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GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

SOL-GEL SYNTHESIZED 45S5 BIOACTIVE POWDER AND GLASS CERAMICS

CAN ORAL

A THESIS SUBMITTED FOR THE DEGREE OF

MASTER OF SCIENCE

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PROF. DR. AHMET YAVUZ ORAL

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T.C.
GEBZE TEKNİK ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ

45S5 BIYOAKTİF TOZ VE CAM SERAMİKLERIN SOL-JEL YÖNTEMİYLE SENTEZLENMESİ

CAN ORAL
YÜKSEK LİSANS TEZİ
MALZEME BİLİMİ VE MÜHENDİSLİĞİ ANABİLİM DALI

TEZ DANIŞMANI
PROF. DR. AHMET YAVUZ ORAL

GEBZE
2020

GEBZE TEKNİK ÜNİVERSİTESİ	**YÜKSEK LİSANS JÜRİ ONAY FORMU**

GTÜ Fen Bilimleri Enstitüsü Yönetim Kurulu'nun 29/01/2020 tarih ve 2020/07sayılı kararıyla oluşturulan jüri tarafından 03/02/2020 tarihinde tez savunma sınavı yapılan Can ORAL'ın tez çalışması Malzeme Bilimi ve Mühendisliği Anabilim Dalında YÜKSEK LİSANS tezi olarak kabul edilmiştir.

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...../...../..... tarih ve ...../..... sayılı kararı.

SUMMARY

Bioglasses are the first known biocompatible materials. It is a bioactive material widely used in tissue engineering and scaffolds for implants. Although quaternary bioglass is a biocompatible glass with changing compositions of SiO_2, CaO, M_xO_y (metal oxide) and P_2O_5, a 45 wt.% ratio of Si and a 5:1 molar ratio of Ca/P should be maintained to acquire 45S5 Bioglass.

45S5 Bioactive glasses and glass-ceramics are produced traditionally via melt-quenching method. Implementation of sol-gel method allows us to synthesize this material at lower temperatures. The foremost sought conclusion of this thesis is to find if it is possible to synthesize 45S5 Bioglasses and related glass-ceramics with a different phosphorous (P) precursor via sol-gel method.

Porous microstructure caused by sol-gel method of bioactive glass and ceramics usually have improved properties other than the production of glasses and glass-ceramics at lower temperatures. 45S5 bioactive glass with weight ratios of 45% SiO_2-24.5% Na_2O-24.5% CaO-6% P_2O_5, will tried to be synthesized by the sol-gel technique. The precursors used for synthesizing the bioglass are tetraethyl ortho-silicate (TEOS), $Si(OC_2O_5)_4$, as the source of silica; sodium nitrate ($NaNO_3$), as the source of sodium oxide; calcium nitrate tetrahydrate, $Ca(NO_3)_2 . 4H_2O$, as the source of calcium oxide and finally, dibutyl phosphate, $C_8H_{18}O_3P$, instead of tri-ethyl phosphate (TEP), $(C_2H_5)_3PO_4$ as precursors for phosphorus pentoxide.

Solutions prepared with dibutyl phosphate while maintaining 5:1 Ca/P ratio with acidic catalyzers (i.e. nitric acid or acetic acid) will be aged and dried. Dried gels obtained after this procedure, will be grinded. After heat treating the samples, glass-ceramic powders will be obtained and these samples will be further analyzed via XRD, SEM and EDS.

Key Words: 45S5, Bioglass, Glass-Ceramic, Sol-gel, Dibutyl Phosphate, Biocompatibility .

ÖZET

Biyocamlar bilinen ilk biyouyumlu malzemelerdir. Doku mühendisliğinde ve implantlarda yaygın olarak kullanılan biyoaktif bir malzemedir. Kuaterner biyo-cam, değişen SiO_2, CaO, M_xO_y (metal oksit) ve P_2O_5 bileşimlerine sahip biyouyumlu bir cam olmasına rağmen, 45S5 Bioglass elde etmek için ağırlıkça% 45 oranında Si ve 5:1 Ca/P molar oranı muhafaza edilmelidir.

45S5 Biyoaktif camlar ve cam-seramikler geleneksel olarak ergitme-suverme yöntemi ile üretilmektedir. Sol-gel yönteminin uygulanması, bu malzemeyi daha düşük sıcaklıklarda sentezlememizi sağlar. Bu tezin en çok aranan sonucu, 45S5 Bioglass ve ilgili cam seramiklerin farklı bir fosfor (P) öncüsü ile sol-gel yöntemi ile sentezlenmesinin mümkün olup olmadığını bulmaktır.

Biyoaktif cam ve seramiklerin sol-jel yönteminin neden olduğu gözenekli mikroyapı genellikle düşük sıcaklıklarda cam ve cam-seramik üretimi dışında gelişmiş özelliklere sahiptir. Ağırlık oranları %45 SiO_2-%24.5 Na_2O-%24 CaO-%6 P_2O_5 olan 45S5 biyoaktif cam, sol-jel tekniği ile sentezlenmeye çalışılacaktır. Biyocamın sentezlenmesi için kullanılan öncüler, silika kaynağı olarak tetraetil orto-silikat (TEOS), $Si(OC_2O_5)_4$; sodyum oksit kaynağı olarak sodyum nitrat ($NaNO_3$); kalsiyum nitrat tetrahidrat, $Ca(NO_3)_2 \cdot 4H_2O$, kalsiyum oksit kaynağı olarak ve son olarak, fosfor pentoksit öncüleri olarak, tri-etil fosfat (TEP), $(C_2H_5)_3PO_4$ yerine, dibütil fosfat, $C_8H_{18}O_3P$'dır.

Asidik katalizörler (yani nitrik asit veya asetik asit) ile 5:1 Ca/P oranı korunurken dibutil fosfat ile hazırlanan çözeltiler eskimiş ve kurutulacaktır. Bu işlemden sonra elde edilen kurutulmuş jeller öğütülecektir. Numunelerin ısıl işlemden geçirilmesinden sonra, cam-seramik tozları elde edilecek ve bu numuneler XRD, SEM ve EDS ile daha analiz edilecektir.

Anahtar Kelimeler: 45S5, Biyocam, Cam-Seramik, Sol-jel , Dibüthil Fosfat, Biyouyumluluk.

ACKNOWLEDGEMENTS

First of and foremost, I would like to thank my academic advisor, Prof. Dr. Ahmet Yavuz ORAL for his guidance and encouragement with his immense knowledge and for giving me this opportunity to discover myself.

Besides my advisor, I would like to thank to Mehmet SEZER, Seda KOL, Mehmet Emre AKÖZ, Vala Can AŞKAN, Onur Alp AKSAN, Adem ŞEN and Ahmet NAZIM for their contribution, collaboration and help during this time range to face each and every problem together as a wonderful team.

I am also grateful and thankful to my beloved wife Aylin ORAL for his valuable support and to my friends; Mustafa Yunus KAYA and Hüseyin Alptekin SARI who are encouraging and motivating me all the time to be able to face all my difficulties.

This study thought me that I can overcome and accomplish everything by working hard, planning and believing. From now on I promise that I will always improve myself.

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LIST of ABBREVIATIONS and ACRONYMS

Abbreviations and Acronyms	**Explanations**
º	Degree
Ɵ	Theta
µm	Micrometer
nm	Nanometer
M	Molarity
C	Celsius
Ca	Calcium
P	Phosphorus
Na	Sodium
NaN	Sodium Nitrate
CaNT	Calcium Nitrate Tetrahydrate
HP	Hydroxyapatite
HCP	Hydroxycarbonateapatite
XRD	X-Ray Diffraction
SEM	Scanning Electron Microscope
EDS	Electro Dispersive Spectrum
h	Hour
ml	Milliliter

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1. INTRODUCTION

Materials designed for the use in conjunction with the living body are called “Biomaterials”. In medical appliances, specific properties are required from these materials such as; mechanical compatibility and toughness for the physical movements, biocompatibility (non-toxicity), bioinertness (corrosion resistance), bone reconstruction and substitution [1].

Biomaterials are grouped as metals, ceramics, polymers and composites. Ceramics that are used as reconstructive or substitutive purposes in body are known as “bioceramics” [2]. Bioceramics can be synthesized as bioactive glasses, bioactive glass-ceramics, polycrystalline ceramics (i.e. hydroxyapatite) and bioactive composites [3].

Metals (i.e. Sodium (Na), Zinc (Zn), Aluminum (Al)…), calcium (Ca) and phosphate (P) containing oxide systems are known as “Bioglasses”. Their controllable chemical properties, high bonding capabilities with tissues and bones coupled with easy to manufacture required shape and size, makes bioglasses a top candidate for biomedical applications [4]. Produced by crystallization of suitable glasses with poly crystalline structured materials that react with bone and tissues are known as “bioactive glass-ceramics”. Their mechanical properties make them more suitable for high load bearing applications such as bone reconstructions or replacements.

In this study; 45S5 Bioglasses and Glass-ceramics are tried to be obtained via Sol-Gel instead of melt-quenching as in commercial use with Dibutyl Phosphate (Di-P); a known reagent in the synthesis of Hydroxyapatite (HA), synthesized samples characterized with X-ray Diffraction Diffractometer (XRD), Scanning Electron microscope (SEM) and Energy Dispersive Spectrometer (EDS). Differences caused by changes in the amount and types of catalyzers are investigated.

2. BIOMATERIALS

Other than medications, synthetic or natural all materials used in conjunction with body tissues to adjust, treat or cure any conditions; ailment or damages alike, are biomaterials. They are in continuous or cyclic contact with the body tissues and fluids. During this contact, they should not cause any unwanted ramifications. The researchers used the terms “biomaterials” and “biocompatibility” to indicate the biological performance of the materials. Biocompatible materials are named as biomaterials, and biocompatibility is defined as the ability of the material to respond appropriately to the body system. Biocompatibility is the most important feature of a biomaterial. Biocompatible biomaterials are materials that do not interfere with the normal development of the surrounding tissues and do not cause unwanted reactions such as inflammation or clot formation in the body [1-6].

Biomaterials used in the medical field can be grouped into two groups: biomaterials to replace hard tissue and to replace soft tissue. However, such a grouping may not always apply. For example; a hip replacement and a heart valve may consist of both polymer and metal [2].

2.1. Properties of Biomaterials

Biomaterials must satisfy following specifications for them to be used a long time without any complications.

2.1.1. Biocompatibility

Biocompatibility is the most incontrovertible feature of a biomaterial. It is a concept that expresses the biological performance of a foreign material contained in a living organism in contact with organs or tissues. Biocompatible materials are materials that do not interfere with the normal development of the surrounding tissue and do not cause harmful reactions in the body. Biocompatibility is defined in two ways, structural and surface compatibility. Physical, chemical and biological

compatibility of the material to the texture is the surface and the mechanical adaptation of the material to the body tissue is the structural biocompatibility [3].

2.1.2. Bioactivity

Bioactive materials are those which form a special biological reaction at the interface of the material, which provides the formation of a bond between the material and the tissue. A biocompatible material might not be bioactive by definition [7].

2.1.3. Mechanical Properties

One of the most important features for the design of implants after biocompatibility is that the elastic and mechanical properties of the implant and bone to match. The mechanical properties of the material such as modulus of elasticity, compression and bending strength should be close to that of the bone [2,8-10].

2.1.4. Chemical Resistance

Another issue to be considered for biomaterials is corrosion. Body environment is a variable environment that causes wear to the implant. The products that will be formed as a result of abrasion or corrosion might pose a danger to the body. The high mechanical or chemical wear resistances of the materials used provide great convenience in medical applications [8].

2.2. Categorization of Biomaterials

Biomaterials are divided into 4 major groups as;

- Metallic biomaterials,
- Ceramic biomaterials,
- Polymeric biomaterials,
- Composite biomaterials.

2.2.1. Metallic Biomaterials

Metals and metal alloy materials are preferred as biomaterials because of their strong metallic bonds, their durability, ease of production and resistance to wear. On the other hand, they have some major disadvantages such as, usually very low biocompatibility, susceptibility to corrosion, being very hard compared to tissues and cause allergic reactions or toxicity that may cause due to metal ion releases from these implants [2,7,8].

2.2.2. Polymeric Biomaterials

Polymers have a wide range of uses as biomaterials as they can be prepared in many different compositions and shapes. For some medical applications their mechanical strength is below average. They can also swell up from body fluids or may cause toxicity. Due to their flexible structures and good biocompatibilities, they are frequently preferred as implants [9,11,12].

2.2.3. Composite Biomaterials

The materials that is biocompatible and formed as a result of combining two or more materials with different physical or chemical structures in order to eliminate their, some if not all, weaknesses of each other are called "composite biomaterials" [2,13]. General use of bioceramics in human body is shown in Fig.2.1 [3].

2.2.4. Ceramic Biomaterials

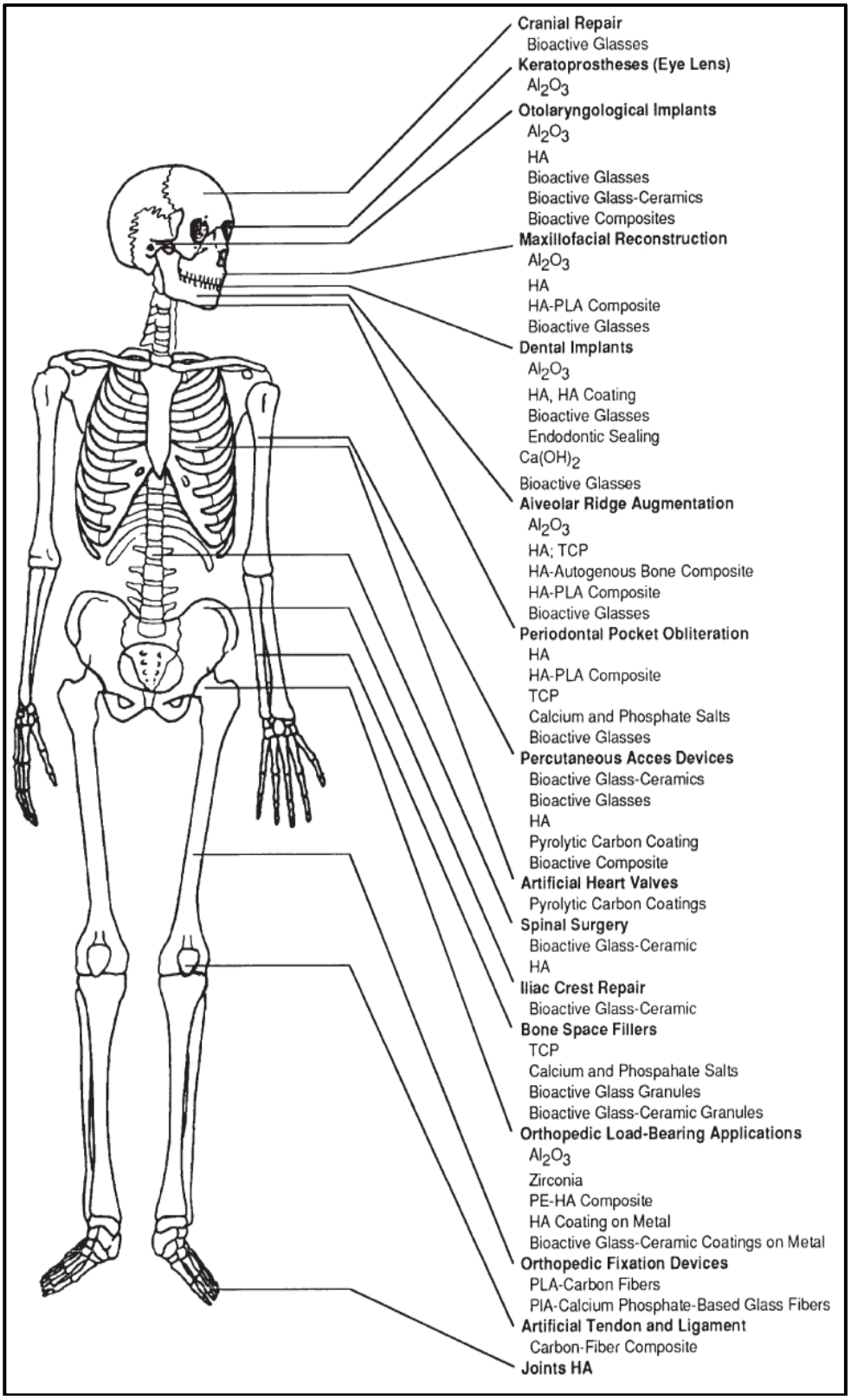

Fig 2.1: Uses of bioceramic materials in human body.

Specially designed glasses, ceramics and glass-ceramics are called bioceramics to enhance bodily functions. Bioceramics could be used in different areas of the body according to their properties palate. They can be grouped under 3 major categorizes [3-10].

2.2.4.1. Bioinert Ceramics

Implants that are isolated from the rest of the body by the tissue formed after their application and do not to react with the body or the bodily fluids are under this group such as Alumina and Zirconia, which are used for their toughness while being biocompatible and bioinert respectively [14,15].

2.2.4.2. Biodegradable Ceramics

After completing their purposes, these materials degrade and dissolve in the surrounding tissues and after degradation they became indistinguishable inside the body. These materials are known to form bone structure while degrading [10, 16].

2.2.4.3. Bioactive Ceramics

Materials that cause a bond due to chemical reactions on the interface between the tissue and the material and produce specific reactions are known as bioactive materials such as i.e. Hydroxyapatite, bioglasses, bioactive glass-ceramics [17].

2.3. Bioglasses and Glass-Ceramics

2.3.1. Bioactive Glasses

Bioactive glasses are biomaterials where chemical bonding occurs between tissue and implant as a result of the replacement of some silica groups in the body with calcium and phosphorus [18]. Bioactive glasses have high bioactivity. However, the areas of use of bioactive glasses with low fracture toughness have been limited to medical applications requiring low strength.

The ability to control the chemical properties and bonding of biomass to tissues is the main feature that distinguishes these materials from other bioactive ceramics and glass-ceramics. For any medical application, it is possible to design a desired type of bioglass. This also applies to bioactive glass-ceramics; however, they find a more limited application area due to their heterogeneous microstructures [19].

The three most important differences that distinguish bioactive glasses from ordinary commercial glasses in terms of chemical composition are the low percentage of SiO_2 (below 60%), high Na_2O and CaO accompanied with high CaO/P_2O_5 ratio [20,21].

Due to these properties, the surface of the material placed in a liquid medium is highly reactive. The main components in many bioactive glasses are SiO_2, Na_2O, CaO and P_2O_5. The first and so far the best resulted bioactive glass composition is 45S5. All the classified compositions are shown with codes associated with the types of compositions. Many bioactive silicate glasses created later are based on the formula given with code 45S5. It contains 45% SiO_2 by weight and the Ca/P ratio is 5: 1. It is not possible to connect to bone with lower CaO/P_2O_5 ratios [22].

The composition of the first bioactive glass created and tested by Hench and Ethridge is given in Table 2.1. [23].

Table 2.1: Composition of 45S5.

Component	SiO_2	CaO	Na_2O	P_2O_5
Wt. %	45.0	24.5	24.5	6.0

The composition is chosen for being very close to a ternary eutectic point, making it easy to melt [7].

Amorphous structure of 45S5 can be seen in Fig.2.3[24].

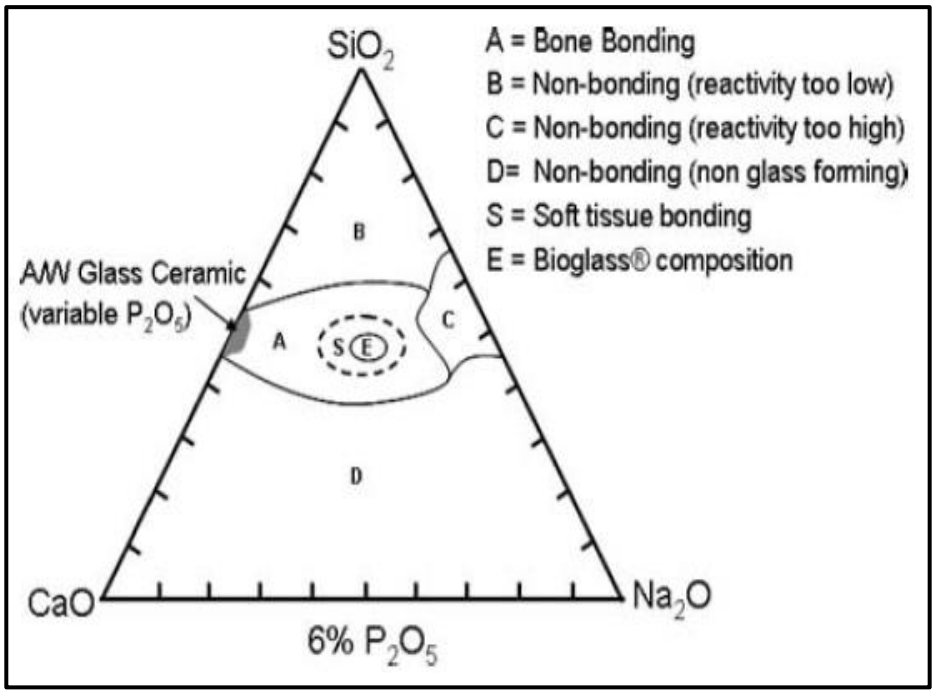

Fig 2.2: Composition of bioglasses.

Phosphate in the content of bioactive glass ensures that the glass is bioactive. The role of phosphate in bioactive glass only arises when it helps nucleate the calcium phosphate phase on the surface. When a large amount of P_2O_5 is present in the glass, bone binding does not occur. Silicate content, on the other hand, ensures that the glass is fully melted and homogenized [16,17].

The most important properties of bioactive glasses besides bioactivity; they have amorphous structure and relative mechanical weaknesses. The bioactivity of bioactive glasses is higher than hydroxyapatite bioactive ceramic [3].

Bioactive glasses have low mechanical properties that cannot be used in heavy load applications. However, they can be used as a coating despite their deficiencies such as low strength [3].

Hench used the term "bioactive glass" to describe the interfacial binding between tissue and implant [3]. The most common feature of these materials is that they form a carbonate hydroxyapatite (HCA) layer on the surface, first described by Hench [23] and then Davies [25].

Interfacial reactions of formation HCA on the interface of bioglasses is shown in the Table 2.2 below [3].

Table 2.2: Interfacial reactions of formation HCA on the interface of bioglasses.

Stages	Reactions
1	Exchange of Na^+ or Ca^{+2} with H^+ or H_3O^+ from solution: $Si–O–Na^+ + H^+ + OH^- \rightarrow Si–OH + Na^+ + OH^-$
2	Loss of soluble silica in the form of $Si(OH)_4$ to the solution resulting from breakage of Si–O–Si bonds and formation of Si–OH at the glass/solution interface: $Si–O–Si + H_2O \rightarrow Si–OH + OH–Si$
3	Condensation and repolymerization of a SiO_2-rich layer on the surface depleted in alkalis and alkaline-earth cations: (RO)3–Si–OH + HO–Si–(OR)3→(RO)3–Si–O–(OR)3 + H2O
4	Migration of Ca^{+2} and PO^{-3} 4 groups to the surface through the SiO_2-rich layer forming a $CaO–P_2O_5$-rich film on top of the SiO_2-rich layer, followed by growth of the amorphous $CaO–P_2O_5$-rich film by incorporation of soluble calcium and phosphates from solution.
5	Crystallization of the amorphous $CaO–P_2O_5$ film by incorporation of OH^- or CO^{-3} anions from solution to form a mixed hydroxyl-carbonate apatite layer.
6	Agglomeration and chemical bonding of biological moieties in the HCA layer

The basis of the ability of biomaterials to bind to the bone are chemical reactions that occur between the material and body fluid. Chemical reactions occur as a result of the formation of the HCA layer to which the bone can be attached. Binding occurs as a result of back-to-back reactions. The most important of these are solid state reactions; The formation of Si-OH groups in the first kinetic reaction, the development of the SiO_2 layer on the glass surface, the formation of amorphous calcium phosphate in this layer and the formation of HCA on the surface. In the first stage, H^+ or H_3O^+ and Na^+ ions are separated from the surface of the glass. This reaction takes place very quickly and causes the pH to rise above 7.4. With the dissolution of the network structure and the movement of hydroxyl ions, the breaking of the -Si-O-Si-O-Si- bonds takes place at the same time. Fracture takes place regionally and causes silica to be released in solution as silicic acid [$Si(OH)_4$]. At this stage, with the loss of sodium, $Si(OH)_4$ groups are formed in the surface layer rich in silica and distortions are seen in the silica bonds. The formed surface layer has a very porous structure. Calcium and phosphate ions provide the formation of amorphous calcium phosphate layer on the surface of

the glass. The calcium phosphate layer is usually located above the silica structure and crystallizes in the HCA structure by the combination of carbonate ions from the α-CaP phase in the solution. The nucleation and growth mechanism of HCA is accelerated by the presence of hydrated silica on the surface. Since this surface is chemically and structurally very close to natural bone, it is possible to bind body tissues to the surface. As the reaction continues, the HCA surface layer grows to 100 μm to form the binding site. This thickness in the HCA layer creates a suitable interface for bioactive binding between the tissue and the implant to continue. These reactions take place within the first 12-24 hours after the material is placed. The first 5 stages are completed with the reactions formed on the material interface. Binding to the tissues takes place at the 6th stage [3,4].

2.3.1.1. Production of Bioactive Glasses

Known glass production methods are used for bioactive glass production. Raw materials should be pure. The properties of glass vary depending on the raw materials. Processes such as mixing, melting, homogenization and shaping the glass should be done by preventing foreign substances from mixing and without losing the volatile components. Samples can be formed by casting or injection molding. Softening annealing takes place in the critical temperature range of 450-550°C due to the high thermal expansion coefficients of bioactive glass compositions.

Another way to produce bioactive glass is sol-gel method. Glass production using the sol-gel method consists of 4 stages: mixing, gelling, aging and drying usually followed by a heat treatment [26].

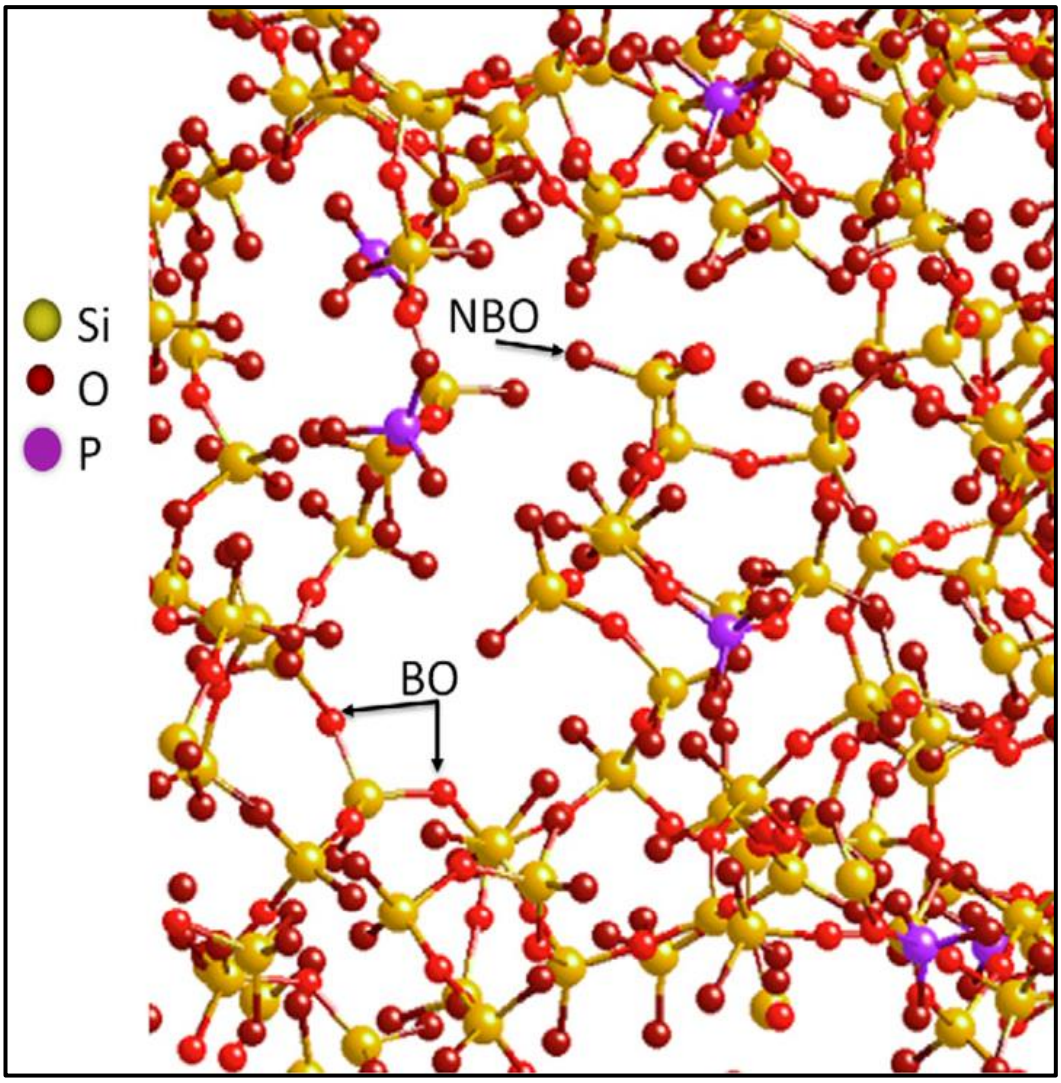

Fig 2.3: Amorphous structure of 45S5 Bioglasses; NBO: Non-binding BO: Binding Oxygen atoms.

2.3.2. Bioactive Glass-Ceramics

Glass-ceramic is a multi-crystalline material produced by controlled crystallization of glasses suitable for crystallization. Glass-ceramics, which are designed for medical purposes and form strong bonds by reacting with tissues and / or bones, are known as bioactive glass-ceramics.

The fact that glass-ceramics are bioactive is the most important factor that enables them to be used as implants. Today, glass-ceramics with very good bioactivity, such as glass-ceramics containing apatite crystal phase, have been developed. For this reason, researchers have focused on increasing the strength and workability of materials [27].

The most important bioactive glass-ceramic, apatite and volastonite ($CaOSiO_2$) crystals and residual CaO-SiO_2 rich glass matrix are the three phase silica phosphate materials used for medical purposes. This material was named apatite/volastonite (A/W) glass-ceramic by Yamamuro [27] and Kokubo [28]. Bioactive A/W glass-ceramic has excellent mechanical properties and forms a very high interfacial bond strength with bone.

Bioactive glass-ceramics contain less SiO_2 and more CaO than traditional glass-ceramic systems. P_2O_5 is generally used as a nucleate in bioactive glass-ceramics. Especially in order to produce bioactive glass-ceramic materials with apatite crystal phase, P_2O_5 content can be increased over %30 or even %40.

2.3.2.1. Production of Bioactive Glass-Ceramics

Bioactive glass-ceramics can be produced with a variety of methods, plasma spraying being the most widely used one.

The most known method in glass-ceramic production is the classical glass-ceramic production method. This method; consists of preparing a homogeneous glass, giving the desired shape to the glass and transforming the glass into glass-ceramic by controlled crystallization process. Nucleation of phases and controlled crystal growth occur as a result of controlled heat treatment.

Another production method of glasses and glass-ceramics is sol-gel technique. In this method, unlike traditional glass production, it is based on solutions at room temperature rather than melting at high temperatures. Generally, alkoxides and metal salts are used as starting materials. The solutions prepared by mixing with water, acid or alcohol turn into gel as a result of hydrolysis and condensation reactions. Then, the gels are transformed into glass by heat treatment. Glass-ceramic is produced by pressing and sintering amorphous powders obtained by sol-gel method.

3. SOL-GEL

Sol-gel method; is a technique in which materials such as glass, ceramics and composites can be produced for various application areas by preparing the solution, gelling and removing the solvent from the system. This method makes it possible to control the grain size, layer thickness, particle distribution of different structure and composition of the produced materials. Sol is a suspension of colloidal (1-100 nm diameter solid particles) particles formed in a liquid. These particles form a network structure in solution as a result of various reactions. If it is gel; it is a linked polymeric chain of continuous web, having an average length of more than 1 micrometer.

Thanks to the sol-gel method, homogeneous and high purity materials can be produced at lower temperatures. Figure 3.1 shows the sol-gel method and the types of materials that can be produced [29].

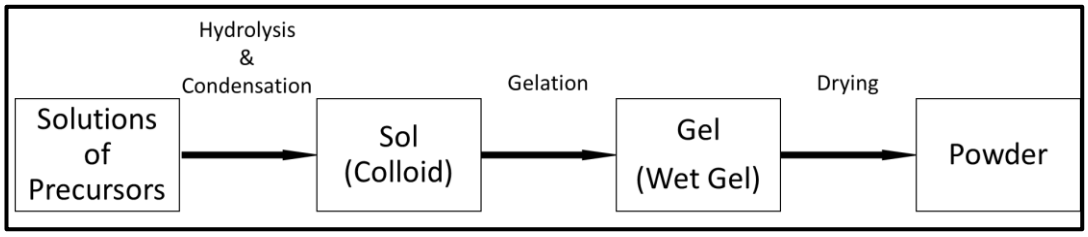

Fig 3.1: Sol-gel process.

Metallic salts and metal alkoxides are used as starting materials in the sol-gel method. Examples of metal salts are compounds such as $HfCl_4$, $AlCl_3$. Metal alkoxides, which can easily react with water, are known as the best starting materials due to these properties.

The solvents to be used are determined according to the chemical structure of the starting materials used in the sol-gel method. While alcohol is used as solvent for metal alkoxides, water is used for some oxides and ceramics. Catalysts are only materials that speed up the reaction without reacting. Sol-gel treatment takes place in six stages:

- Hydrolysis
- Condensation

- Polymerization
- Gelling
- Aging
- Drying

3.1. Steps of Sol-Gel

3.1.1. Hydrolysis

In alkoxide hydrolysis, the negatively charged OH- group is added to the positively charged metal ion. The positively charged proton passes into the alkoxyl group and ROH is released. The reaction is bi-directional. On the one hand, water molecules are released and hydroxide bonding, i.e., gelling takes place, on the other hand, cointegration occurs. Hydrolysis may vary depending on the desired product. In general, it can be expressed as follows

$$M(OR)_x + xH_2O \rightarrow M(OH)_x + xROH \tag{3.1}$$

Here ROH is a by-product. It can be removed from the environment by evaporation. All of the metal alkoxides, except silicon and phosphorus, are instantly hydrolyzed to hydroxide or oxide. Acid or base catalyst is required for the hydrolysis of silicon alkoxides. Still, the reaction is slow.

The change in the reaction rate can lead to deterioration of the homogeneity of the product obtained, especially when it takes place in the hydrolysis phase. Various factors such as water amount, catalyst type, solvent concentration and temperature affect the rate of the hydrolysis reaction [30].

3.1.2. Condensation

The products resulting from hydrolysis build an oxygen bridge in the condensation reaction.

- Water released condensation:

$$M\text{-}OH + M\text{-}OH \rightarrow M\text{-}O\text{-}M + H_2O \quad (3.2)$$

- Alcohol released condensation:

$$M\text{-}OR + M\text{-}OH \rightarrow M\text{-}O\text{-}M + ROH \quad (3.3)$$

As a result of these reactions, the products are hydrolyzed or recombined and condensed [31].

3.1.3. Polymerization

In the sol-gel method, the polymerization reaction takes place in three stages:

1. Formation of particles as a result of polymerization of monomers,
2. Growth of the formed particles,
3. It is the process of connecting the particles in a chain and then thickening and gelling by forming a network structure in the liquid.

pH, temperature, reaction time, aging temperature, aging time, concentration, catalyst and amount of catalyst are effective in the formation of the polymerization process [32,33].

3.1.4. Gelation

As a result of hydrolysis and condensation reactions, the bonds between particles form clustered gel at a single large cluster. At this gel point, the viscosity of the solution rises very quickly, but its flexibility decreases. No endothermic, exothermic or any chemical changes occur during the gelling phase, only a sudden increase in viscosity occurs [30-34].

Since the gelling phenomenon occurs when hydrolysis and condensation reactions occur, all factors affecting these reactions also affect gelling. Depending on

the reaction rate and shape, the resulting gel and thus the microstructure of the final product can be controlled [35,36].

3.1.5. Aging

Aging is the stage after gelling in the sol-gel method. At this stage, the structure of the semi-stable gel turns into a stable structure. The length of this procedure can take hours or days, depending on the structure of the gel. The longer this period, the more stable and denser structure occurs. During this period, properties such as pore size and internal structure continue to change as the condensation continues. Due to this step, the thickness of the structure increases and the rate of porosity decreases [37,38].

3.1.6. Drying

Drying in gels can be explained as removing the excess solvent from the structure. After the formation of the gel, it is very important to dry it without allowing crack formation. Breaks during drying occur due to capillary forces. In the drying process, the stresses caused by the volume change and the capillary forces in the gel pores should be at the lowest level.

During the drying of the gel, the gel shrinks and there are large amount of pores in the solid formed. While some of the solvent remaining during the drying process evaporates, the pores of the formed solid remain wet. At this stage, the overall size of the sol-gel solution is significantly reduced, and as a result, a stable solid with water particles trapped in the pore structure is obtained [39].

3.2. Factors Affecting Sol-gel Method

The properties of sol-gel matrix such as porosity, surface area, polarity and hardness are affected largely by hydrolysis and condensation reactions, selection of precursor materials, pH of the sol, structure and concentration of the catalyst, water-precursor material molar ratio , solvent, temperature, aging and drying.

Attention should be paid to the selection of precursors to control the condensation rate and prevent the system from sedimentation. Metal alkoxides are the most important precursor materials.

The type of catalysts that play an important role in the sol-gel method affects the structure and morphology of the resulting sol-gel products. Catalysts determine the speed of the process by changing the rate of hydrolysis. The strength and concentration of the catalyst type affect the hydrolysis reaction. Acidic catalysts produce linear polymers, while basic catalysts produce highly dense particulate structures. In addition, when using the basic catalyst, the condensation reaction takes place faster, while using the acidic catalyst, the hydrolysis of the alkoxide precursors takes place faster.

The solvent must be carefully selected so that the sol-gel process is not obstructed, unwanted side reactions are avoided and all chemical components are homogeneously combined. Therefore, depending on the compatibility of the precursors and active organic binders, more than one solvent is often used in the sol-gel method.

The rate of water-precursor in the sol solution plays an important role in the reaction rate and the physical properties of the materials to be produced. The hydrolysis reaction is accelerated by increasing the water-alkoxide ratio (R) [40].

3.3. Advantages and Disadvantages of Sol-Gel Method

Advantages of the sol-gel method:

- In this method, since the processes usually take place at low temperatures, the risk of thermal decomposition is very low.
- Very high purity glass can be produced.
- It is easy to interfere with chemical reactions. Pore size and mechanical strength can be controlled.
- Loss due to evaporation is prevented by production at low temperatures.
- Sol-gel method can be applied to various compositions. In addition, compositions that cannot be produced due to phase separation and

crystallization occur, as they can be applied at temperatures much lower than those used in conventional glass melting.

- Glass materials with a much more homogeneous structure can be produced at a lower melting temperature and time.
- It is possible to produce ceramic materials in complex shapes such as fiber, bulk and thin films.

Disadvantages of the sol-gel method:

- The raw materials used are generally expensive and sensitive to moisture.
- In this method, transactions are multi-stage and long-lasting.
- Since contractions and volume decreases may occur during operations, unwanted cracks may occur.
- Excess pores may occur.
- Production is limited in large-scale special applications.
- Prepared solutions may affect health negatively.
- It may be difficult to keep the solution at constant viscosity during gel formation. [41]

3.4. Application Areas of Sol-Gel Method

In the sol-gel method, it is possible to obtain the properties of the material such as density, refractive index, hardness, flexibility, abrasion resistance as desired by controlling the parameters in the process steps. With this method, some special glasses are produced or their surfaces are covered. With the sol-gel method; it is possible to produce composite materials, ceramic fibers for optics, materials with a wide viscosity range, refractories, membranes, optical and chemical sensors. It is also used in thin film, optical coating, coating of high temperature superconductors, solar cells and photochromic applications [42,43].

4. EXPERIMENTAL

4.1. General Overview of 45S5 Bioglass and Glass-Ceramic Synthesis

In this study, bioactive glass and bioactive glass-ceramics are tried to be synthesized via sol-gel method with respect to the SiO_2-Na_2O-CaO-P_2O_5 containing 45S5 system. In our knowledge, none of the studies in the literature uses Di-P as the P source for bioactive glasses or glass-ceramics powder production. P_2O_5 precursor is chosen as Di-P, an available source of P in HA synthesis, instead of widely used TEP. This leads to the observation of whether Di-P is employable or not for the synthesis of 45S5 bioglass quatertiary system and formation of HCA on the surfaces of bioglass-ceramics.

Crystallographic analyses of powders after each heat treatment step are done via XRD.

Microstructures and the HCA layer on the surfaces of 7, 14 and 21 day incubated samples in SBF are observed via SEM.

Elemental analysis of samples chosen for SBF are done in SEM via EDS.

General overview of 45S5 Bioglass and Glass-Ceramics powder and pellet preparation is shown at below flowchart as Fig 4.1.

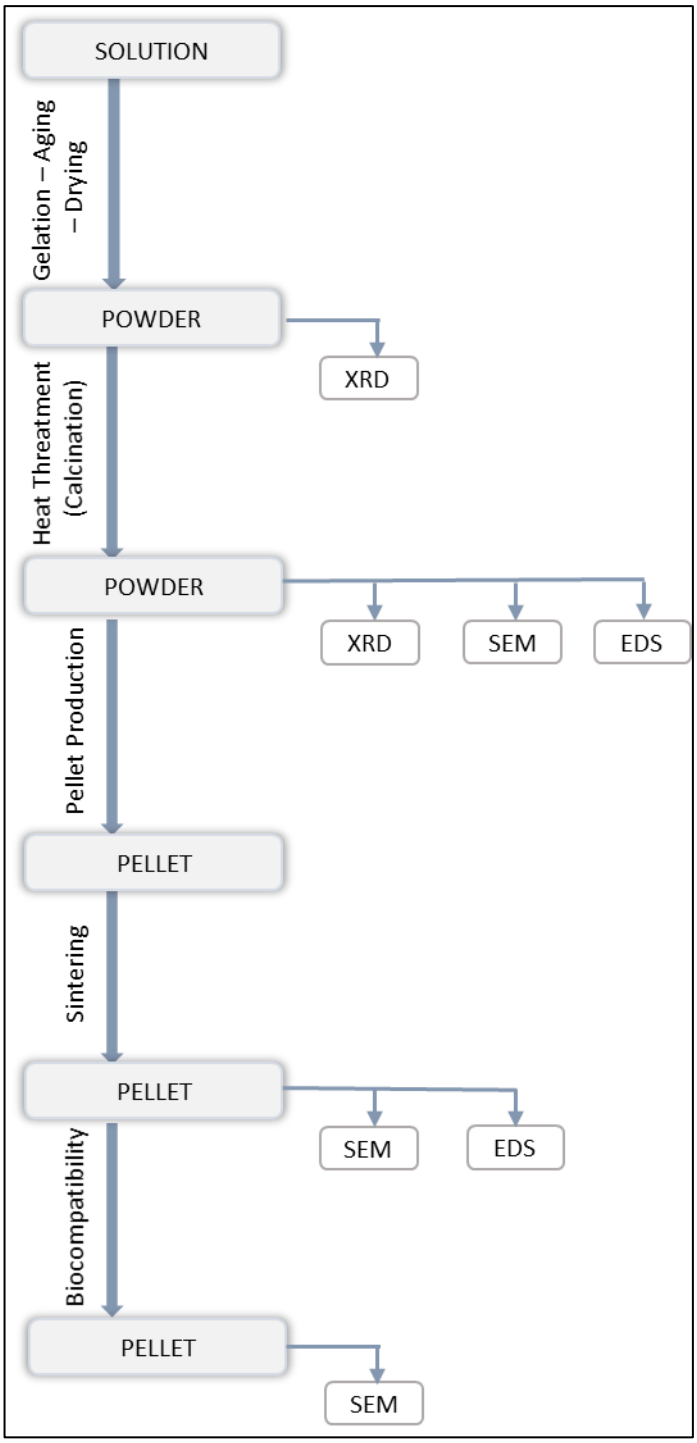

Fig 4.1: General overview of 45S5 Bioglass and Glass-Ceramics Production.

4.2. Preparation of Sol-Gel, Aging and Drying and Pellet Preparation

Preparation of solutions is generalized as in the following Fig 4.2.

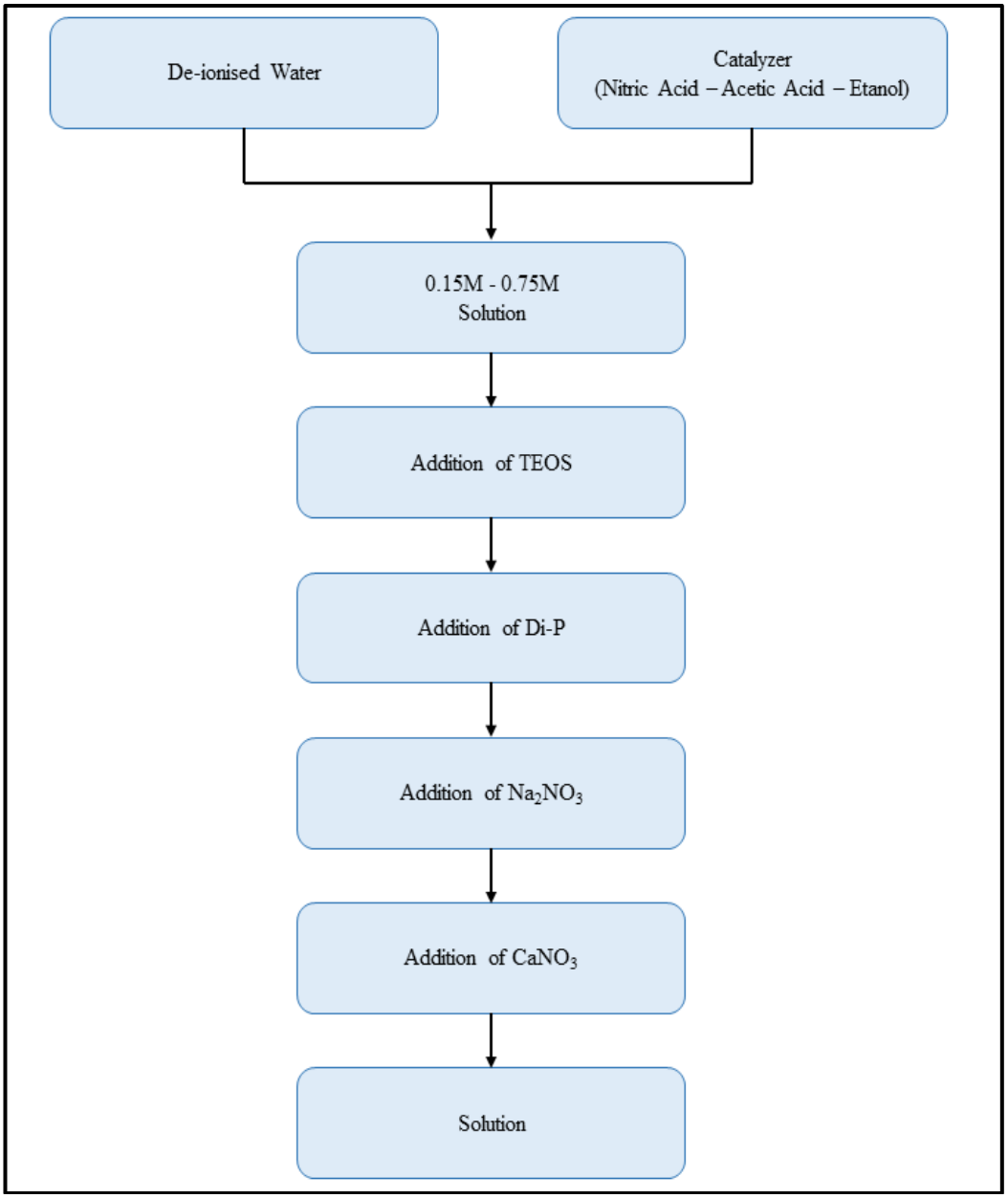

Fig 4.2: Preparation of solutions.

SiO_2-Na_2O-CaO-P_2O_5 containing 45S5 system is taken as the base line. Different solvents and molarities are experimented on to synthesize wt. %45 SiO_2, %24.5 CaO, %24.5 Na_2O and %6 P_2O_5 quatertiary system bioglasses and glass-ceramics. Used chemicals for preparation of solutions is given in below Table 4.1.

Table 4.1: 45S5 Precursors chemical formulae.

Chemical	Formula	Mole (g/mole)	Purity
Tetraethyl Orthosilicate (TEOS)	$[Si(OC_2H_5)_4]$	208.329	%99.90
Dibutyl Phosphate (Di-P)	$[CH_3(CH_2)_3O]_2P(O)H]$	194.21	%96.00
Triethyl phosphate (TEP)	$(C_2H_5O)_3PO$	182.15	%99.80
Sodium Nitrate (NaN)	$[Na(NO_3)]$	84.99	%99.00
Calcium Nitrate Tetrahydrate (CaNT)	$[Ca(NO_3)_2.4H_2O]$	236.15	%99.00

In order to synthesis aforementioned bioactive glass composition with different solvents, 10 times mole amount of all the components deionized water and precalculated amount of acid or alcohol is mixed. Chemical formulae of these solvents are shown in the Table 4.2 below.

Table 4.2: Catalyzer formulae.

Chemical	Formula	Mole (g/mole)	Purity
Nitric Acid (NA)	HNO_3	63.01	%65.00
Acetic Acid (AA)	CH_3CO_2H	60.05	%99.99
Ortho-Phosphoric Acid (oPA)	H_3PO_4	98.00	%85.00
Ethanol	CH_3CH_2OH	46.07	%99.99

Samples and chosen chemical compositions for the synthesis is given in the Table 4.3 below.

Table 4.3: Samples and chemical compositions.

Sample	TEOS Amount (g)	P Source	P Source Amount (g)	NaN Amount (g)	CNT Amount (g)	Catalyzer	Catalyzer Amount (g)
SG-01	7.810	Di-P	0.855	3.394	5.211	NA	0.875
SG-02	7.810	Di-P	0.855	3.394	5.211	NA	0.175
SG-03	7.854	TEP	0.774	3.393	5.211	NA	0.204
SG-04	7.807	Di-P	0.853	3.394	5.211	NA	0.189
SG-05	7.780	Di-P	0.858	3.400	5.215	AA	1.305
SG-06	7.818	Di-P	0.856	3.398	5.212	AA	0.271
SG-07	7.799	Di-P	0.859	3.400	5.215	oPA	2.562
SG-08	7.799	Di-P	0.852	3.385	5.219	oPA	0.511
SG-09	7.814	Di-P	0.849	3.394	5.218	Ethanol	23.738
SG-10	7.299	-	0	0	3.578	NA	1.381

To synthesize SG-01 sample, nitric acid and deionized water is mixed with magnetic stirrer on the hot plate for 15 minutes to prepare 0.75M solution. Then TEOS is added to this mixture very slowly and waited for another 60 minutes while stirring to let hydrolysis reactions time. After that dibutyl phosphate was added to the system and waited for another 60 minutes. Then sodium nitrate and calcium nitrate tetrahydrate were added to the solution with 60 minutes of interval and final solution is mixed for another hour. After that, mixing was stopped.

For observing the effect of different concentrations of acids to the synthesizability of 45S5 system, for SG-02 sample, nitric acid concentration was lowered to 0.15M. Other than that, synthesize procedure is the same as SG-01.

To compare the produced samples with the literature as a control group with lowest amount of possible nitric acid addition, SG-03 was synthesized with triethyl phosphate in 0.07M nitric acid concentration. At lower molar acid concentrations, solution was not able to dissolve required amount of TEOS. Again for the comparison, a 0.07M amount of nitric acid was utilized in the production of sample SG-04 with

dibutyl phosphate. After mixing required amount of acids with water, synthesize procedure continued same as SG-01.

For the SG-05 and SG-06 samples, instead of nitric acid, acetic acid was used. SG-05 was the sample with high molar acidity with 0.75M and SG-06 was the lower one with 0.15M. After required amount of acetic acid is mixed with water, synthesize procedure continued same as SG-01 and SG-02.

Although the samples SG-07 and SG-08 were synthesized similar to SG-01 and SG-02; SG-07 with 0.75M and SG-08 with 0.15M molar acid concentrations, ortho-phosphoric acid was chosen for the synthesis of these samples. This procedure is only done for bioglass powder preparation due to ortho-Phosphoric acid being another phosphorous source and to find whether choosing this acid may change the nitratine intensity in the XRD peaks.

Solution SG-09, tried for the synthesis of 45S5 bioglasses and glass-ceramics was ethanol and water mixture. 5 times the amount of the moles of the precursors of ethanol mixed with previous amount of deionized water. Due to the high amounts of alcohol required to solve TEOS in water-ethanol mixture with respect to previous acids, no lower amounts of alcohol have been tried. Synthesize procedure continued as in SG-01 after the preparation of water-alcohol mixture.

Final solution SG-10 was synthesized to observe the bioglass powders in the case of a sodium free concentration with excessive amounts of nitric acid, 1.25M acid concentration. 70S30C bioglass composition was utilized for this specimen, which has a ratio of wt. %70SiO2 and %30CaO containing bioglass. After preparing water-acid mixture, synthesize steps continued as in SG-01 but the addition of P source as shown in the table.

After mixing procedure, all the samples left in the room temperature for 2 days to observe gelation process. Wet gels undergone a 3 day aging procedure at 70°C in the drying oven followed by a 2 day drying process at 150°C over hot plates in the fume hood. Overall steps that solutions undergone are shown in the Fig 4.3.

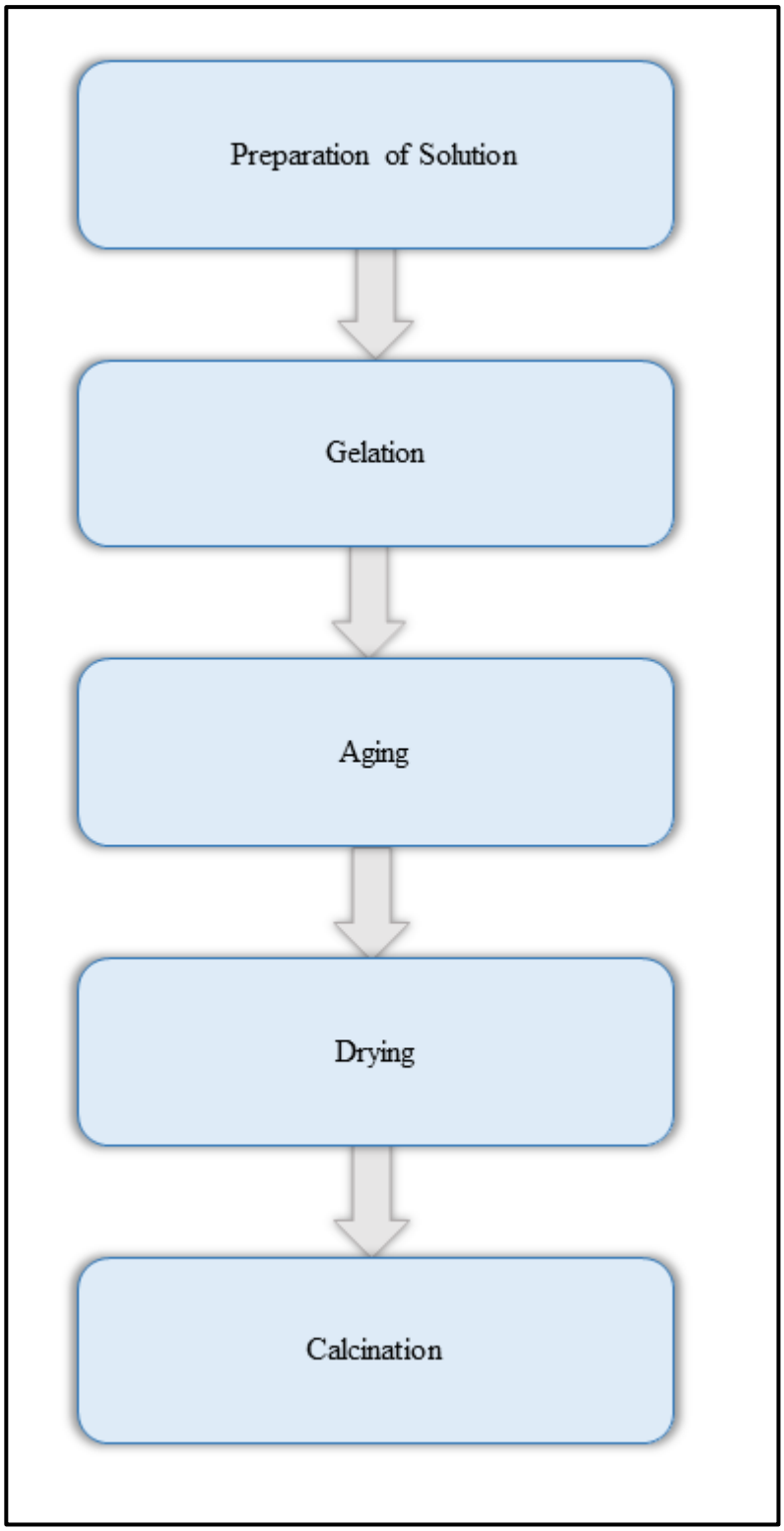

Fig 4.3: Generalization of steps that samples have undergone.

After drying, all the powders but SG-10 heat treated for 3 hours at 550°C, 600°C and 1050°C respectively for observing the nitratine crystals decomposition and crystallization of $Na_2Ca_2Si_3O_{18}$ and $Na_2Ca_2PO_4$ predominant crystals for the 45S5

Glass-ceramics and analyzed with XRD. SG-02, SG-06 and SG-09's, 1050°C calcinated samples were pressed with cold isostatic press at 250 MPa for 5 min into pellets and heat threated for 3 hours at 1050°C. These pellets further used for biocompatibility and elemental distribution analysis. SG-10 are compared with the rest of the dried samples at 150°C.

4.3. Preparation of Simulated Body Fluid (SBF)

1000 ml pure water at 37°C (body temperature) and 1.097 mole of HCl was mixed followed by the chemicals which were shown in fig 4.4 in the order. The pH value was measured as 7,5. This solution preparation method was based on Kokubo SBF model.

Under the case of biocompatibility, due to the depletion of Ca^{+2} and P^{+3} ions in the SBF while formation of the HAP coating, every 2 days solution should be changed to prevent dissolvation of pellets. Pellets were left in the simulated body fluid solution for 7, 14 and 21 days separately. After 7, 14 and 21 days the pellets were observed in SEM (Scanning Electron Microscope) in order to see the HCA coatings formed on the pellets.

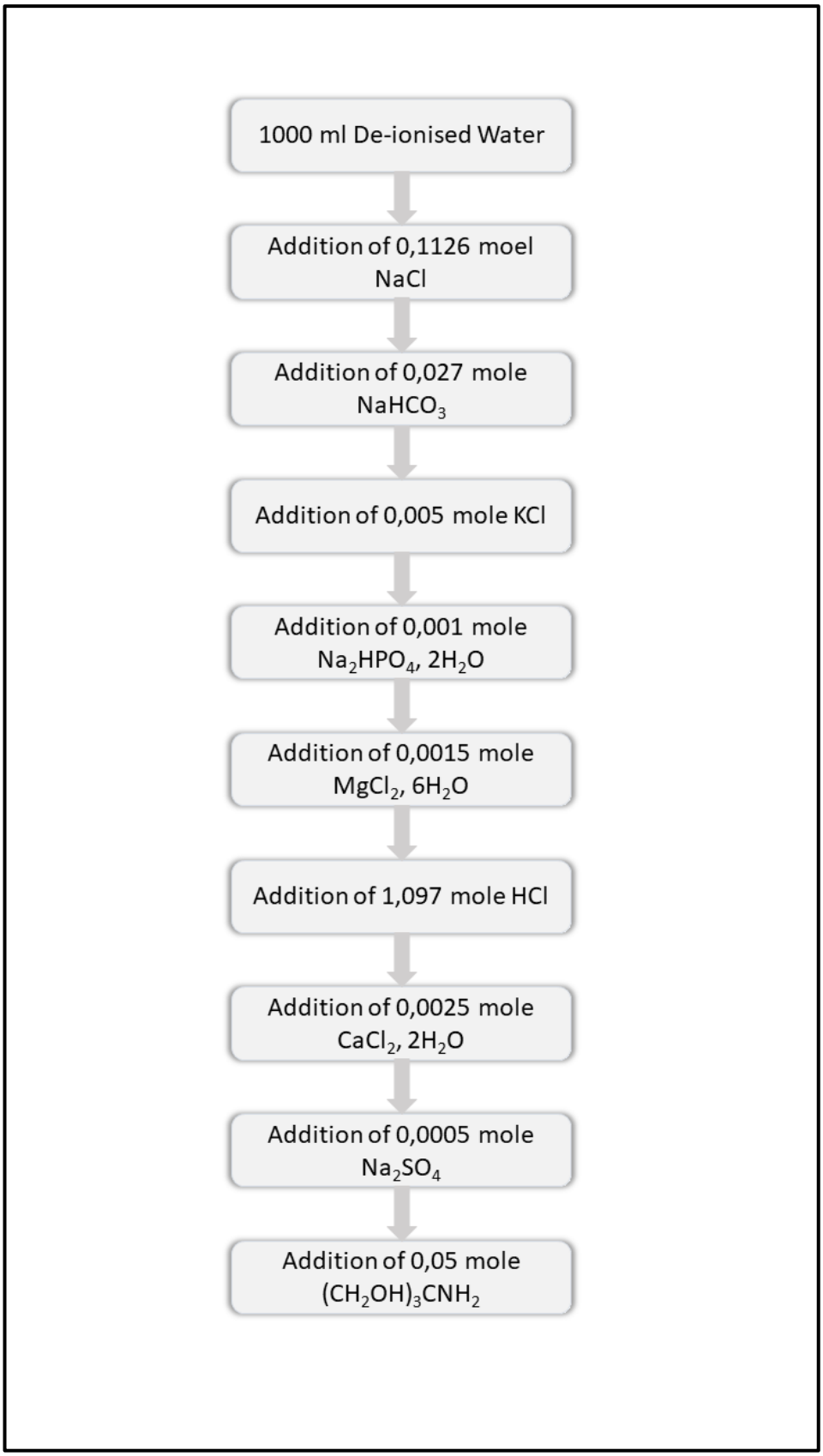

Fig 4.4: Preparation of SBF.

4.4. Chemical Composition, Phase Analysis and Microstructure of Pellets

The samples were analyzed in D8 ADVANCE Brucker X-ray Diffraction device (XRD) at a range of 20-70° with 1 degree/ min speed under Cu-Kα (wavelength 0,154 nm) radiation ambient. SEM was used to determine the HCA formation and the presence of porosity. In order to analyze the pellets with SEM, they were coated with gold for them to be conductive.

EDS is a device which is connected to the SEM. In EDS analysis the distribution of the elements (Na, Ca, Si, P, O) in pellets were investigated.

5. RESULTS AND DISCUSSION

5.1. X-RAY Diffraction (XRD) Analysis

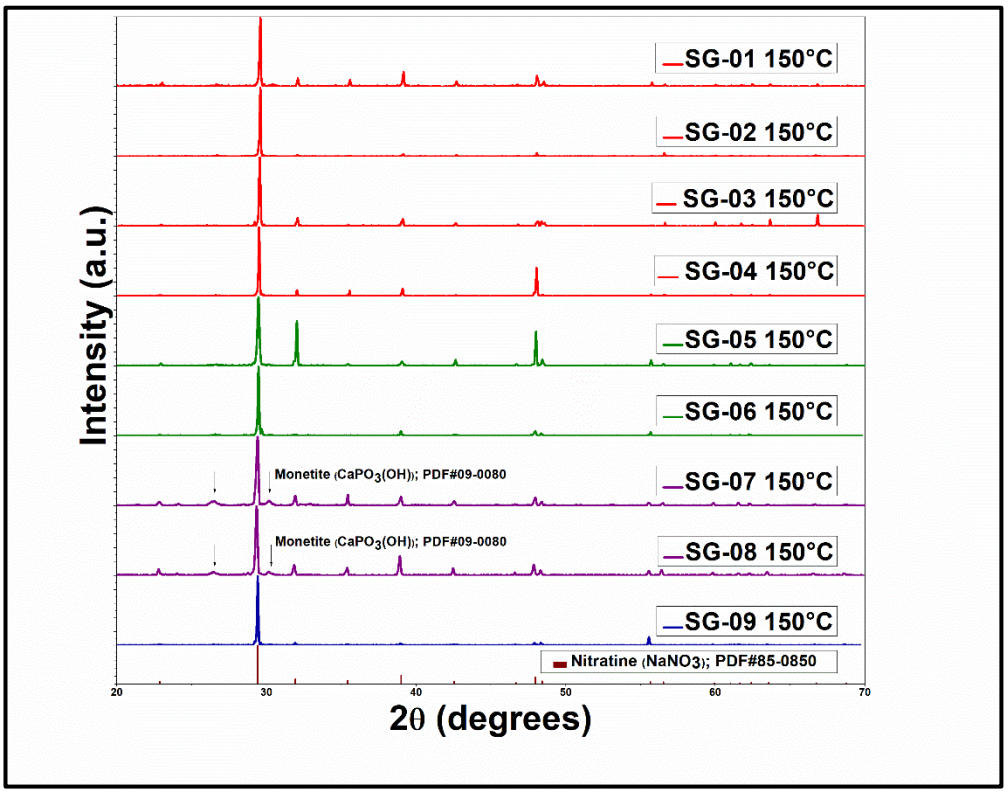

Fig 5.1: XRD Analysis of SG-01 through SG-09 at 150°C.

XRD analysis of as-dried powders SG-01, 02, 03, 04, 05, 06 and 09 at 150°C revealed nitratine ($NaNO_3$, PDF#85-0850), in the presence of traces of zeolite (SiO_2, PDF#87-1591). In powders SG-07 and SG-08 in addition to the former crystal phases, Monetite ($CaPO_3(OH)$, PDF#09-0080) was found. From Figure 5.1 it can be seen that as-dried samples were not amorphous. Neither the change in molar concentration nor the chosen catalyzer did not allow amorphous 45S5 Bioglass to form in dried gels. All the samples but SG-10 had peaks, on the contrary to the literature.

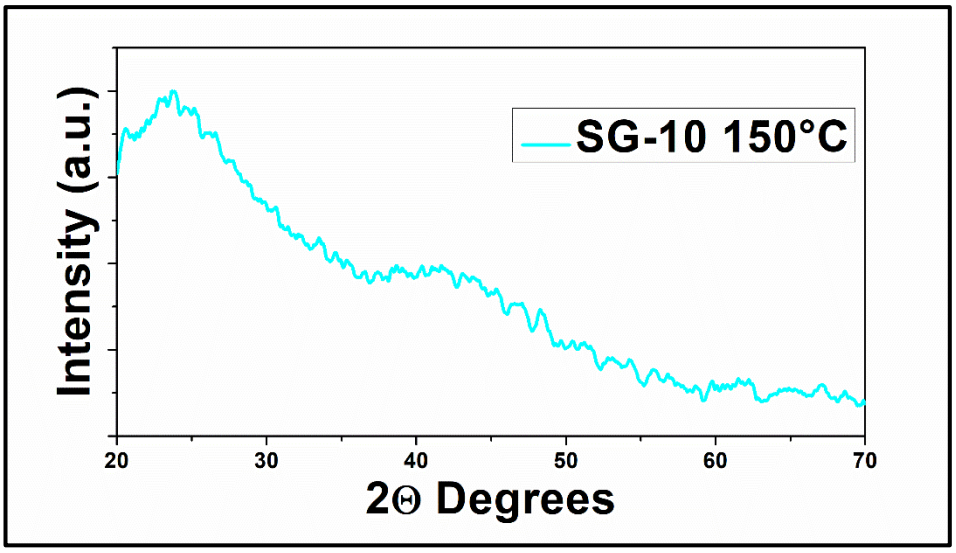

Fig 5.2: XRD Analysis of SG-10 150°C.

XRD analysis of SG-10 at 150°C, Fig 5.2, it can be seen that in the absence of Na, amorphous Bioglass 70S30C could be synthesized via sol gel method.

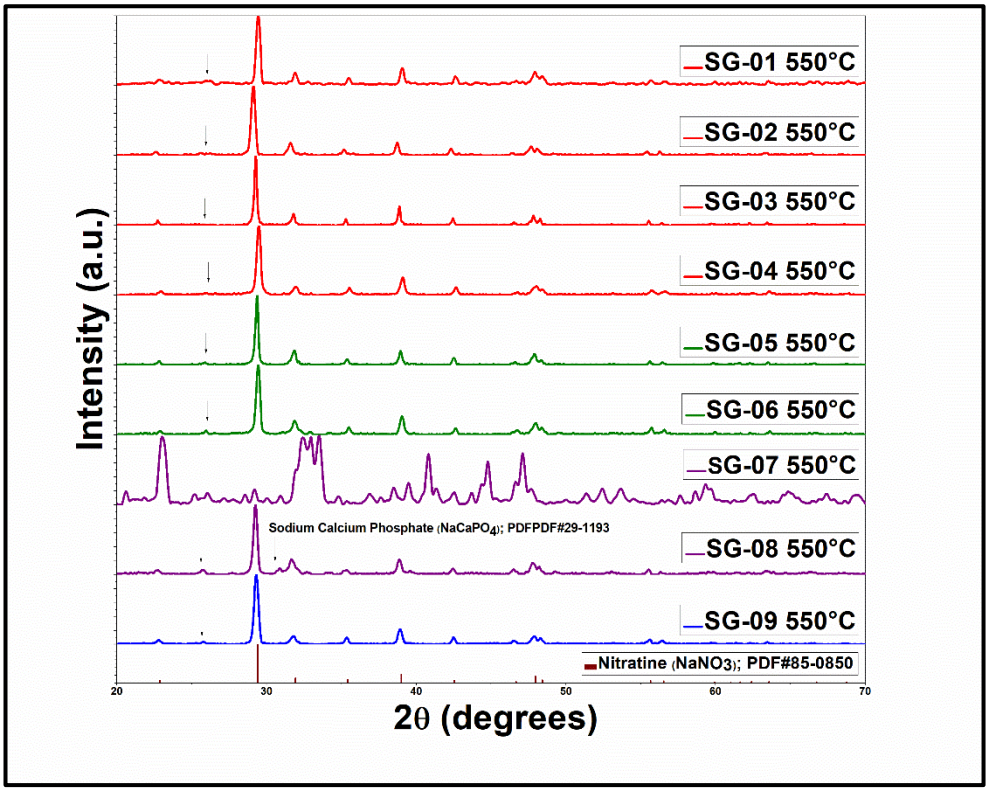

Fig 5.3: XRD Analysis of SG-01 through SG-09 at 550°C.

XRD analysis of as-dried powders SG-01, 02, 03, 04, 05, 06 and 09 at 550°C revealed nitratine (NaNO3, PDF#85-0850), in the presence calcium silicate (Ca_2SiO_4, PDF#86-0399). In powder SG-08 in addition to the former crystal phases, sodium calcium phosphate ($NaCaPO_4$, PDF#29-1193) was found. In powder SG-07, due to high amounts of phosphorus, sodium calcium phosphate is predominant form of crystalline phases and nitratine intensity is relatively lower. Peaks marked with and arrow could not be determined.

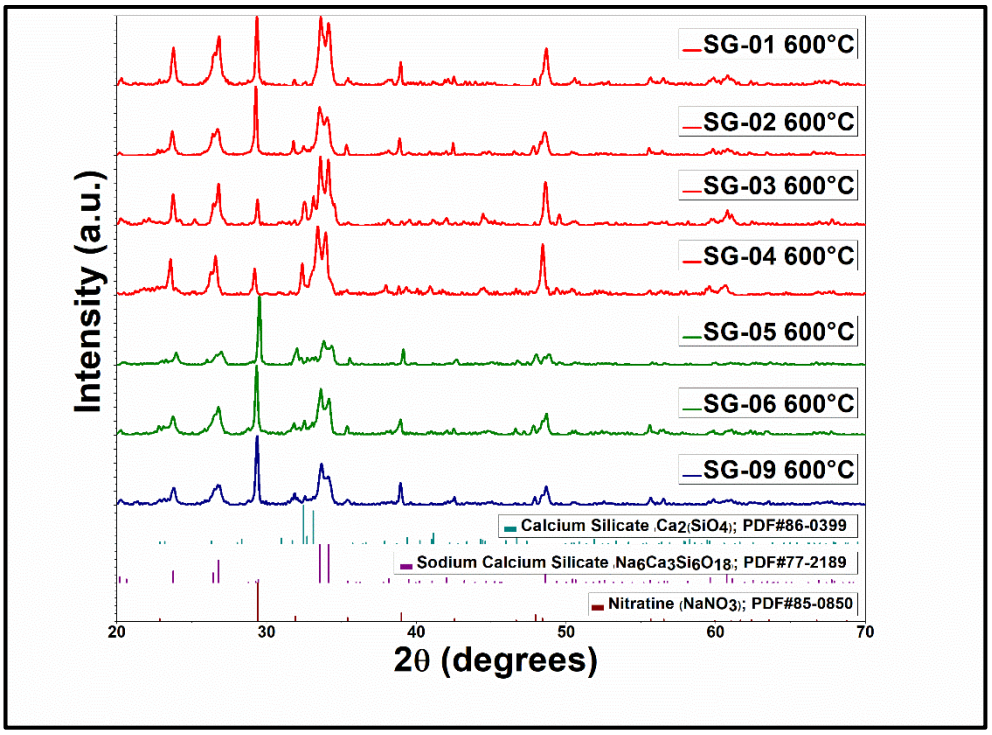

Fig. 5.4: XRD Analysis of SG-01 through SG-06 and SG-09 at 600°C.

XRD analysis SG-01, 02, 03, 04, 05, 06 and SG-09 at 600°C shows sodium calcium silicate ($Na_6Ca_3Si_6O_{18}$, PDF#77-2189) and nitratine ($NaNO_3$, PDF#85-0850) phases with addition of calcium silicate ($Ca_2(SiO_4)$, PDF#86-0399). Nitratine could still be found in the system.

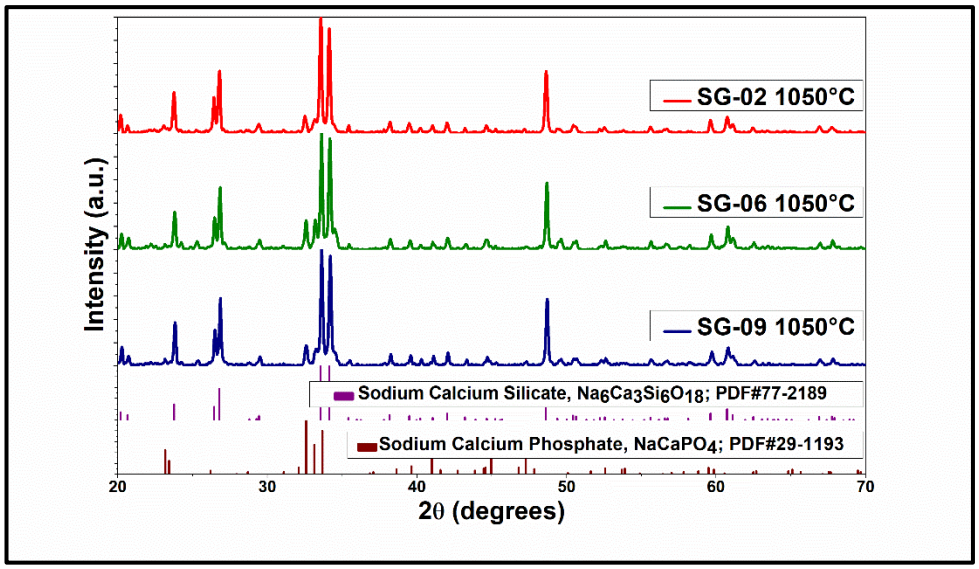

Fig.5.5: XRD Analysis of SG-02, SG-06 and SG-09 at 1050°C.

From Fig 5.5, it is observed that in all the samples formed glass-ceramics as sodium calcium silicate ($Na_6Ca_3Si_6O_{18}$, PDF#77-2189) and sodium calcium phosphate crystals ($NaCaPO_4$, PDF#29-1193).

5.2. EDS Analysis

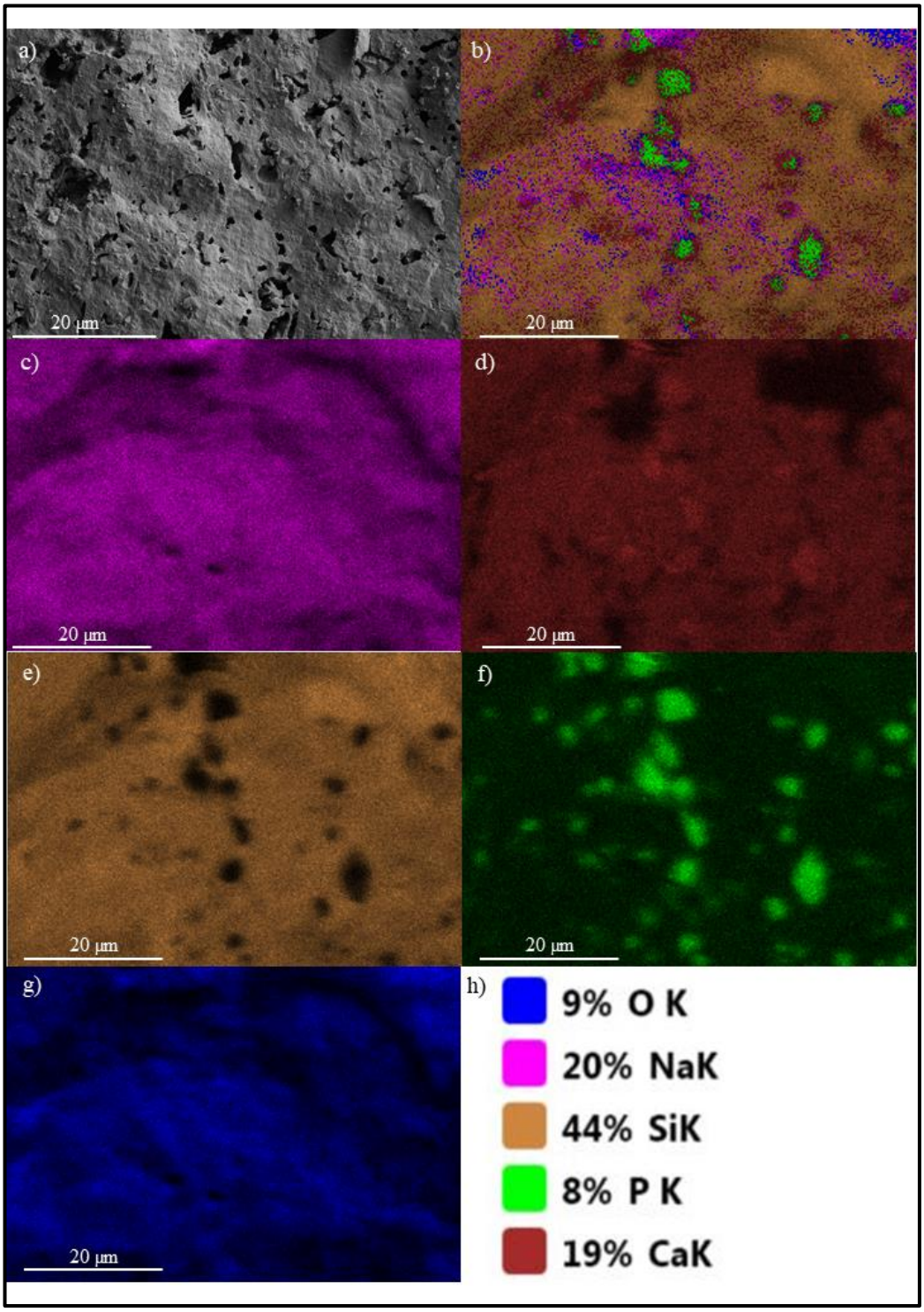

Fig.5.6: Elemental dispersion of a) SEM image of surface b) Superimposed Na, Ca, Si, P and O respectively c) through g) in sample SG-02.

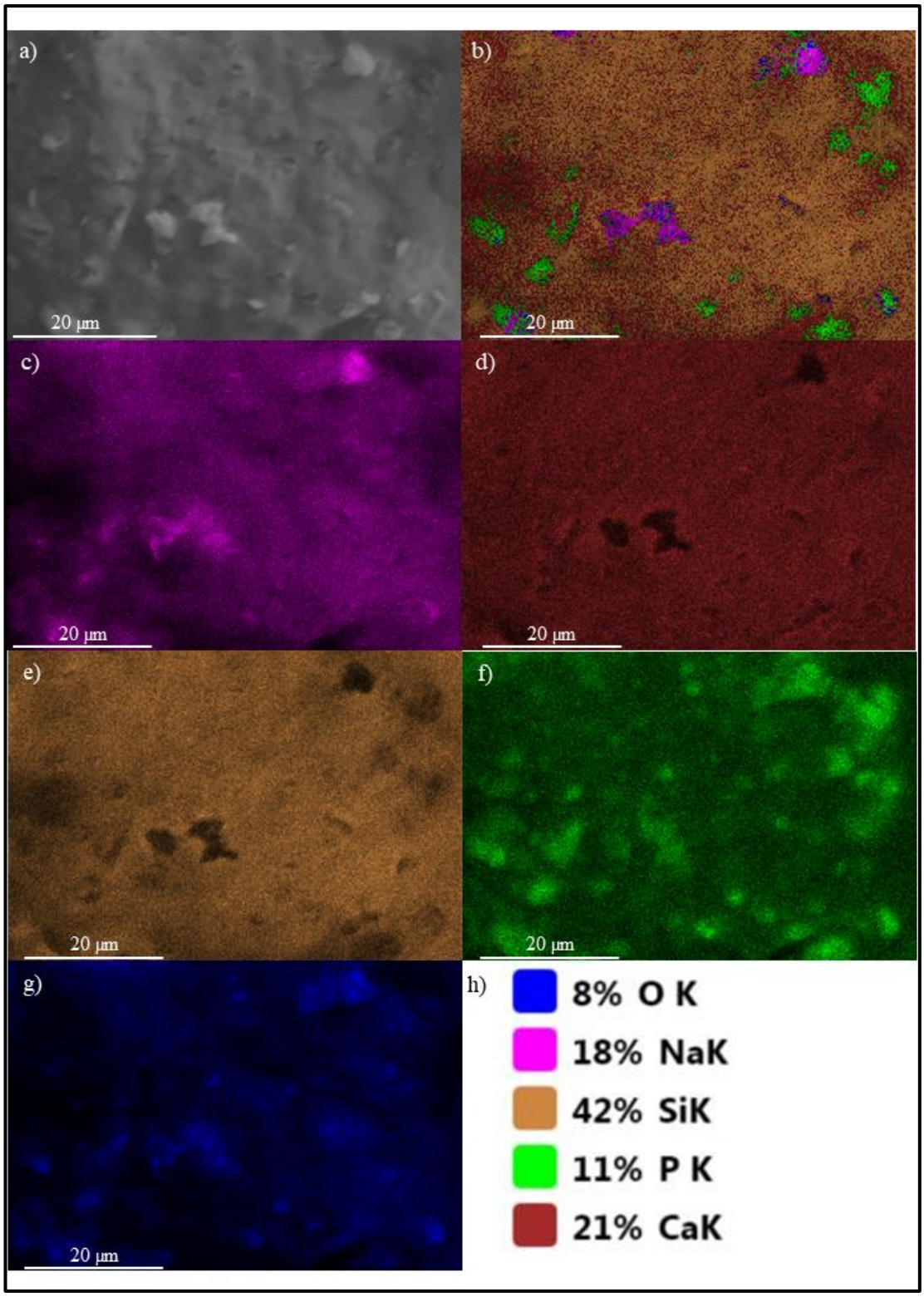

Fig.5.7: Elemental dispersion of a) SEM image of surface b) Superimposed Na, Ca, Si, P and O respectively c) through g) in sample SG-06.

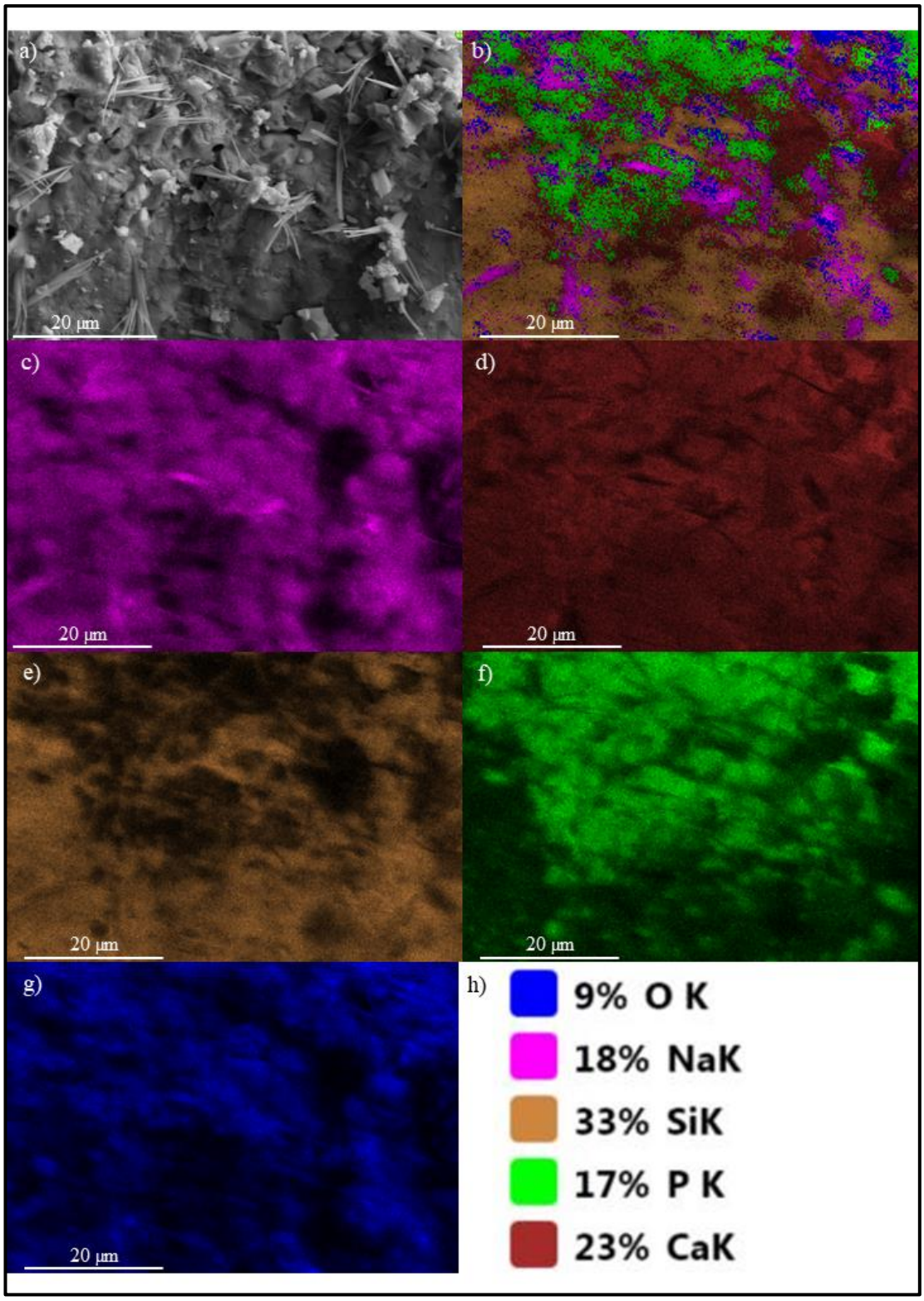

Fig. 5.8: Elemental dispersion of a) SEM image of surface b) Superimposed Na, Ca, Si, P and O respectively c) through g) in sample SG-09.

Atomic dispersion, weight and net intensity of samples SG-02, SG-06 and SG-09 displayed by EDS measurement in figures. “a” represents normal image, “b” represents atomic dispersion of normal image specified with colors, c, d, e, f and g represent phase dispersions of Sodium, Calcium, Silicium, Phosphate and Oxygen respectively. As seen in the XRD analyses, $Na_2Ca_2Si_3O_{18}$ and phosphorus containing $NaCaPO_4$, phases are not homogeneously dispersed on the surface.

5.3. SEM Analysis and Biocompatibility

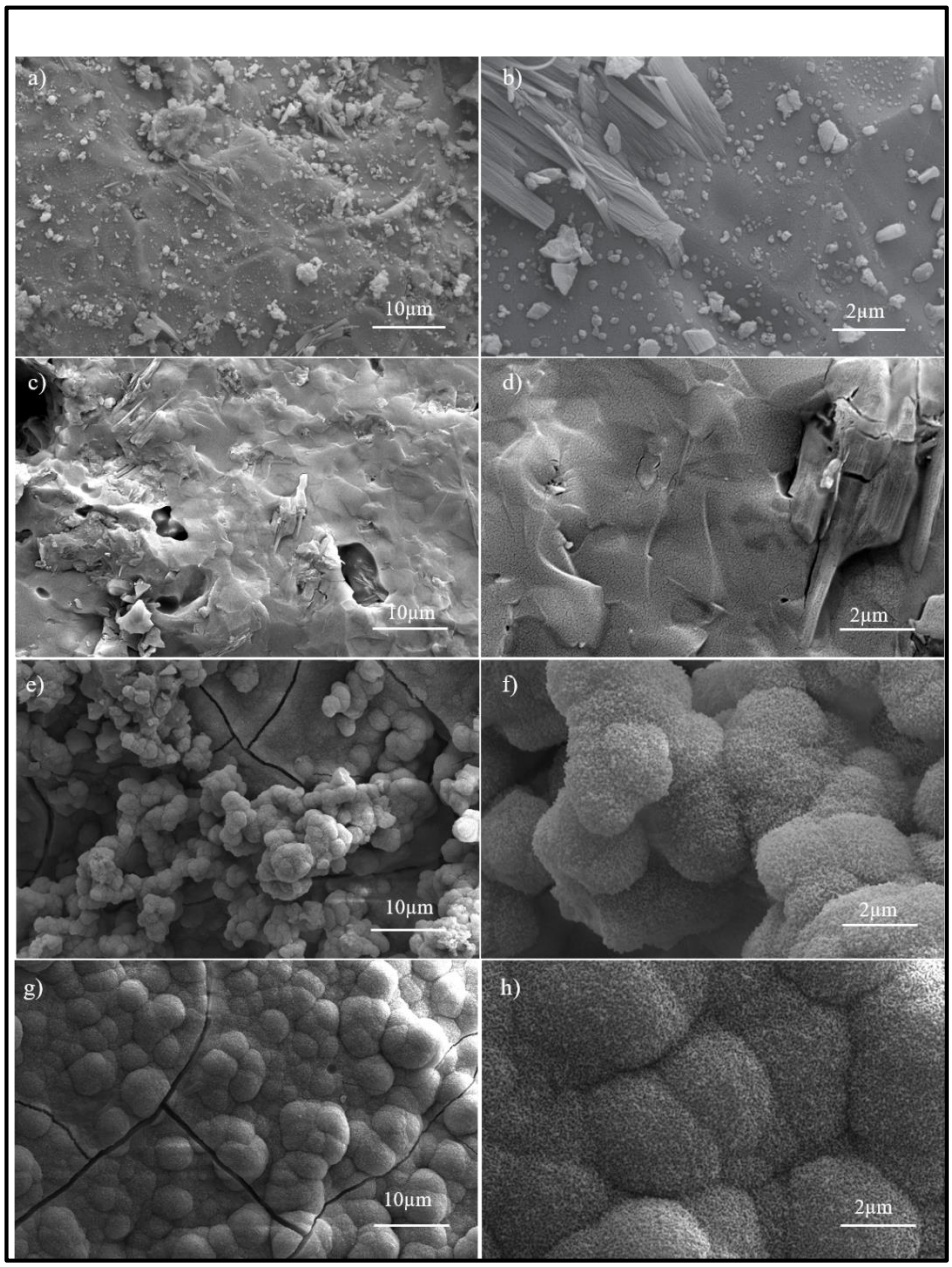

Fig. 5.9: SEM images of SG-02 a) Low magnification SG-02 powder b) High magnification SG-02 powder c) Low magnification SG-02 pellet d) High magnification SG-02 pellet e) Low magnification SG-02 7 day in SBF f) High magnification SG-02 7 day in SBF g) Low magnification SG-02 14 day in SBF h) High magnification SG-02 14 day in SBF.

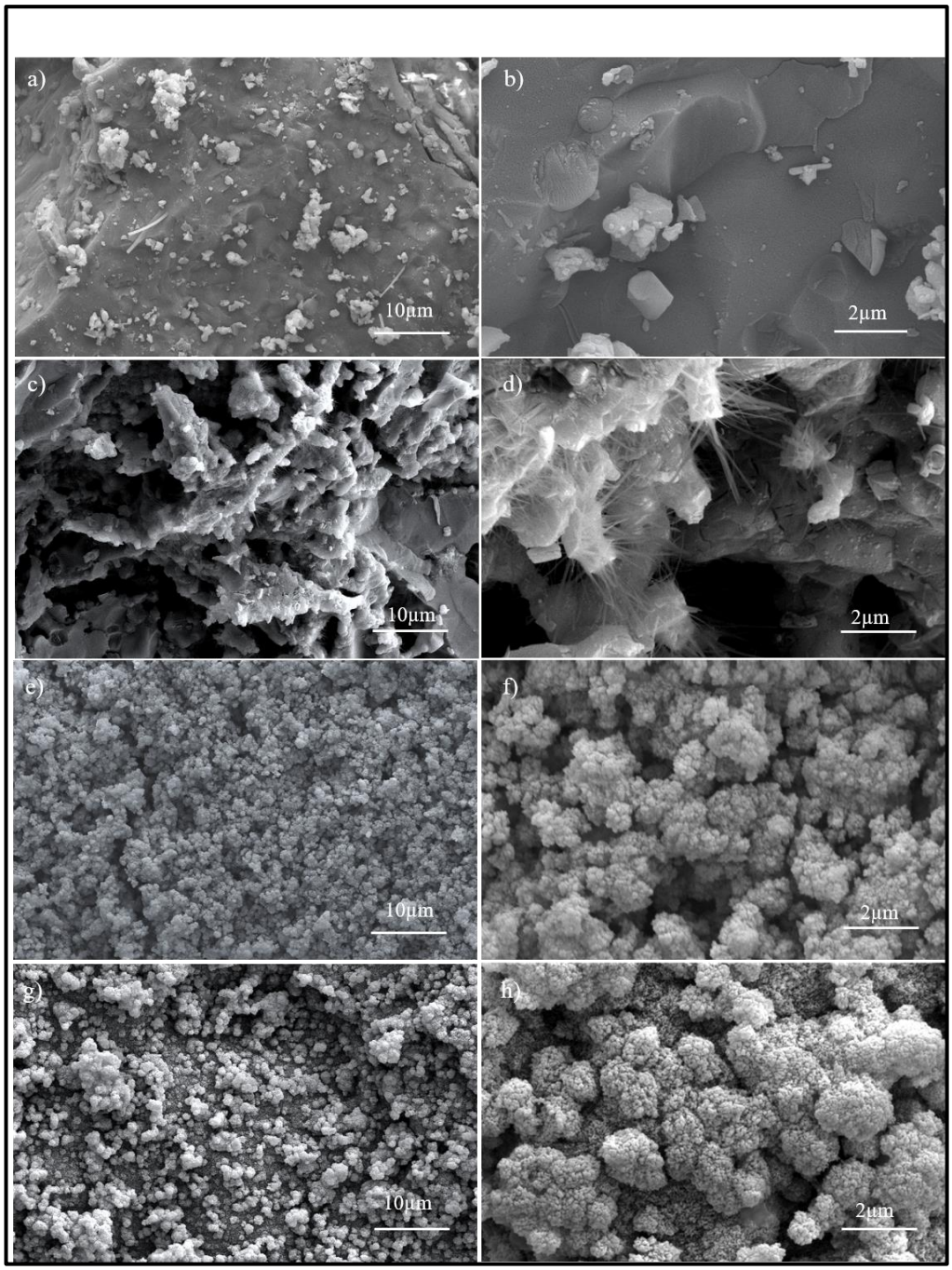

Fig. 5.10: SEM images of SG-06 a) Low magnification SG-06 powder b) High magnification SG-06 powder c) Low magnification SG-06 pellet d) High magnification SG-06 pellet e) Low magnification SG-06 7 day in SBF f) High magnification SG-06 7 day in SBF g) Low magnification SG-06 14 day in SBF h) High magnification SG-06 14 day in SBF.

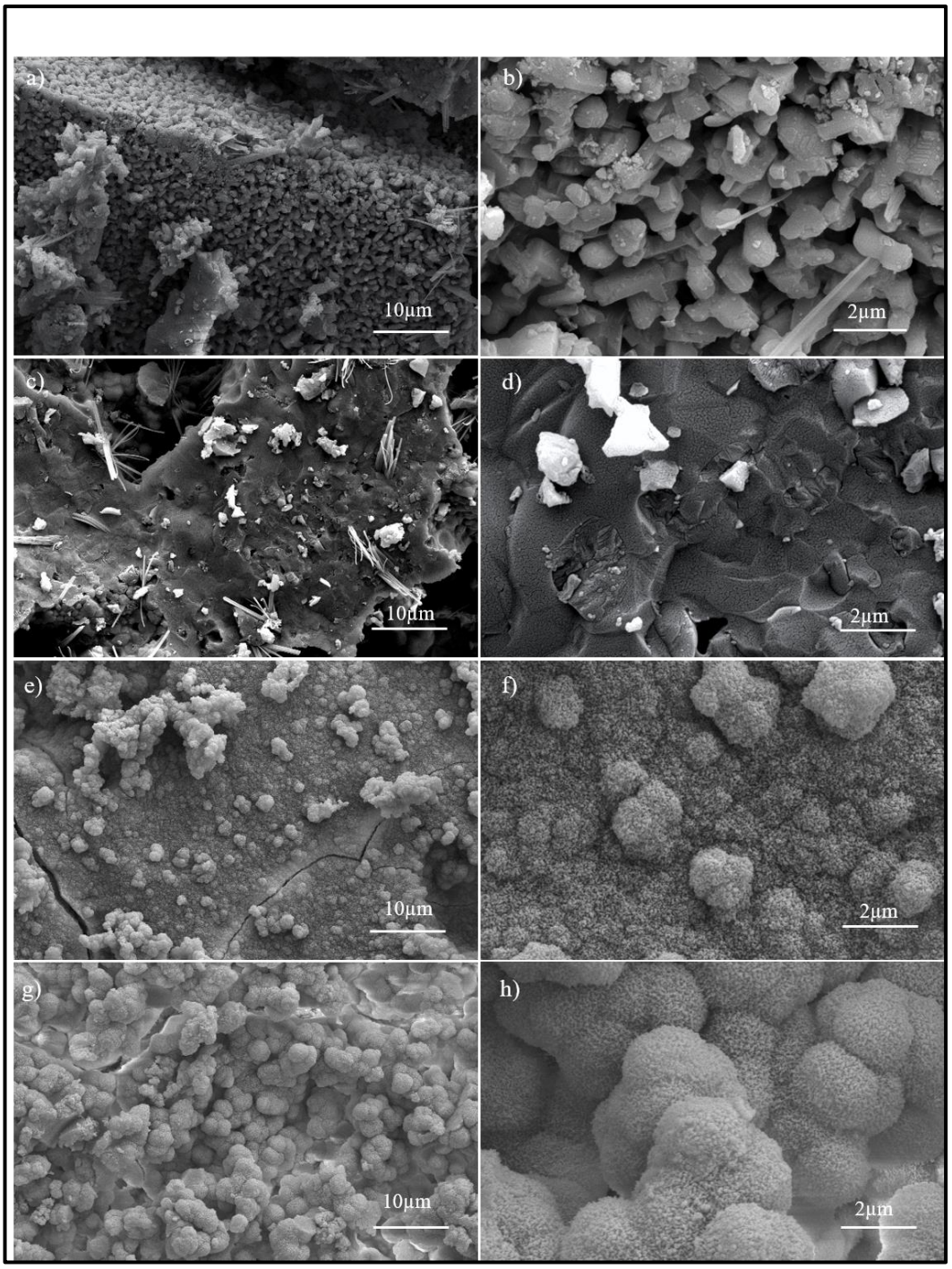

Fig 5.11: SEM images of SG-09 a) Low magnification SG-09 powder b) High magnification SG-09 powder c) Low magnification SG-09 pellet d) High magnification SG-09 pellet e) Low magnification SG-09 7 day in SBF f) High magnification SG-09 7 day in SBF g) Low magnification SG-09 14 day in SBF h) High magnification SG-09 14 day in SBF.

From Fig. 5.9 to Fig. 5.11 at high magnification and low magnification enlarged SEM images of samples SG-02, SG-06 and SG-09 are given. Images a and b are the glass-ceramics and c and d are the glass-ceramic pellets. Lower images which were named as e through h are the results of after the samples immersed into SBF solution to observe the biocompatibility of the glass-ceramic pellets 7 and 14 days respectively.

In figures porous structure of samples could be seen in low magnification images. This large surface area has the positive effect for the interaction between the pellets and the SBF during the formation of HCA on the pellets.

6. CONCLUSION

- According to this sturdy, 45S5 Bioglasses could not be synthesized via sol-gel method with nitrate containing precursors. On the other hand related glass-ceramics were successfully produced.
- It was observed that the addition of Na to the system may requires oxides as precursors for 45S5 Bioglass sol-gel synthesis procedure.
- As seen in XRD results, dried and heat treated up to 550°C powders show similar properties and all contain predominantly nitratine.
- XRD results show that $Na_6Ca_3Si_6O_{18}$ and phosphorus containing $NaCaPO_4$ crystals were dominant in the produced glass-ceramics.
- XRD results indicates that higher P concentrations lowers the Glass-Ceramic formation temperature which coincides with P_2O_5 generally being used as nucleate for CaP phase.
- In the SEM images, the surface of the samples show that a very rough structure and some regions are porous.
- In the EDS analysis, it is seen that there is significant phase separation on the surfaces of the pellets.
- Similar to beginning P concentration indicates that Nitric Acid is more suitable for the synthesis of 45S5 Glass-Ceramics than Ethanol or Acidic Acid.
- It was seen that every sample that undergoes biocompatibility test show that HCA formation on the surfaces begins before 7 days and covers the surface of that material by 14 days.

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