgeon is imported from overseas and the cost varies depending on the material, size and complexity of the deformities.

According to survey by Department of Statistic Malaysia, Malaysian household income for 2014 is less than RM 6200 (Statistics, 2015). Thus, patient with craniofacial deformity due to certain circumstances may not be able to undergo faster operation as current implant and surgical cost may incur about RM 7000~10000 (Azizan, 2012).

Although rapid prototyping technology has started to be utilized in Malaysia since the year 2000 (Yusoff *et al.*, 2009), research bodies like SIRIM and educational institution have just started to produce three-dimensional (3D) bio-model to aid the surgeon to quickly analyse and plan surgeries on bone deformities. In fact, locally produced implants are still focusing on titanium as main implant material through metal injection molding process for small implant and forming of imported titanium sheet for bigger implant.

On the other hand, polymeric material such as polymethyl methacrylate (PMMA) has started to be used since 1940s for craniofacial reconstruction. Indeed, in 2004, Department of Neurosurgery of Hospital Kuala Lumpur has indicated the success of PMMA cranioplasty for 49 patients with cranial defect due to MVA(Azmi *et al.*, 2004). Despite of ease of use and low cost, exothermic burn reaction, lack of incorporation with surrounding bone tissue and inflammation due to residual monomer are major concerns that restrict the application (Shah *et al.*, 2014).

1.3 Justification of the study

This research is important to find and characterize potential material to replace metal such as titanium in craniofacial reconstruction. From this single research, a novel polymer composite is expected to emerge.

The success to produce a local designated characteristic of filament which is compatible with the affordable 3D printer and could be applied for the craniofacial reconstruction application, will bring us one step ahead in term of medical technology development that commercial filament could be replaced. It is also eliminating the dependence to the high cost and high processing technology of medical devices.

1.4 Objectives of the study

1.4.1 General objective

To determine the properties of 12 (PA 12) composites fabricated utilizing rapid prototyping machine

1.4.2 Specific objectives

1. To characterize the thermal properties and melt flow rate characteristic of pure polyamide 12 and polyamide 12 composites.
2. To compare the mechanical and topological properties of pure polyamide 12 and polyamide 12 composites prepared via injection molding.
3. To compare the mechanical and topological properties of selected polyamide 12 composites prepared via 3D printing.

1.5 Hyphotheses

1. The incorporation of filler will have no significant difference on melt flow rate characteristic of polyamide 12 composites.
2. There are no significant differences between mechanical and topological properties of pure polyamide 12 and polyamide 12 composites prepared via injection molding.
3. There are no significant differences between mechanical and topological properties of selected polyamide 12 composites prepared via 3D printing.

CHAPTER 2

LITERATURE REVIEW

2.1 Bone

Human skeleton is made up of 80% cortical and 20% cancellous bone. Cortical bone is a dense and compact part that supports the body. The hard structure protects the internal organ from injuries when subjected to external momentum. In contrast, cancellous or trabecular bone is porous and spongy. It is filled with red bone marrow.

The combinations of porous and spongy structure result in a lower bone strength. Bone is built up from mineral and protein where nearly 60% of the bone weight is consisted of calcium and phosphate. 90% of the protein is made up from type one collagen fibres (Hadjidakis and Androulakis, 2006). Deposition of collagen promotes the bone formation called osteoblast which produced unmineralized bone matrix. The bone matrix will undergo a maturation process with an increase of mineralization rate. The mechanical properties of bone are summarized as Table 2.2.

Table 2.1: Mechanical properties of bone reproduced from Witte *et al.* (2008)

Bone type	Compressive strength (MPa)	Tensile strength (MPa)	Modulus (GPa)	Impact strength (J/m^2)
Cortical bone	164-240	35-283	5-23	4-70
Cancellous bone	Not reported	1.5-38	0.10-15.70	Not reported

While this data could be used as reference, the mechanical properties of bone varies and attributed from many factors. Bone development and strength are often portrayed as an end result of dietary calcium in any of advertised milk product on television. Nevertheless, based on experiment conducted on rat, high impact exercise resulted to a greater bone strength, compared to dietary calcium (Welch *et al.*, 2008). Myth that women are prone to get fractures when involve in an accident are instead a true fact as sexual dimorphism in tibial strength are apparent in pre and early puberty (Macdonald *et al.*, 2006). Ethnicity differences also attribute to the bone mechanical properties. For instance, bone density of African American and Hispanic children are denser than Caucasian children, which lead to a significantly higher bone strength (Wetzsteon *et al.*, 2009) . On the other hand, loading rate and sampling position during experiment also attribute to the variation of the mechanical bone properties (Motherway *et al.*, 2009) .

Mechanical properties of the bone could be evaluated via many methods. Current practical method is the prediction through finite element analysis (FEA) software. FEA is an additional package in CAD software that works by simulating the stress distribution on an object after subjected to a specific force. FEA could also be used to identify the failure of the designed object to withstand the external forces, thus new design with an appropriate material could be proposed. This simulation tool is essential and could be used for preparing a new proposed implant. Meanwhile, mechanical properties of human bone could also be acquired via direct mechanical testing on the bone itself. It will produce the true value of the mechanical properties. Yet, a cadaver and ethical approval are required for the purposes.

2.2 Skull

A skull comprises of cranial and facial bones. Details of skull anatomy could be observed as in Figures 2.1 and 2.2. Cranial is made up of 8 bones whereas another 14 bones completed the facial structure (Schuenke *et al.*, 2007). The details of the skull are stated in Table 2.1.

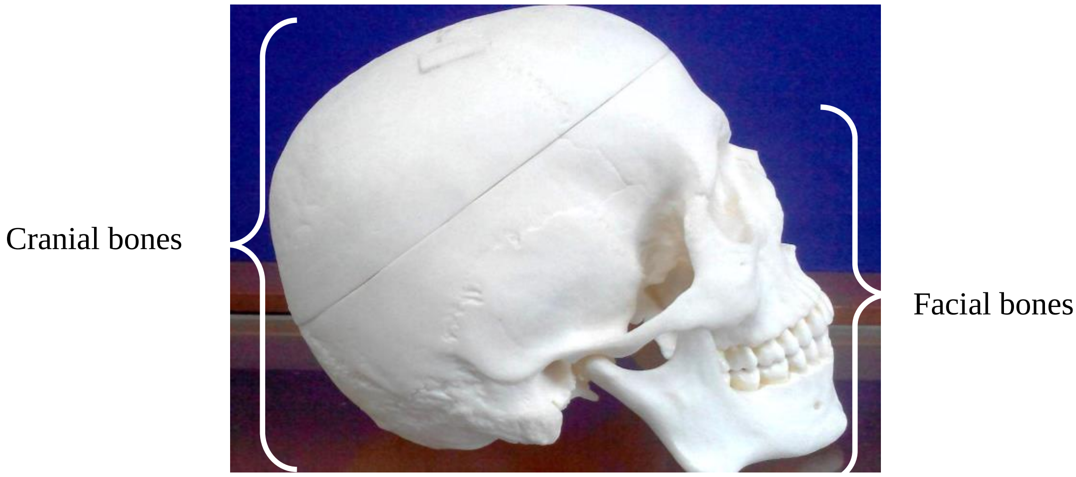


Figure 2.1: Lateral view of human skull

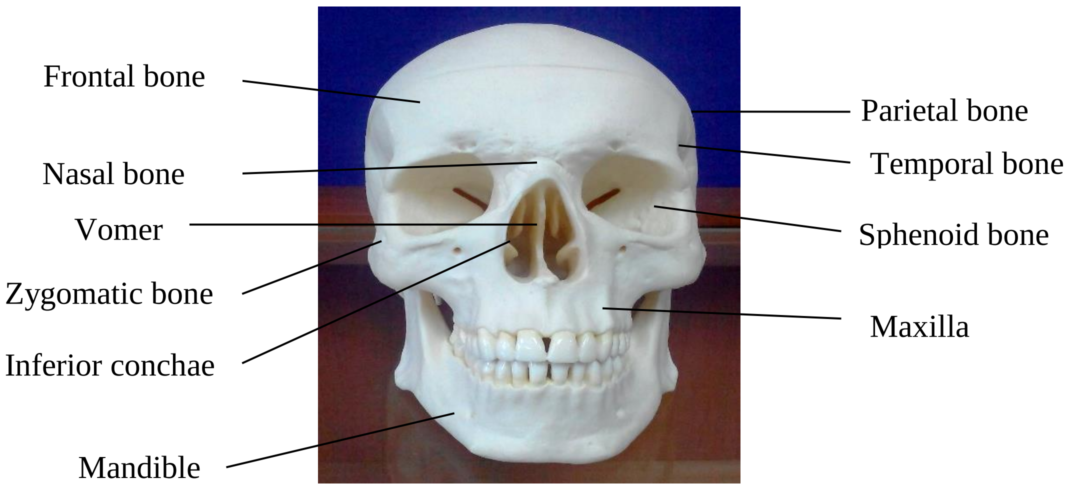


Figure 2.2: Anterior view of human skull

Table 2.2: Cranial and facial bones with their quantity

Cranial bones	Quantity	Facial bones	Quantity
Frontal bone	1	Mandible	1
Parietal bone	2	Maxilla	2
Temporal bone	2	Zygomatic bone	2
Occipital bone	1	Nasal bones	2
Sphenoid bone	1	Lacrimal bones	2
Ethmoid bone	1	Palatine bones	2
		Inferior conchae	2
		Vomer	1

2.3 Craniofacial fractures

MVA is the main cause for the craniofacial fractures in developing countries such as India, Saudi Arabia, Malaysia and China. (Shankar *et al.*, 2012; Abdullah *et al.*, 2013; Pohchi *et al.*, 2013; Mijiti *et al.*, 2014). It is contributed by the road network expansion, the number of vehicles on the road and also the attitude of the driver. Studies in different developing countries also concluded that the cases are mainly attributed by the men with age ranged between 20 to 30 years old. It should be noted that, in Saudi Arabia, women are not allowed to drive and alcohol is also prohibited.

In developed countries such as Germany, interpersonal violence (IPV) recorded as the main factor for craniofacial fractures (Schneider *et al.*, 2015). It is resulted by the uncontrolled behaviour under an influence of alcohol. The second factor is the fall incidents followed by MVA cases. It is also mainly attributed by the people ranged between 20 to 30 years old. Different values in a community of developing and developed countries, apparently contributed to a different main factor of craniofacial fractures. Summary of the main causes of the craniofacial fractures and fractured parts as reported by several studies are as in Table 2.3.

Table 2.3: Main causes of the accident and fracture parts by selected countries

Author	Country	Cause of accident	Fracture parts
Pohchi *et al.* (2013)	Malaysia	MVA, falls, IPV	Zygoma, nasal bone, orbital bone
Shankar *et al.* (2012)	India	MVA, IPV, falls	Zygoma, Unilateral LeFort
Mijiti *et al.* (2014)	China	MVA, IPV, falls	Zygoma, maxilla, nasal bone
Abdullah *et al.* (2013)	Saudi Arabia	MVA, falls, IPV	Maxilla, mandible
Schneider *et al.* (2015)	Germany	IPV, falls, MVA	Zygoma, orbital floor

2.4 Craniofacial reconstruction

Reconstruction of craniofacial bone anomalies involves either autograft, xenograft, allograft or alloplast augmentation techniques. Autograft is where the autologous bone is being transferred from identified certain parts to another part of the same human body. Autologous bone is the gold standard for craniofacial reconstruction. It is normally readily available and could be used to serve the patients. While source of autologous bone is typically from the patient own bone, however, preservation method is an important aspect that needs to be considered in order to prevent an infection. For example, bone flap removed during decompressive craniectomy in order to prevent brain swelling will be preserved in tissue bank via cryopreservation (CP) or subcutaneous pockets (SP) method. While SP method requires additional surgical procedures, in contrast, bone flap preserves via CP method is prone to resorb. However the site surgical infection rates for both method are similar (Cheng *et al.*, 2014). Except the flap is contaminated or due to other indication, the patient's own bone should be considered for implantation with the intention to reduce the cost incurred by the patients (Lemee *et al.*, 2013).

The intention to use autologous bone sometimes leads to a secondary operation. Mandibular reconstruction for example, may need a bone graft from fibula part. An operation to remove defect mandibular part will be conducted together with the fibula cutting, which requires synchronization from both oral maxillofacial surgeon and orthopaedic team. The operation will take time and more time is needed for the recovery. The patient would need to spend more time at the hospital and prone to get hospital acquired infection.

Utilization of autologous bone offers a significantly affordable surgical cost, yet, complication such as haematoma, infection and flap displacement are among the major concern raised by the clinicians (Bobinski *et al.*, 2013) that surgical revision is required. Besides, high complication rates in paediatric patients following autologous bone implantation are also unacceptable (Martin *et al.*, 2014). Thus, alloplastic biomaterial is always become the material of choice for the application.

Whereas, xenograft is where the bone is being transferred from different species to another, such as from bovine to human. Allograft is another available option where the bone is transferred from donor site. Whereas alloplast is the fourth option where alloplastic biomaterial is being used. Though these four augmentation methods are established methods, the treatments with xenograft remain controversial. Transmission of microorganism as well as ethical issue (Collignona and Purdy, 2001) are among the matter of concern. However, xenograft is proved to be a reliable grafting material as it shows neither signs of implant mobility nor the rejection after being applied as sinus augmentation (Rahman *et al.*, 2014).

2.5 Biomaterials

Natural or synthetic material to be used for implantation in human body is called biomaterial. Biomaterial is designed to be able to adapt and function in surrounding biological environment. A biomaterial should possess adequate mechanical characteristics, has surface texture that support cell adhesion, biocompatible and reproducible (Ramakrishna *et al.*, 2001). Natural biomaterials such as cornea, skin, nerve, muscle and so on are depended on donor's availability, thus limits the applications. Despite of providing similar mechanical properties and is compatible with the recipient, pre-treatment such as preservation and sterilization are again a serious issue that need to be considered to prevent any complications (Ali *et al.*, 2013).

Synthetic biomaterials could be classified into metallic, polymeric, ceramic and composite materials. Metallic materials are widely used in load bearing application due to its natural high strength and high elastic modulus. Polymeric materials are getting attention due to its various properties, composition and easy processing. However, its flexibility and lack of mechanical properties impede the application.

Polymers could be divided into two categories which are resorbable and non-resorbable. Resorbable polymer is made up from natural sources such as cellulose and starch. Sometimes extracted starch and cellulose, are blended together with synthetic polymers to make it resorbable. Non-resorbable polymer is made up of long repetition of hydrogen and carbon atom chains which produce strong molecules bonding. While ceramics are well known for its biocompatibility, its delicate mechanical properties and fabrication difficulty limits the manipulation. Ceramics could be classified into three different group which are bioinert, bioactive and bioresorbable (Thamaraiselvi and Rajeswari, 2004). Being a mix of previously stated materials, composites seem a likely prospect to penetrate the biomaterials field as it possesses the blended properties of those materials even though the processing method need to be looked at. Figure 2.3 summarized the classification of biomaterial.

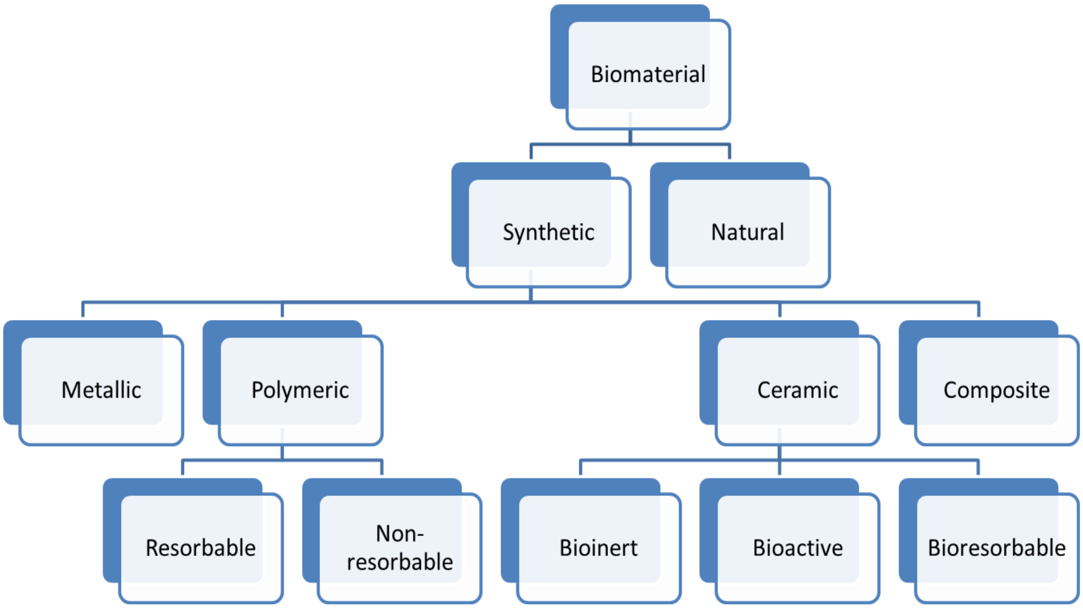


Figure 2.3: Classification of biomaterials

2.5.1 Metallic materials

Implant material such as gold and silver is believed to be first used in 3000 B.C by Incas of Peru to repair trephination defects (Thorne, 2007).It is then evolved to a metal implant like aluminium as well as titanium and are reported to be used in craniectomy (Gordon and Blair, 1974). However the usage of aluminium has been stopped after implanted patients were reported to suffer from several complications such as epilepsy (Aydin *et al.*, 2011). Furthermore, study of effect of aluminium exposure on rat model concluded that the aluminium is positively associated with alzheimer disease and it is also led to progressive dementia (Walton, 2007).

Titanium was first reported to be used for seven cranioplasty cases in Australia (Simpson, 1965) and still remains the material of choice for the application in craniofacial reconstruction as it possesses high mechanical strength. The mechanical strength is reported to be comparable to the cortical bone. However the elastic modulus of titanium is extremely higher than human bone. Mismatch of this property hinders the development of surrounding tissue after implantation. The mechanical properties of several metallic implants are summarized in Table 2.4

Table 2.4: Tensile properties of metallic implants reproduced from Witte *et al.* (2008)

Material	Tensile strength (MPa)	Modulus (GPa)
Titanium (TiAl6V4, cast)	830-1025	114
Titanium (Ti1l6V4, wrought)	896-1172	114
Stainless steel 316L	480-620	193

Inhomogeneous young modulus between titanium implant and surrounding bone tissue led to stress shielding effect phenomenon. Stress shielding effect is the phenomenon where the loaded stress is not well distributed and shared between the implant and existing bone which resulted to an increase of bone porosity and possibility of bone re-fracture and implant loosening (Niinomi and Nakai, 2011).

Application of metal implant often lead to an argument as it is easily corroded. The exposure to high stress and load, especially in orthopaedic application accelerates the formation of wear debris which leads to fatigue wear and finally affect the life span of the implant. As a result, metal based implants usually undergo surface modification process such as HA coating in order to improve the chemical, biological as well as the mechanical properties (Liu *et al.*, 2004).

2.5.2 Polymeric materials

Polymeric materials are vastly used as biomedical devices. Resorbable polymer such as polylactic acid (PLA), polylactic glycolic acid (PLGA) and polyglycolic acid (PGA) as well as non-resorbable polymer of polyethylene (PE), polymethyl methacrylate

(PMMA), polyamide (PA) and polyether ether ketone (PEEK) are prevalent implantation material for craniofacial reconstruction.

Resorbable polymers are preferable to cater the paediatric patients with craniofacial deformities. Resorbable polymers such as PLA and PLGA permits the growth of surrounding bone tissue while it gradually loose the mechanical integrity. Hence, patients treated with resorbable polymers experienced stable implant fixation simultaneously with the progression of bone healing (Cohen *et al.*, 2004).

Although many new polymeric materials started to be used as biomaterials, problem in processing and reproducibility as well as other disadvantages impede the application in craniofacial reconstruction. In fact, up to date, polymeric materials for craniofacial reconstruction are restricted to non-resorbable of PMMA, PEEK, PE and PA (Thorne, 2007; Visscher *et al.*, 2016).

2.5.2.1 Polymethyl methacrylate

Polymeric material such as polymethyl methacrylate (PMMA) is the commonest material for craniofacial bone reconstruction (Chiarini *et al.*, 2004). It has excellent properties such as biocompatible, biologically inert, rigid and widely used to repair craniofacial deformities. PMMA usually comes with a packaging set of powder and liquid. Powder component contain of PMMA polymer and benzoyl peroxide (BPO) whereas liquid part contain of methyl methacrylate (MMA) monomer, N,N-Dimethyl-p-toluidine (DMPT) which acts as activator and hydroquinone which function to stabilize the liquid monomer. DMPT initially decompose the BPO. Free radical molecules resulted from the decomposition, initiates the polymerization process. Mixing of these two components with instructed ratio by the supplier will result to a polymerization. Although PMMA offers ease of handling, its brittleness, shrinkage and also exothermic reaction that release heat during polymerization may damage surrounding bonding tissue. In addition to that, maximum temperature inside PMMA sample with nearby tissue being exposed over a prolonged period is recorded more than 50ºC, that preoperative implant preparation is highly recommended (Golz *et al.*, 2010).

2.5.2.2 Polyether ether ketone

Current polymeric material that is getting attention from surgeons and researchers is polyether ether ketone (PEEK). PEEK possess excellent mechanical properties and the properties is said to be comparable with cortical bone (Shah *et al.*, 2014). However this material is lack of osteointegrative properties, that led to various complication such as infection and implant loss (Khonsari *et al.*, 2014). Moreover, the melting point of PEEK is around 343°C, which could only be processed via high end rapid prototyping machine that equipped with higher heating capabilities such as selective laser sintering (SLS). Though exclusive and expensive in nature, the introduction of PEEK as PSI processed via current additive manufacturing (AM) techniques has helped patients with craniofacial deformities to regain their regular cosmesis (Lethaus *et al.*, 2011) .

2.5.2.3 Polyethylene

PE is mainly classified by its density, molecular weight and branching. It has started to be used commercially for craniofacial reconstruction in 1984 (Ellis and Messo, 2004). Commercially available high density polyethylene (HDPE), MedPor is one of the famous brand that is widely accepted for craniofacial reconstruction. It is due to the ability of the material to induce bone ingrowth owing to its porous structure.

Ultra-high molecular weight polyethylene (UHMWPE) is another type of polyethylene that is getting attention for its wear and tear resistance. The excellent wear and tear resistance make it prevalent for hip and knee implant. However, UHMWPE is also introduced as commercial orbital floor implant under a trade name of SYNPOR®.

Although MedPor and SYNPOR® are well established material, they have their disadvantages such as a need to be trimmed in operation theatre in order to suit the patient's defect. Thus, this open an opportunity to further improve the existing commercial implant with pre-fabricated patient specific implant.

2.5.2.4 Polyamide

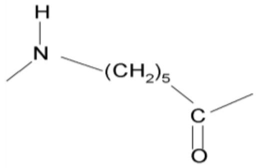
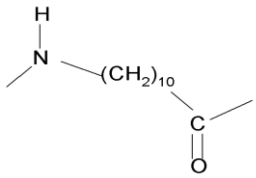
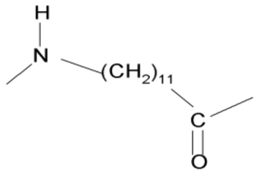
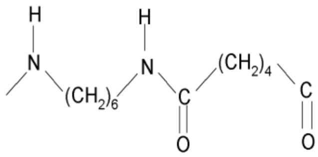
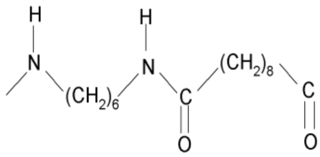
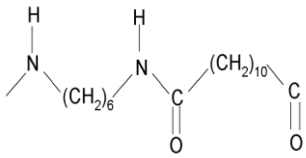
Polyamide (PA) is biocompatible, could be simply contoured and sutured. PA also enhanced the growth of fibrous tissue and has been successfully used as an orbital floor implant (Breitbart and Ablaza, 2007). Moreover, it has been used to produce skull model pre surgical planning and young surgeon training (Wanibuchi *et al.*, 2010). Hygroscopic factor makes it not durable, that certain material need to be incorporated to tailor the properties.

Extensive research has been carried out to tailor the properties and at the same time create a new value added material. For example, PA 6,6 has been incorporated with 65 wt% of nano hydroxyapatite (n-HA) and it showed remarkable molded tensile properties with tensile strength of 87 MPa (Jie, 2004).This newly blended material is proved to be biocompatible as it showed non cytotoxic effect when cultured with mesenchymal stem cells (MSCs) (Wang *et al.*, 2007). The material was also successfully implanted in one patient in China to construct the condylar via SLS (Li *et al.*, 2011), indicating its potential as an alternative material for implantation. However, evaluation with more patients and longer follow up is necessary.

Polyamide 12 (PA 12) is another type of polyamide that is getting attention for its easy processing. It possesses low melting temperature and high flowability. PA 12 could be prepared from lauryl lactam (Kim and White, 2003) and also aminolauric acid (McKeen, 2014). PA 12 is the current material of choice for selective laser sintering (SLS) due to its relatively lower cost than PEEK. High flowability properties make it appropriate for SLS process. Although prominent in SLS segment, SLS graded PA 12 is never being applied to other processing method. Current manufacturer for PA 12 are 3D Systems and EOS that supplied PA 12 using a commercial name of Duraform® and PA2200, respectively (Goodridge *et al.*, 2012). Production of Duraform® and PA2200 are dedicated for their SLS machine. Investigation on tensile properties of specimens produced by these materials revealed that specimens using PA2200 produced higher tensile properties as compared to specimens of Duraform® (Zarringhalam *et al.*, 2006).

Since the introduction of polyamide 6,6 (PA 6,6) by Carothers in 1934, various type of polyamide has been developed and commercialized. Details of currently available PA, their properties (Fumihiko, 1995) and repeating unit of molecular structure are summarized in Table 2.4. Polar molecular (-CO- NH-) structure in polyamide chain is accidentally mimics the structure of collagen (Li *et al.*, 2011), an essential factor that promotes the osteoblast. Thus, this collagen mimicked structure could be manipulated by introducing PA as potential biomaterial for craniofacial reconstruction.

Table 2.5: PA and their properties

Polyamide	Melting point	Tensile strength (MPa)	Tensile modulus (GPa)	Molecular structure (Repeating unit)
PA 6	220	72.50	2.35	
PA 11	187	78.40	2.84	
PA 12	178	49.00	1.29	
PA 6,6	260	78.40	2.80	
PA 6,10	213	58.80	1.96	
PA 6,12	210	60.80	1.96	

2.5.3 Ceramic materials

Focus of ceramics for biomaterial application started with the emerging of bioinert ceramics. Alumina (Al_2O_3) is among the bioinert ceramics that has been employed as dental and bone implants due to its outstanding wear and friction properties (Thamaraiselvi and Rajeswari, 2004). The properties are attributed by the surface energy and smoothness of the alumina. Alumina is also thermodynamically stable due to hexagonal crystal structure itself and also because of octahedral interstitial sites being occupied by aluminium ions.

Another bioinert ceramics that's getting attention for its excellent mechanical properties is zirconia (ZrO_2). Zirconia is widely incorporated between 9 to 15 wt% as radio pacifying agents in acrylic bone cements (Lewis and Mladsi, 2000). Although barium sulphate is another radio pacifying agent that's broadly employed in acrylic bone cement as alternative to zirconia, it reduced the tensile strength (Ginebra *et al.*, 2002). While the addition of zirconia improved the tensile strength, fracture toughness and resistance to fatigue crack propagation (Ginebra *et al.*, 2002), it showed an adverse effect on impact strength and surface hardness (Asopa *et al.*, 2015).

Incorporation of zirconia in other material such as wollastonite, reduced the total pore volume which reflected to an increase of wollastonite's density. It's also improved the bending strength and modulus as well as degradation rate and degradability (Li *et al.*, 2015). Thermal properties of zirconia incorporated material, is also proved to be more stable as compared to the virgin PEEK. Addition of 3 wt% of zirconia raised the degradation temperature of PEEK to nearly 43°C although no changes is observed in glass transition temperature (Mishra *et al.*, 2012). Single form of zirconia is classified as bioinert. However, the incorporation of zirconia into other material showed an enhancement in apatite formation ability which revealed that zirconia is able to induce the bioactivity of the material (Masudi *et al.*, 2011; Li *et al.*, 2015).

The usage of individual alumina and zirconia for craniofacial reconstruction are nowhere to be found in literature. Excellent wear and friction resistance make alumina more appropriate to be used as coating for total hip replacement articulating surface during 1950s to 1960s, before being stopped after received post-operative pain complaints from respected patients (Ali *et al.*, 2013).

Bioactive ceramics is commercially available as it is being developed to cater the needs. For instance, NovaBone® is a bioactive glass particle which composed of 45% each of silica dioxide and sodium oxide, with 5% calcium and phosphate respectively. Bioactive glass will response biologically at the material interface which results into bond formation between tissue and material (Elshahat, 2006). While prominent in accelerating the material and tissue bonding, bioactive glass is also said to possess an antibacterial effect which covers clinically important pathogens (Lepparanta *et al.*, 2008). The brittleness and rigidity of bioactive glass make it not possible to be contoured preoperatively which typically combined with polymer matrix such as PMMA is preferable (Peltola *et al.*, 2012).

Calcium phosphate based materials is resorbable materials that is gaining interest for its excellent mechanical and biological properties. Often, the motivation of using calcium phosphate based material is due to its similar mineral component to natural human bone (Berberi *et al.*, 2014). Current widely used calcium phosphate based materials are hydroxyapatite (HA) and tricalcium phosphate (TCP). However, HA is relatively more popular material for human bone incorporation, although no significant evidence of biodegradation following long terms of implantation (Ogose *et al.*, 2005; Yamasaki *et al.*, 2009).

TCP with formula of $Ca_3(PO_4)_2$ exists in three crystalline forms such as α, α', and β (Mehdikhani *et al.*, 2012) . β-TCP is thermally stable below 1180°C, while α-TCP between 1180ºC to 1400°C and α'-TCP above 1470ºC (Ryu *et al.*, 2002). While alpha phase is in monoclinic structure, beta phase is in rhombohedral structure and can be synthesized through two different methods which are hydrothermal (Ohashi *et al.*, 2004) and precipitation method (Chen *et al.*, 2008). Although these two methods are totally different, interestingly, β-TCP produced by these two different methods however, showed non cytotoxic effects when exposed to normal human osteoblast cell (NHOst) (Nazir *et al.*, 2012).

In orthopaedic field, β-TCP is combined together with various materials such as human recombinant, mesenchymal stem cells, bone marrow and etc. In that particular combination, β-TCP showed its resistance against compression of surrounding soft tissues, as well as osteogenicity and osteoconductivity (Liu and Lun, 2012). Clinical evaluation utilizing β-TCP as bone augmentation material also exhibited a promising result. β-TCP were used in human high tibial osteotomy procedure and alveolar reconstruction (Gaasbeek *et al.*, 2005; Horch *et al.*, 2006) and it showed complete consolidation after 12 months, indicating its optimal biocompatibility.

Other than biological properties, incorporation of β-TCP into a polymer matrix also proved to enhance the mechanical properties of composites. Addition of β-TCP in PEEK for instance, improved the tensile modulus. Tensile strength also exhibited optimum value at 20 wt% of incorporation (Petrovic *et al.*, 2006).

2.5.4 Composites

Biomaterials for craniofacial reconstruction evolved from a material which is supposed to have sufficient mechanical integrity to a material with additional biological properties (Holzapfel *et al.*, 2013). The usage of either metal, ceramic or polymeric materials alone are unable to provide multi-functional materials.

Composites is introduced for craniofacial reconstruction to not only provide structural support to the defect part but also integrate with surrounding bone tissue to induce regeneration process. This could be done by incorporating ceramics such as calcium phosphate based materials or zirconia to the matrix. Calcium phosphate based materials as well as zirconia possess chemical similarity to the natural human bone, which play a crucial role in bone tissue healing (Kokubo *et al.*, 2003).

As previously stated in section 2.5.1, calcium phosphate based HA for example, is the material of choice for titanium coating (Liu *et al.*, 2004). HA is also filled in polyethylene based material to form a new bioactive polymer composites, HAPEX™ (Wang *et al.*, 2000). The usage of bioactive glass is another example where it is covered on the PMMA surface to induce tissue (Peltola *et al.*, 2012). The bioactivity of the materials are depended on coating materials or filler degradation mechanism. While the matrix function as structural host after implantation, the coating or filler will slowly degrade and stimulate cellular regeneration process.

2.6 Additive manufacturing

Additive manufacturing (AM) is relatively new in dentistry. While CAD/CAM is being used in dentistry for preparation of crowns and bridges through dental CAD/CAM, the manufacturing part uses a technique called subtractive manufacturing.