Naturally Derived Biomaterials and Its Processing

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Abstract The rich Indonesian biodiversity has been viewed as an infinite resource of naturally inspired and derived biomaterials. The utilization of these natural materials for biomaterial applications necessitates additional steps to the currently established conventional synthesis methods. Some of these steps have been successfully developed at a lab scale with suitable controlling parameters resulting into an optimum overall synthesis processes. Further optimization and fine tuning on the parameters are required to translate the innovation into a commercialization. More efforts from biomaterial researchers and a supportive policy from the Government are essentially needed to foster the development of biomaterial and its applied technology resulting into low-cost yet effective medical devices to support the national health care program. This chapter concentrates its discussion on selected naturally derived biomaterials, their sources and their processing which have been developed in Indonesia. These include synthesis of hydroxyapatite from coral, land snail and egg shells via precipitation reaction, sol-gel, hydrothermal and biomimetic methods, new synthesis of membrane and encapsulation using template derived from a flower plant, and synthesis of zirconia for dental restoration.

Keywords Biomaterials · Biomimetic · Coral · Natural · Precipitation · Sol-gel

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1 Introduction

In one definition, a biomaterial is any substance (other than a drug) or combination of substances synthetic or natural in origin, which can be used any time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ or function of the body (Von Recum and Laberge 1995). By this definition, natural products can be applied as biomaterials of natural in origin which its historical use dates back to 3000 BC when the ancient Egyptians used sutures made from animal sinew, coconut shells, wood and ivory to repair injured skulls and replace teeth (Ratner et al. 2004). Theoretically, any material natural or man made can be a biomaterial as long as it serves the stated medical and surgical purposes for ultimately safely implantation in or on the human body. Nature has provided a range of materials (mainly polymers and minerals) with remarkable functional properties. Natural was defined as something that is present in or produced by nature and not artificial or man made, and most often the definition is assumed to mean something good or pure (Fratzl 2007). Among the advantages of using natural materials for implants is that they are similar or familiar (biomimetics) to materials in the body systems.

Indonesia is the largest archipelagic country in the world having undeniable richness in species and ecosystems from its more than 17,000 islands with large rainforest, 87,000 km^2 of coral reefs and 24,000 km^2 of mangrove areas. The archipelago (Fig. 1) is the heart of the Coral Triangle, the global hotspot for marine life and the world's richest coral species biodiversity. In June 2010, a group of seven international research institutions has founded the Indonesian Biodiversity Research Center (IBRC) with headquarter located in Bali. The Center aims to promote biodiversity stewardship in Indonesia through collaborative research and educational programs, to increase biodiversity research in Indonesian scientific communities, and to build lasting research networks between Indonesian and US research centers. The Indonesian Ministry of the Environment estimates that more than half of Indonesia's species are still unrecorded while there is still much to be discovered.

In this chapter, we concentrate our discussion on selected naturally derived ceramic biomaterials, their sources and their synthesis or processing which required additional steps rather than the conventional processes for synthetic origin. Special attention is given to natural biomaterials and processes developed in Indonesia. These include, among all, synthesis of hydroxyapatite (HAp) from coral, land snail and egg shells via precipitation reaction, sol-gel, hydrothermal and biomimetic methods, new synthesis of membrane and encapsulation using template derived from a flower plant, and synthesis of zirconia from abundant raw materials found in Indonesia for dental restoration.

Fig. 1 The Indonesian archipelago (Google)

2 Natural Source of Ceramic Biomaterials

Ceramic biomaterials (bioceramics) have been used as active biomaterials for promoting regeneration of tissues, healing of traumatic disease, or restoring physiological functions. They found the applications in dental restorations, filling of bony defects, rebuilding bone at facial, cranial and other parts (Hench 1991). Bioceramics are mostly produced from synthetic raw materials, but natural sources are also available such as corals and shells which are found abundant in many places in Indonesia.

2.1 Corals

Due to its porous nature and high content of calcium carbonate, coral and its derived HAp have been used as bone grafts, spinal fusion, bone filler and orbital implants since 30 years ago with proven biocompatibilty and resorbability (Guillenium et al. 1987; Ige et al. 2012). Its porous structure is a range similar to that of cancellous bone (150–500 μm) and thus makes it ideal for ingrowth of blood vessels (Ben-Nissan 2003). Apart of their exoskeleton structure, coral grafts can act as a carrier for growth factors thus improving their osteoinductivity or osteogenicity (Louisia et al. 1999). The use of coral derived bone graft prevents the transmission of human immunodeficiency virus, hepatitis B, hepatitis C and other similar diseases (Suzina et al. 2005). There are many commercial brands of coralline HAp available in the market since decade ago, such as Biocoral, Pro-osteon and Interpore (Damien and Revell 2004). Figure 2 shows example of bone graft produced from coral.

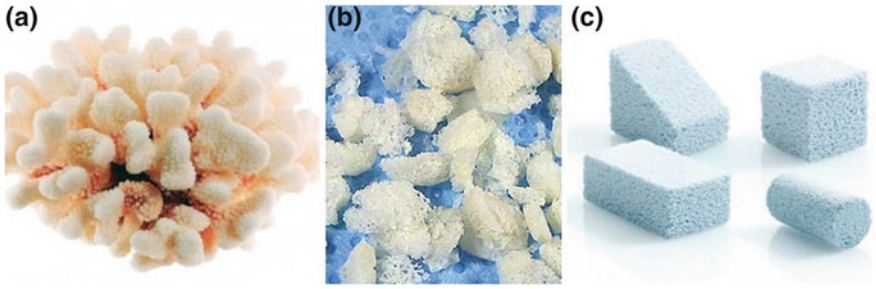

Fig. 2 **a** Porite coral, **b** chemically treated pieces of coral, **c** coralline HAp bone graft

Production of bone grafts from natural coral for medical applications, such as orthopaedic and cranio-maxillo-facial surgeries, needs a set of rigorous protocols of preparation and purification. As part of conservation efforts, only dead coral from *Poratidae* family (*Porites* or *Goniopora* species) is usually harvested as raw materials for the production of coralline HAp (Damien and Revell 2004). The coral material is cut into smaller pieces (blocks and granules) then chemically treated followed by freeze drying and radiosterilized before subjected to a series of biocompatibility tests (Suzina et al. 2005). There are several techniques widely utilized to synthesis HAp directly from corals, including hydrothermal and microwave processes, and sol-gel coating (Balázsi et al. 2007).

In a simple hydrothermal method, the coral is subjected to a temperature of 900 °C to decompose all carbonate phases and remove all organic materials. The preheated coral, calcium carbonate, is then converted into HAp by chemical exchange reaction with diammonium phosphate resulting in pure coralline HAp powders with both aragonite and calcite phases (Sivakumar et al. 1996). Under a controlled hydrothermal exchange process, a mix product of calcite ($CaCO_3$) and β-tricalcium phosphate (β-TCP) can be derived from coral sand grains with retaining porous structures, making them suitable as bone scaffolds (Chou et al. 2007). The use of a mineraliser (KH_2PO_4) can accelerate the exchange process and eliminate the formation of intermediary phases, while without the mineraliser, aragonite is converted at high temperature and pressure into calcite, which was subsequently converted to β-TCP and finally to HAp. The use of mineralizer gives a better retention of the original structure of the coral such as the pore interconnectivity (Xu et al. 2001).

2.2 Shells

Numerous shells are found in nature and some of them have been evaluated for possible biomaterials. As an example, cockle shell which has almost similar mineral composition to that of coral suggesting its potential to be used as a material for orthopaedic applications (Awang-Hazmi et al. 2007). The nature of the mollusc

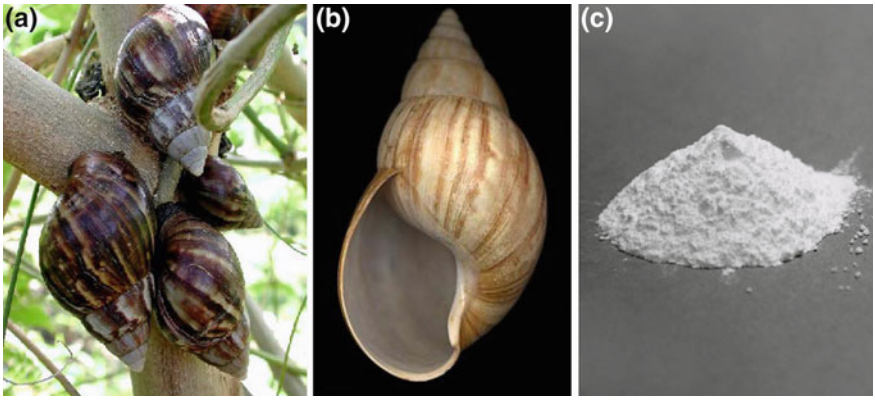

Fig. 3 **a** *Achatina fulica* snail, **b** its shell, **c** HAp powders

shell, in-terms of both mineral composition and porous structure, makes it an ideal bioceramic materials candidate with exceptional mechanical properties (Rodríguez-Navarro et al. 2006). Apart of marine mollusc, there are thousands of land snail species, including *helix aspersa*, *helix pomatia* and *achatina fulica* which can be easily found in Indonesia. Their shell is rich in calcium carbonate thus can be used as a source for bioceramic production. Figure 3 shows images of *achatina fulica*, its shell and HAp powders.

In view of utilizing the abundant source (and waste product) of land snail shells, various Ca-phosphates powders, specifically monetite, fluorapatite, have been produced from *helix pomatia* shells via a simple economical method. The empty shells were washed, dried, crushed and ball milled to obtain 100 μm size powders, then stirred at 80 °C while reacted with drops of H_3PO_4 for 8 h. The liquid part was then evaporated in an incubator at 100 °C for 24 h to finally collect the Ca-phosphates powders (Kel et al. 2012). Another HAp synthesis can be done from *achatina fulica* shells by a reflux method. It is started with drying and milling the shells to obtain powders continued by deproteinization in basic solution, followed by reflux in weak acid solution and ended by heat treatment and gelatinization.

3 Synthesis of Naturally Derived Bioceramics

3.1 Hydroxyapatite Powders

One important bioceramics that is progressively developed by many researchers is HAp, $Ca_{10}(PO_4)_6(OH)_2$, a bioceramic material with chemical composition similar to that of mineral in bone and tooth. It has excellent biocompatibility and can be directly attached to the bone and does not pose toxicity. In addition, apatite structure accommodates ion exchange by substituting hydroxyl ion (OH^-) with

other ion. Therefore it can also be used for filter application, such as for sorption of bivalent metal (Río et al. 2006).

Based on its chemical composition, one of the requirements for the synthesis of HAp is by providing calcium donor which can be taken from natural resources. It is expected that by taking calcium donor from natural resources, we can decrease the cost of HAp production. There are many potential raw materials for calcium donor, one of them is *achatina fulica* shells which are provided in the huge amount in Indonesia. Another natural resource material for calcium donor that is provided in the huge amount in Indonesia is egg shells. Egg shell contains 50.2 % calcium, 12 % magnesium and 21 % natrium (Freire et al. 2000) thus is highly prospected as calcium donor for the synthesis of HAp. However, there is limited study reported on the synthesis of calcium from these natural resources. Both shells are commonly treated as waste product, therefore, synthesis of calcium from this natural sources can support the green environment program in the country.

Calcium from *achatina fulica* shell is provided in the form of two types of calcium carbonate ($CaCO_3$): aragonite and calcite. Aragonite and calcite has similar composition but different crystal structure. The former is easier to be dissolved in sea water and is considered as metastable structure. Therefore, if both of these carbonates exist in the same shell, it is preferable to have calcite at the outer while aragonite at the inner of the shell. However, since the outer shell is normally coated with a protein namely periostracum, the dissolution of this calcium sources can be avoided.

One pertinence method for HAp synthesis from *achatina fulica* shells is the reflux method. It is considered as the development of distillation method and involves the condentation of vapors that is followed with returning of condensate to the origin system. This reflux method is started with drying the shell that is followed with milling to obtain the appropriate raw materials size. This step is very important, because fine particles are required for optimum interface reaction during reflux process. Therefore after milling process, shieving for filtering the appropriate size of the shell powder is required. After that deproteinization is performed by base solution and followed with reflux in weak acid solution. The last step is heat treatment and gelatinization. Heat treatment is important step in reflux method and influences the morphology, crystallinity and surface area of the particles (Khalid et al. 2013). Figure 4 shows the flow chart of HAp synthesis from *achatina fulica* shells.

On the other hand, one option to synthesize HAp from egg shell as calcium donor is by solution combustion method. This method is one of chemical approach for the fabrication of nanomaterials by mixing the oxidizer and fuel and heating up this mixing and ended with calcination of the heated powder. In the beginning, egg shell solution is made with HNO_3 and is followed by mixing the solution with phosphate and other solution (i.e. acid or base). Result of these steps is a transparent gel of HAp. The last step is heat treatment of HAp gel to transform it into powders. In the solution combustion method, common parameters to be optimized are the fuel type, the fuel to oxidizer ratio and initial furnace temperature (Ghosh et al. 2011). Different fuel type might affect on the morphology of the product, whereas

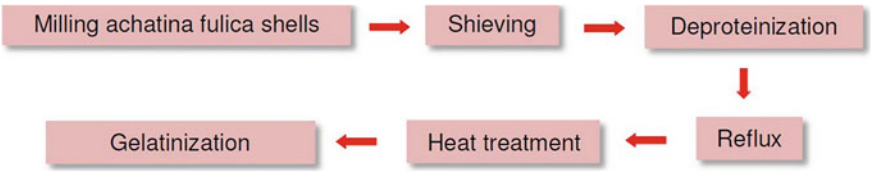

Fig. 4 Flow chart of HAp synthesis from *achatina fulica* shells

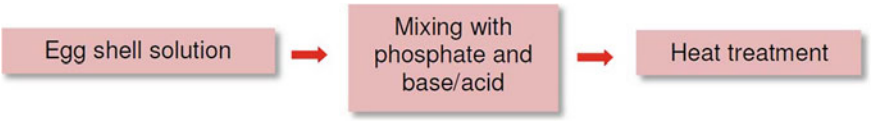

Fig. 5 Flow chart of HAp synthesis from egg shells

different fuel to oxidizer ratio affect the heating temperature and in turn lead to agglomeration of the product. On the other hand, initial temperature has significant effect on the existence of unburnt layer of the synthesan during the process. Figure 5 shows the flow chart of HAp synthesis from egg shell.

3.2 Hydroxyapatite Membranes

Among the important biomaterial membranes is scaffold membrane which is essential for many biological activities. This membrane also important element for the bone transplantation and normally in order to increase the performance of the membrane for this purpose, other materials is required for the growth initiation of new cell, such as by HAp membrane. As in the case of HAp synthesis, it is important to provide raw material for its production in the huge amount in nature, to keep sustainability of production as well as to support the green environment program. Additional important reason related with membrane scaffold application is the egg shell has complex structures that consist of protein fibers, porous structure and connected each other. This raw material is also provided in a huge amount and therefore progressively developed as template for anorganic materials growth.

One of the method to grow HAp membrane utilizing egg membrane as the template is by biomimetic method, a method that imitates model, system or element in nature. In biomimetic synthesis, synthesis of target molecule through a series of reaction and requires intermediate structure. In this case, HAp is the target molecule whereas the egg membrane is the intermediate structure. HAp source can be prepared from SBF solution, where egg membranes are immersed for certain period and through it HAp membranes grow. SBF is a solution with similar chemical composition and concentration to human blood plasma with other condition such as

pH and temperature are also kept identical with this plasma. The solution releases calcium and phosphate during immersion of egg membrane and induces the formation of HAp on the egg membrane. The growth of HAp on the membrane is indicated by the increase of fiber diameter that becomes in order of several micrometres.

Normally, more HAp grows on the egg shell as a function of immersion period in the SBF solution. Several important parameters that affect the formation of HAp membrane by biomimetic method are pre-treatment, heat treatment and template. Among important pre-treatment that accelerate the formation of HAp is by NaOH treatment (Miyazaki et al. 2002). For the case of egg membrane, immersion of egg membrane in NaOH solution increases the porosity size of the membrane. On the other hand, the membrane template might influence the mechanism of formation of the apatite (Sun et al. 2006).

Another way to synthesize HAp membrane is by mixing alginate-chitosan as the membrane template and followed with the growth of HAp on the membrane. Alginate is a substance extracted from seaweed and refer to alginic acid and its derivatives. For the alginate extraction, seaweed is dissolved in a hot solution of sodium carbonate for hours resulting into dissolved sodium alginate and undissolved substance (cellulose) that is subsequently removed. Chitosan is a biobased polymer and produced by deacetylation of chitin. The source of this material is exoskeleton of crustacean, such as crabs and shrimps. This material is biodegradable and biocompatible in nature and can be synthesized into various type of morphology such as membranes, sponges, gels, scaffolds, microparticles, nanoparticles and nanofibers (Anitha et al. 2014). Chitosan has potentiality for various applications such as drug delivery and tissue engineering. Alginate and chitosan have opposite charges, with positive for chitosan and negative for alginate. Therefore, mixing of these substances might create a stable structure with a strong chemical bonding and can produce a membrane template relatively fast with controllable porosities.

For membrane template applications, it should be considered that the membrane has interconnected porosity in order to support cell migration, gas diffusion, nutrition and other functions. The growth of HAp on alginate-chitosan membrane template will increase biocompatibility of the membrane, and therefore improve cell adhesion, the growth and formation of new tissue. As has been explained previously, HAp can be made from SBF solution, such as the famous Kokubo solution (Kokubo et al. 2004). This solution is acellular solution with inorganic ion concentration approaching the extracellular solution in human body. The solution can be prepared by dissolving NaCl, $NaHCO_3$, KCl, $K_2HPO_4 \cdot 3H_2O$, $MgCl_2 \cdot 6H_2O$, $CaCl_2$ and Na_2SO_4 in distilled water, whereas pH of this solution kept at 7.4 and temperature at 36.5 °C (Hayakawa et al. 2000). By this method, immersion time might affect degree of crystallinity of the product, whereas pH of the solution influences the kinetic of HAp formation.

Another potential raw material for HAp membrane template is *hibiscus tiliaceus*, a species of flowering tree which is commonly found in Indonesia. HAp membrane synthesis from this source is started by cleaning the hibiscus tiliaceus raw material,

which is then heated at certain temperature (such as 500–700 °C) for several hours in order to create active carbon membrane support. HAp formed on this membrane by impregnation the membrane in the SBF solution, in the similar way as the case of egg shell and alginate-chitosan membrane previously explained.

4 Other Naturally Derived Biomaterials Processes

4.1 Micro-Capsules

Controlled release of drug in the textile application has been progressively developed in recent years for the purpose of skin care and medication. Coating is the method implemented for this application with a controllable release kinetics by the number of layers in the system (Martin et al. 2013). In addition, initial surface condition of textile fiber should be considered related with incorporation of drug and its release kinetic (Labay et al. 2014). For the purpose of skin care and wound prevention, textile lubrication should also be considered in order to reduce friction against the skin (Gerhardt et al. 2013).

Recently for the controlled released application, textile is coated with micro-capsule that contain active compound. Micro-capsule is a product of encapsulation, where one compound, either in the form of solid, liquid or gas, is wrapped by other compound such as thin film of polymer (Jackson et al. 1991). Commonly, active compound such as drug is wrapped inside the capsule (shell material). Active compound is released through porosities on micro-capsule, which can be due to differences in pH, osmosis pressure, temperature and air pressure. The release can also be due to mechanical loading and self reaction of the active compound, which is a function of time.

Silica is one of raw materials that can be used for micro-capsule due to its biocompatibility characteristics. One of the methods to produce micro-capsule from silica is by mixing emulsion and sol-gel. In this method, three main stages should be performed: precursor preparation, emulsification of precursor and solidification of micro-capsule. As an example, precursor for silica micro-capsule can be made from tetraethyl orthosilicate (TEOS), HCl, dan tetrahydroxybenzophenone (THBP) solutions that are emulsified in siklohexane with the addition of sorbitan monostearate (span 60) as surfactant. HCl is used as acid catalyst whereas THBP is active compound to be encapsulated. The volume of TEOs precursor and the rate of emulsification have significant effect on the morphology and micro-capsule particle size. In addition, increasing TEO concentration might increase the particle size. On the other hand, the addition of surfactant has significant effect on the morphology of silica particle product. Emulsification step will produce micro droplet that in turn is solidified by sol gel reaction. The final product of these processes is encapsulation active compound in the micro-capsule.

One potential application of micro-capsule in drug delivery is for hyperthermia cancer therapy. At this method, cancer tissue is heated within 44–45 °C, temperature at which cancer cell can be destroyed with minimum damage to the normal tissue. For this purpose chemotherapy active substance is attached on nanomagnetic particle and encapsulated by micro-capsule. One requirement for nano-magnetic particle for this application is sufficient biocompatibility. Therefore for this purpose, this nano-magnetic particle is encapsulated with polymer that has sufficient biocompatibility and biodegradability. As an example is producing nano-magnetic particle from $NiCl_2 \cdot 6H_2O$ precursor and encapsulated with alginate and chitosan shell.

For drug delivery applications, core-shell structure of micro-capsule offer variety of advantages in the released controlled of the active substances. One of the famous methods for producing miro-capsule with core-shell structure is by sol-gel method through Stober route utilizing silica template. Stober route process was found in 1968 and obtained by series of reaction between silica precursors with alcohol and water as well as alkali catalyst, which were used to produce homogeneous silica particle in the size of micro-capsule (Stober et al. 1968). In certain case, in order to increase the homogeneity of the silica particle, dispersion particle such as chitosan is added. Chitosan has excellent biocompatibility and increases the absorption of drug and has been applied in various applications such as tissue engineering, drug delivery system, encapsulation and wound healing.

There are various methods to produce micro-capsule such as polymer encapsulating bioactive antioxidant by electrospinning method in the food industries (Fernandez 2009). Another method is electrostatic dry powder coating which can be used in the production of drugs in the pharmaceutical industry, with the particle cores lower than 1 mm (Szafran 2012). In order to coat membranes on the active particles or catalyst and produce micro/mesoporous structure (Membrane Encapsulated Catalysts or MECs), fluidized bed film coating is viewed as a potential method. As an example of this method is by film coating of spherical zeolite particles with a suspension of nano-alumina in hydroxylpropyl cellulose (HPC) to create MECs (Capece 2011).

In addition to the above method, microfluidic technique is a method to encapsulate living cell. Example of micro-capsule for this purpose is alginate hydrogel microparticles which is obtained from double-emulsion template that is produced using microcapillary device (Martinez et al. 2012). Another method is the pressurized carbon dioxide anti-solvent co-precipitation process. As an example of this method is the encapsulation of propolis in the micro-capsule of water soluble poly (ethylene glycol) or PEG (Yang et al. 2014). In addition, another encapsulation in the food industry area is encapsulation of antioxidant and aromas which is usually exist in oil and easily oxidized such as the encapsulation of vegetable oil in powder of maltodextrin and acacia gum by spray drying method (Fuchs et al. 2006).

Fig. 6 Production process of bioactive glass material

4.2 Bioactive Glass for Cancer Treatment

Another important development in biomaterials is bioactive glass for cancer cell detection with the help of Magnetic Resonance Imaging (MRI) apparatus. Bioactive glass such as α-Fe_2O_3 can be used for cancer cell detection due to its paramagnetic characteristics that will be detected by MRI. Bioactive glass is made of raw glass materials such as SiO_2, CaO, Na_2O dan P_2O_5 and are added with Fe_2O_3. Heating these compounds up to their melting temperatures produces calcium ferrite ($CaFe_4O_7$) and α-Fe_2O_3 as bioactive glass ceramic. The process is relatively simple without the need for high-tech apparatus and nano size particles.

There are several steps used to produce bioactive glass starting from mixing raw materials as mentioned above. The mixing composition is then heated up to liquid state and then followed with fast cooling outside the furnace to obtain glass state of the mixing. The next step is milling to produce fine particles of bioactive glass and followed with two stages of heat treatment. The first step of heat treatment is for the nucleation of bioactive glass and the next step is for the growth of the glass, where it is expected that Fe_2O_3 crystallizes become α-Fe_2O_3. Heat treatment can be performed near the glass transition temperature in an oxidizing atmosphere (Eun-Tae Kang et al. 2013). Figure 6 shows the process step to produce bioactive glass material. In the case of laboratory work, for the purpose of simulating the released of α-Fe_2O_3 in the body fluid, the resulted bioactive glass materials is immersed for certain period in SBF. After this immersion, the weight loss of bioactive glass is measured to indicate the released of the glass. During its application, it is expected that the body fluid carries the glass on the cancer cell then covering the cell, by which it can be detected under the MRI. Immersion in the SBF solution can also be used for detecting the biocompatibility of the glass which is indicated by the formation of bioapatite on the glass surface for the bioactive materials.

4.3 Dental Biomaterials

One of the challenge in dental biomaterials is improving the biocompatibility and mechanical property of composite resin. HAp as previously described has excellent biocompatibility but its mechanical property is considered insufficient for composite resin dental application. Therefore, HAp is mixed with other materials such as zirconia-alumina-silica to form a composite of HAp-zirconia-alumina-silica thus can be used as filler in the composite resin dental restoration.

The above composite is synthesized started from preparing each component. Zirconia is prepared from zirconium chloride precursor with isopropyl alcohol as solvent, while alumina is from aluminum nitrate nano-hydrate precursor with aquadest as solvent. Silica is synthesized from tetraethyl orthosilicate (TEOS) precursor with aquadest as solvent. Each precursor is mixed using a template such as *acacia mangium* pulp, then stirred at a controlled pH, aged for hours up to days, cleaned and dried. The last step of this synthesis is sintering with variation temperature and holding time. For the case of HAp, similar process is applied with different precursor, such as $(NH_4)_2PO_4$ precursor and aqua dm as solvent. These three components are mixed with coupling agent (i.e. mixing of trimethoxypropylsilane and chitosan) to increase the adhesion of filler with polymer dental restoration matrix. The last step is mixing the fillers with coupling agent and dental restoration matrix. Figure 7 shows the step of production of dental restoration material.

There are several important parameters affecting the quality of filler material particles such as concentration and type of coupling agent, pH of mixing colloid and crystallinity of the composite substances. The addition of coupling agent, such as chitosan induces a better binding between filler materials and the matrix. Crystallinity of the composite substances significantly affects the mechanical properties of the filler composite, such as hardness, compressive strength, elastic modulus and stiffness. While pH and composite concentration significantly affect the resulted particle size and in turn affect the mechanical properties of the composite particles.

Related to the material resources in Indonesia, zirconia is provided in a huge quantity. However it is still rarely developed for biomaterials purpose due to lack of research on this material. In addition for the perfect application of this material as biomaterial it is preferable to mix with other materials as stabilizer, such as Y_2O_3, CaO, MgO, La_2O_3, and CeO in order to increase the mechanical properties of the material. The result of these composite mixing can also be used for filler in dental restoration applications.

One of the methods to produce nano-particle zirconia with stabilizer such as MgO is by sol-gel method. Zircona can be taken from $ZrCl_4$, while MgO source is $MgSO_4$ with aquadest as the solvent. In order to increase particle distribution, other substances such as chitosan can be added. The mixture is then aged and dried, followed by calcination process. The last step is homogenization of the powder by mortar milling or ultrasonic homogenizer. Figure 8 shows the step of process to produce nano-particle zirconia with stabilizer. Among important parameters that

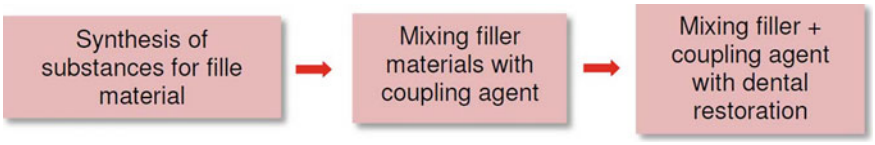

Fig. 7 Production steps of dental restoration material

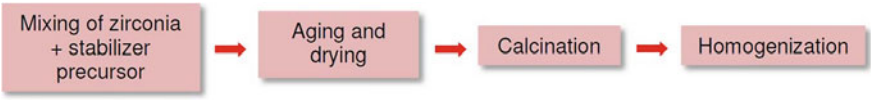

Fig. 8 Production steps of nano-particle zirconia with stabilizer

affect the quality of nano-particle zirconia are calcination temperature, particle distribution and stabilizer composition. Calcination temperature should be determined in order to obtain appropriate particle size, whereas particle distribution is important for the homogeneity mechanical properties. Stabilizer composition affects the particle size of zirconia composite and in turn determines the mechanical properties as well.

4.4 Surface Treatment

Various metals with excellent oxidation resistance such as titanium alloy have been used as implant materials. Additional surface treatment and coating are often applied on its surface to further improve its biocompatibility. Among them are sol-gel and thermal spray methods with HAp, carbon, titania and hydrogel titanate as the coating materials.

For the HAp coating, one of new potential thermal spray methods is high-velocity oxy fuel (HVOF) process (Ramdan 2014). The method is expected to give better degree of crystallinity of HAp and increase the bonding strength with the metal surface (Lima 2005; Gaona 2007). Intermediate layers such as titania and carbon nanotube, are often used to facilitate this bonding. In order to coat HAp on metal implant by HVOF method, a careful surface preparation is required. A series of grinding, polishing or sand blasting is normally performed in order to create flat surface with sufficient roughness to allow a good mechanical interlocking. The oxide layer on titanium alloy should be removed to enhance adhesion property. This can be done by chemical etching that also gives additional contour on the metal surface. Apart of the surface preparation, the precursor for coating, HAp powders, should have sufficient flow ability in dry condition.

HAp coating with HVOF process is very fast and can be accomplished in 10 s. Therefore no diffusion of HAp will take place into the metal substrate leaving the possible bonding mechanism only for mechanical interlocking. In order to increase the bonding strength between HAp and the metal substrate, post-annealing treatment can be performed subsequently. This additional treatment might induce a diffusion of HAp into the metal substrate. Figure 9 shows one optional of HAp coating on the metal substrate by HVOF process.

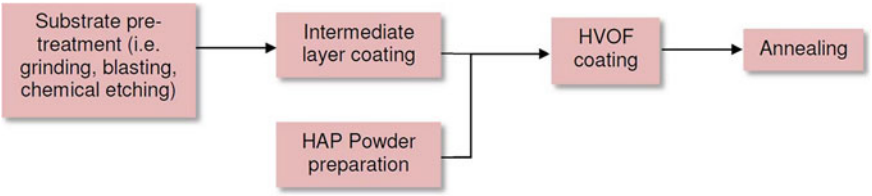

Fig. 9 Flow chart of HAp coating on metal substrate by HVOF method

Another surface treatment to increase biocompatibility of metal implant is by coating with carbon layer. It can be done by dip coat the metal in a carbon suspension. Before the process, as in the case of HVOF coating, several substrate preparation should be done such as grinding, ultrasonic cleaning and an optional immersion in a coupling agent such as chitosan that enhances the adhesion of carbon layer on the metal surface. After that, coating is performed by dipping the metal substrate into the carbon suspension followed by drying. The last step is sintering the coated sample in order to create adhesion between the substrate and carbon. The carbon coated metal surface will allow an easier growth of HAp during biomimetic process in SBF compared to non-coated metal. Figure 10 shows a flow chart of HAp coating by biomimetic process with carbon as intermediate layer.

Another pre-treatment that can be done to enhance HAp biomimetic coating process is by introducing hydrogel titanate intermediate layer through alkali treatment. For the alkali treatment, metal substrate is immersed in NaOH solution to produce hydrogel titanate ($HTiO_3^- \cdot nH_2O$) that is obtained from the reaction between TiO_2 and hydroxyl ion from NaOH. After the immersion process, the metal is heat treated to dehydrate the hydrogel titanate and form a stable sodium titanate ($Na_2Ti_6O_{13}$). Heat treatment can also induce better bioactivity of the alkali treated layer (Lu et al. 2012). After that, immersion in SBF is performed to grow HAp layer on the treated metal surface. Figure 11 shows a flow chart of biomimetic coating of HAp with substrate preparation by alkali treatment.

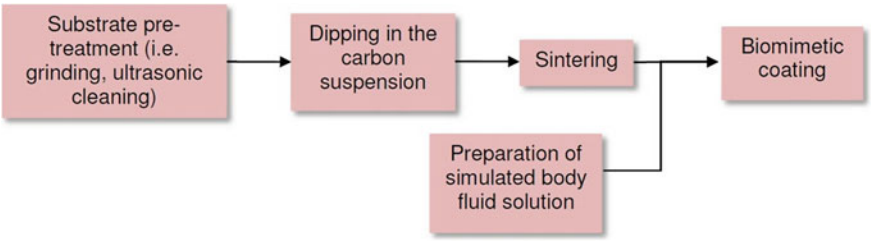

Fig. 10 Flow chart of biomimetic coating of HAp on metal substrate with pre-treatment by dipping in the carbon suspension

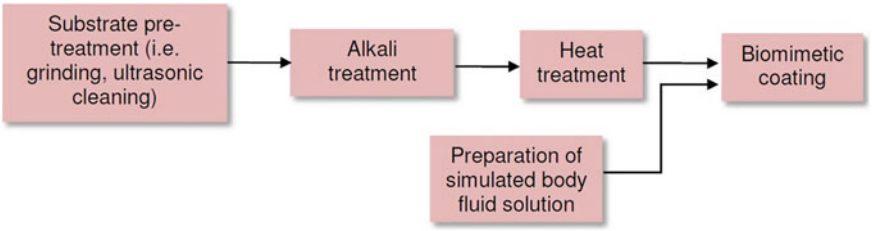

Fig. 11 Flow chart of HAp biomimetic coating on metal substrate with pre-treatment by alkali treatment

5 Perspective

The undoubtful rich Indonesian biodiversity, both its rainforests and coral reefs, has been viewed as the unlimited source of naturally inspired and derived biomaterials. The authors' view on utilization of this biodiversity is not as the source for industrial exploitation of biomaterials synthesis, but rather for learning from the Nature in finding useful biomaterials for the benefit of humanity. This biodiversity must be used wisely and intelligently. It must be conserved. The tragic rapid loss of Indonesia's biologically wealthy rainforests and the increase of threatened native mammals and the destructive exploitation of coral reefs must be prevented.

The utilization of natural resource materials, which are specific yet abundantly available in Indonesia, for biomaterial applications necessitates additional steps to the currently established conventional synthesis methods. These steps have been successfully developed at a lab scale with suitable controlling parameters resulting into the optimum overall synthesis processes. Further optimization and fine tuning on the parameters are required to translate the innovation into a commercial scale. More efforts from biomaterial researchers and a supportive policy from the Government are essentially needed to foster the development of biomaterial and its applied technology resulting into low-cost yet effective medical devices to support the national health care program.

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