

# NOVEL DEVELOPMENTS IN ADVANCED MATERIALS FIELDS: POROUS AND NON-POROUS BIOMATERIALS USED IN REGENERATIVE MEDICINE AND TISSUE ENGINEERING

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**Abstract:** In this brief review, porous and non-porous biomaterials used as scaffolds in regenerative medicine and tissue engineering and new innovative techniques to obtain biomaterials were discussed. Various methods have been presented to obtain advanced materials used as scaffolds, such as (i) 3D printed biomineral composites obtained with bacteria-loaded ink (bactoInk), (ii) the use of vegetable waste, such as rice husks, parsley, spinach or cocoa in the development of bioplastics, (iii) the use of natural biological materials of animal origin (such as bovine bones, corals, snail shells or eggshells) from waste, or (iv) the creation of new biomaterials that can reduce or combat the infection of scaffolds after implantation.

**Keywords:** advanced materials, (non)porous biomaterials, tissue engineering, scaffolds, biocomposites.

## 1. INTRODUCTION

The synthetic or natural solid and sometimes liquid materials are used as biomaterials to construct a medical device for a total/partial replacement of different parts of human components (bones, skin, cartilage, etc) [1, 2, 3, 4, 5], to suport different body structures and organs or used for diagnosis, therapy [6] (drug delivery for example) [7] or reconstruction surgery [8, 9].

Tissue engineering began by obtaining and testing biomaterials with the role of repairing [10-14] or replacing diseased or destroyed soft or hard tissues [15, 16].

The repair of bone fractures or reconstruction of bone cracks is a very complex process of bone regeneration. Over time, the researchers in the field developed starting materials (3D scaffolds) to support different types of cells, from osteoblasts, osteoclasts, or osteocyte cells to bone lining cells [10, 17-19]. Porous structures with interconnected porosity or open cells allow the transport of body fluid respectively the growth and regeneration of bone in the pore areas, and thus a viscoelastic biomaterial with a remarkable regeneration capacity is obtained [20]. By developing the porous scaffolds, it is necessary to have some essential requirements (characteristics) [21-26], briefly presented below in the Figure 1.

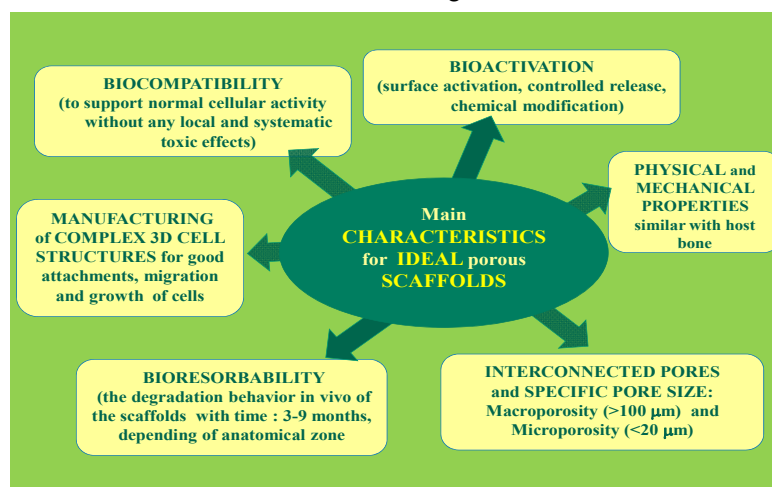


Figure 1. The main characteristics for an ideal porous used as scaffolds

## 2. BIOMATERIALS USED IN REGENERATIVE MEDICINE AND TISSUE ENGINEERING

Scaffolds can be composed of ceramics[11, 27-33], polymers[34-36], metals[12, 13, 17, 18, 37-43] or composites [22, 44-49]. The selection of materials is very important and is closely related to their applications [2, 8, 11, 20, 36, 50-58]. Scaffolds could have applications in replacing soft tissues such as tendons [46, skin [59-61] ligaments [46], blood vessels [62], heart tissue [63] or in hard tissues such as bone and dentin [35, 44, 45, 64]. For soft tissues, scaffolds are made of polymer-based

materials, and for hard tissues, metals, ceramics, and metal- or ceramic-based composites can mostly be used. Bone tissue has a relatively tough and flexible collagen structure compared to other body tissues and it is also reinforced by calcium phosphate nanocrystals. When developing traditional and new biomaterials, the specific characteristics of the main categories of biomaterials used must be taken into account [23, 47, 48, 51, 65-82]. The advantages and disadvantages of the main types of materials used in regenerative medicine and tissue engineering are briefly presented in Figure 2.

| CHARACTERISTICS of BIOMATERIALS used in regenerative medicine and tissue engineering                                                                                             |                                                                                                                                                   |                                                                                                                                                               |                                                                                                                                                                                      |                                                                                                                                               |                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Bioceramics                                                                                                                                                                      |                                                                                                                                                   | Biopolymers                                                                                                                                                   |                                                                                                                                                                                      |                                                                                                                                               | Metallic Biomaterials                                                                                                      |
| <b>Calcium phosphate</b><br>-Biocompatible<br>-Osteoconductive<br>-Nonimmunogenic<br>-well integrated into host tissue<br>-Molding as powders, paste or an ink form into defects | <b>Bioglasses</b><br>-Biocompatible<br>-Osteoconductive<br>-Osteoinductive potential<br>-Supporting cell activity<br>-Tailorable degradation rate | <b>Natural Biopolymers</b><br>-Good biocompatible<br>-Biodegradable<br>-Bioactive on their surface<br>-Low toxicity<br>-Binding sites for cells and molecules | <b>Synthetic Biopolymers</b><br>-Biocompatible<br>-Improved control over mechanical prop.<br>-Control of high degradation rate<br>-Improvement of cell adhesion<br>-Easy fabrication | <b>Hydrogels</b><br>-High water holding capacity<br>-Suitable for cell growth and Encapsulation<br>-Controlled drug or growth factor delivery | <b>Metals or Alloys</b><br>-Biocompatible<br>-High strength<br>-High thermal and corrosion resistance;<br>-Rigid structure |
| DRAWBACKS of BIOMATERIALS used in regenerative medicine and tissue engineering                                                                                                   |                                                                                                                                                   |                                                                                                                                                               |                                                                                                                                                                                      |                                                                                                                                               |                                                                                                                            |
| -Brittle and hard<br>-Low resorption or degradation rates that has a result in decreasing of mechanical properties                                                               | -Brittle<br>-Difficult to adjust absorption rate                                                                                                  | -Immune reaction due to pathological impurities<br>-Difficult to control degradation rate<br>-Limited thermal, mech. properties                               | -Slow biodegradability<br>-Limited mechanical properties<br>-Inflammatory caused by acid breakdown products                                                                          | -Pore size difficult to control<br>-Limited mech properties<br>-Potential toxic due chemically crosslinking                                   | -Poor or non biodegradability<br>-Disruption of new formed tissue<br>-Local toxicity due secondary metal ions              |

Figure 2. Characteristics of biomaterials for medicine and tissue engineering

**Calcium phosphate** is the most used biomaterial for bone regeneration [11] in implantology (dentistry, orthopedics, etc.) [44, 45, 83] as well as in the administration of drugs and bone regeneration because it has been proven that it has good biocompatibility with the surrounding tissues when implanted in the body. Over time, many types of Ca-phosphates compounds have been studied [11, 30-33, 83], like monocalcium, dicalcium or octocalcium phosphate,  $\alpha$ -Tricalcium,  $\beta$ -Tricalcium, and Tetracalcium phosphate, precipitated or sintered hydroxyapatite [2, 11, 84, 85] etc.

**Bioglasses** especially **bioactive glasses** that belong to the second generation of biomaterials [2, 27, 86] form a chemical bond at the interface between their surface and the surrounding tissue. Also, biological glasses that belong to the third generation of biomaterials, are regenerative materials [2, 86] that improve tissue healing and degrade there (the third generation of biomaterials [2, 28, 29].

When making and preparing scaffolds and implants from **natural polymers**, for tissue engineering and regenerating medicine, *collagen* was one of the most used materials. [2, 34, 87].

Other well known natural polymeric biomaterials used in regenerative engineering are (a) *gelatin* [2, 88, 89] successfully used in a mixture with bioactive glass

nanoparticles, for soft and hard tissue engineering applications, (b) *alginate* [71, 90, 91]-it is very similar to the extracellular structure matrix in tissues and has applicability in tissue engineering, injectable bone cement and drug delivery applications, (c) *chitosan* [2, 92, 93] -it is industrially derived from the chitin of crustaceans and mycelium fungi; despite its many advantages, chitosan has low bioactivity, and as a result, to improve it, it is mixed with hydroxyapatite and bioactive glass [94].

**Synthetic Biopolymers** appeared from the need to replace natural polymers that cause allergies in patients. Synthetic polymers are less immunogenic and do not cause chronic immunogenic inflammation [3, 95, 96].

**Hydrogels** are 3D network of natural or synthetic polymers and can serve as a support to ensure the structural integrity of tissues, control the delivery of drugs and proteins to tissues and cultures, and also serve as adhesives or barriers between tissue and material surfaces [10, 59, 97, 98].

Hydrogels can be obtained from natural polymers known for their application, for example in corneal defects due to their very aqueous environment, biocompatibility, and very transparent nature [3].

There are three large categories of **metallic biomaterials**, namely bioinert (Ti6Al4V, Ti6Al7Nb, Ti2, Ti4, Co-Cr-

Mo, AISI 316L, Pt,etc) bioactive ( tantalum, Co-based alloy/ FA nano-composite), or biodegradable(AZ 31, AZ 91, Zn-xCu (x=1- 4 wt%), Zn-3Cu-xMg (x=0.1, 0.5 and 1.0 wt.%), Fe-35Mn, Fe-10Mn-1Pd, Fe -30Mn-6Si; Tungsten, etc.), which over time have been intensively studied [99].

The requirements of metallic biomaterials including metallic matrix composites [4, 5, 13, 15, 17, 20, 25, 38-42, 43, 68, 73, 80, 100] and their main applications in skeleton systems [2, 8, 11, 52-55, 85, 101] are shown in Figure 3.

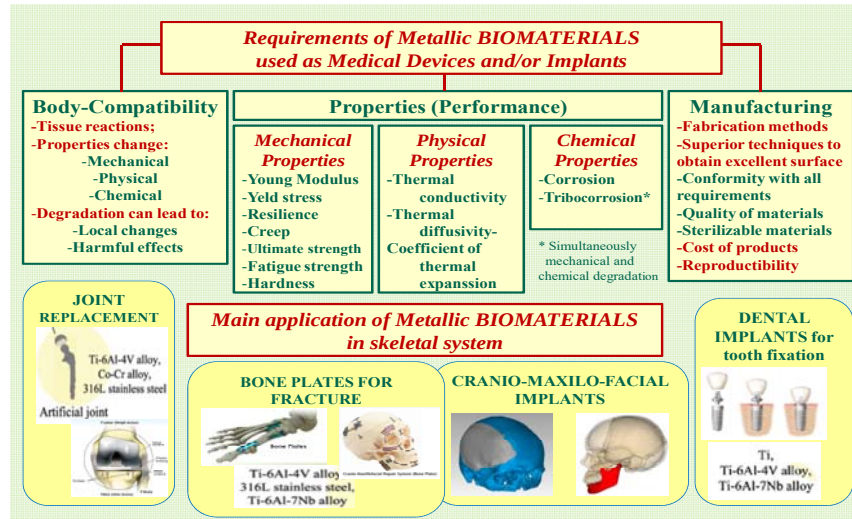


Figure 3. The requirements and main applications of of metallic biomaterials

Composite biomaterials or biocomposites are a special class of materials that combine the advantages of each composite component. Biocomposites can be made by a wide variety of methods and can be mixtures of bioceramics (such as bioactive glass and glass ceramics or hydroxyapatite, tricalcium phosphate, and magnesium phosphate) and natural or synthetic polymers [22, 44-49, 85, 90].

### 3. NOVEL DEVELOPMENTS IN ADVANCED MATERIALS USED AS SCAFFOLDS

Over time, many methods of obtaining scaffolds have been developed, such as: (i) *solvent casting particulate leaching (SCPL)* [3, 23, 102] and (ii) *gas foaming* [3, 103, 105] both allows controlling porosity and pore size, but gas foaming in addition has no harsh toxic solvents (iii) *freeze drying*, which gives the biomaterial of 3D porous sponge structure with high interconnectivity [3, 106, 107], (iv) *electrospinning*, a simple method that controls over porosity, fiber diameter, and pore size and in addition give the high surface area of the obtain biomaterial [19, 64, 67, 108-113] (v) *additive manufacturing*, that produces porous materials with complex shapes and biomimetic structures [3, 49, 57, 76, 100, 114-117], (vi) *the sol-gel method* offers a chemical homogeneity of the ceramics [2, 24, 118-121]; (vii) *space holder sintering method* is applied for metallic scaffold [43, 122-123] and has the advantages of high porosity (45%–80%), interconnected pores, appropriate pore size (200–500  $\mu\text{m}$ ) and good elasticity and compressive strength [43] (viii) *3D bioprinting techniques* [62, 124-126] and so

on. The *3D bioprinting techniques* gives the material fast fabrication of composite structure, high porosity, low temperature process and complex structures.

To build complex 3D biological models, we can use, as novel developments in advanced materials fields, three-dimensional (3D) printing. This allows a controlled deposition of cells, biomaterials, and biological compounds (e.g. bioInks). The development of responsive biomaterials as bioInks and their bioprinting technique are today in the attention of researchers, due to their controllable properties of the material (the response to external or internal stimuli induced by printing can be controlled).

Recently, a novel porous biomaterials was developed by 3D printing by a team of researchers from Switzerland and the United Kingdom [22]

They developed an innovative technique for obtaining bone biocomposites, using an ink loaded with bacteria. One of the advantages of this technique consists in obtaining mineral-based materials with a 3D structure, identical to the initially printed polymeric scaffold, with a high hardness and rigidity and much lighter compared to  $\text{CaCO}_3$  (93% of the weight of  $\text{CaCO}_3$ ). The secret of the success of researchers Hirsch et. al. [22] from the École Polytechnique Fédérale de Lausanne and the University of Cambridge consists in the fact that, inspired by nature, they designed an easy and versatile process based on bacteria, to produce porous composites based on  $\text{CaCO}_3$ , composites composed exclusively of materials derived from nature and similar to the structure of human trabecular bone.

This is achieved by the manufacture of gelatin microgels containing ureolytic bacteria [22], (eg

*Sporosarcina pasteurii*), with the role of mineralizing the bone support (scaffold). Hirsch et al. chose this type of bacteria (*S. pasteurii*) due to its high urease activity and biosecurity. These microgels are locked to

form a 3D printable granular bio ink (BactoInk) [22] that can be transformed into load-bearing biocomposites by microbe-induced precipitation of calcium carbonate, as can be seen in Figure 4.

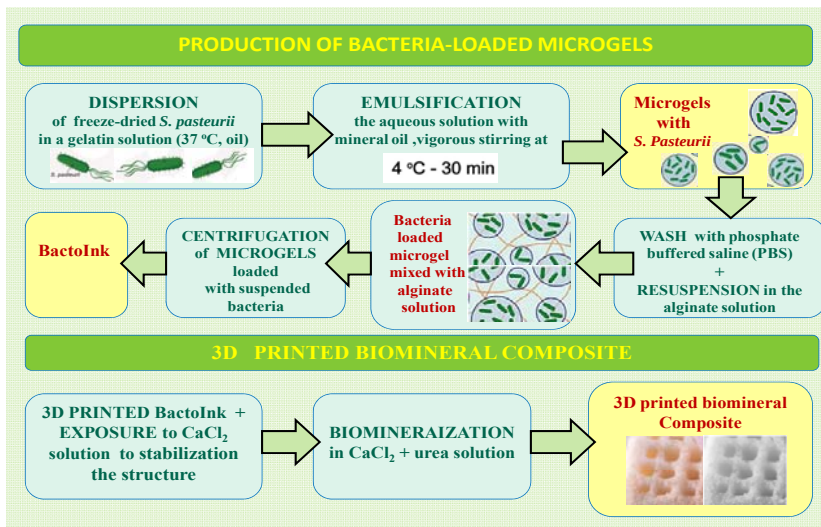


**Figure 4. Fabrication of 3D printed biomineral composites (production of bacteria-loaded microgels and biomineralization of 3D printable granular bioink (BactoInk) through microbially-induced  $\text{CaCO}_3$  precipitation**

For the success of making these bone biocomposites, it is necessary that the microgels be biocompatible, solidifies under conditions compatible with bacteria, and be sufficiently concentrated to allow 3D printing.

Nowadays, in the context of increasing resistance of bacteria to antibiotics and to prevent implant infections, it determines the need for alternative solutions, such as antibacterial implant coating, that combining antimicrobial peptides (AMPs) and silver nanoparticles (AgNPs) for dual impact [127]. AMPs, nanoparticles, metal ions, cationic polymers release antimicrobial agents, induce killing by contact or prevent bacterial adhesion and fouling.

A non-traditional way to obtain biomimetic mineralized hybrid scaffolds through mineralization was followed by Ye and his collaborators [128]. They developed by *sol-gel* method, the mineralized scaffolds which are characterized by the fact that they can kill different pathogens by contact, such as *Escherichia coli*, *Streptococcus gordonii* as well as cytocompatible human bone marrow-derived mesenchymal stromal cells.

In Figure 5 are represented schematic the intrafibrillar – mineralized collagen with antimicrobial peptides coatings [128].

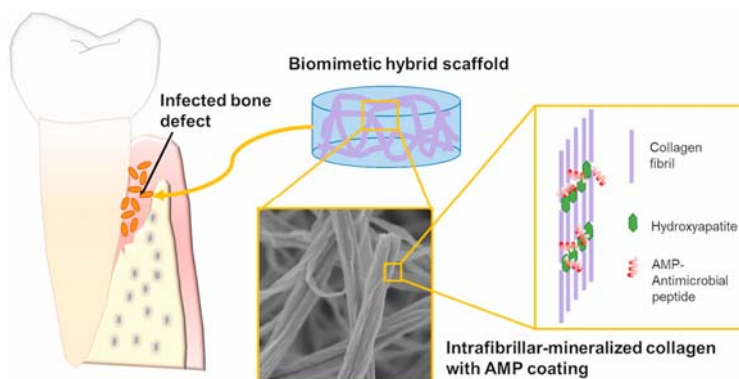


**Figure 5. Schematic presentation of intrafibrillar –mineralized collagen with antimicrobial peptides coatings [128].**

The use of the one-pot *sol-gel* method aims to produce mesoporous bioactive glass (MBG) matrices based on  $\text{SiO}_2\text{-CaO-P}_2\text{O}_5$  doped with metallic AgNPs and has as a result reducing infection, regeneration and bone repair

after disease or trauma. The amount of hydroxyapatite in the mineralized fibers determined the rheological behavior of the scaffolds without influencing the amount of recruited peptides and the resulting increase in

hydrophobicity. The obtained scaffold is a highly hydrophilic mineralized collagen scaffold that which gives an ideal substrate to form a dense and stable coating of the antimicrobial peptides.

To develop better implants for biomedical applications, the *sol-gel* technique has allowed the creation of new generations of bioactive glasses with great potential. Avram *et. al.* [24] made by the sol-gel method three

different types of calcium phosphate glasses from ternary system  $\text{SiO}_2\text{-CaO-P}_2\text{O}_5$ : the reference sample P (Fig. 6 a) not doped with metals, which is the basic composition, (Table 1 ), the second sample, PA type is doped with silver (Fig. 6 b) and the third sample PC, is doped with copper (Fig. 6 c) [24]. They determined the minimum bactericidal dose of each type of glass on two strains of bacteria with high pathogenic potential.

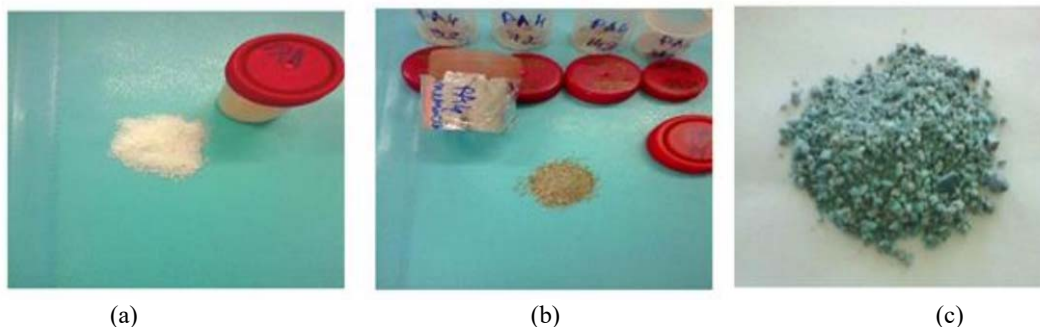


**Figure 6. The three types of phosphocalcic glass (a) sample P; (b) PA samples; (c) PC samples studied from the point of view of bacteriostatic activity [24]**

**Table 1. The composition of the three types of phosphocalcic glass [24]**

| Sample code | $\text{SiO}_2$ | $\text{CaO}$ | $\text{P}_2\text{O}_5$ | $\text{Ag}_2\text{O}$ | $\text{Cu}_2\text{O}$ |
|-------------|----------------|--------------|------------------------|-----------------------|-----------------------|
| P           | 55             | 40           | 5                      | -                     |                       |
| PA          | 50             | 40           | 5                      | 5                     | -                     |
| PC          | 50             | 38*          | 7                      | -                     | 5                     |

They concluded that bioglasses doped with silver (PA sample) have a more effective antimicrobial activity than those doped with copper (PC), but in the long term, during the exploitation period of the implant, which can last from a few weeks to a few years, this difference in the microbial activity of the two compared samples becomes insignificant.

In the case of using bone supports doped with silver, they can also reduce the incidence of infection or even fight it. It is known that implanted scaffolds are treated as "foreign" objects by the body's immune system and can be colonized by bacteria, leading to infection. To give the scaffolds inherent antibacterial properties, the team of *Sánchez-Salcedo et al.*, [26] from Universidad Complutense de Madrid and CIBER de Bioingeniería, Biomateriales y Nanomedicina incorporated silver nanoparticles (AgNPs), which have well-known antibacterial properties, in their scaffold matrix.

They used an innovative one-pot sol-gel method to produce mesoporous bioactive glass (MBG) matrices based on  $\text{SiO}_2\text{-CaO-P}_2\text{O}_5$  doped with metallic AgNPs and combined this with *rapid prototyping (RP)*, which creates structures with ultra-large dimensions. As a result of the antimicrobial tests performed on these new materials, it was shown that the growth of *Staphylococcus aureus* and *Escherichia coli* is reduced (inhibited) due to the presence of AgNPs in the mesoporous bioactive glass matrix.

Because it is difficult to obtain synthetic bone grafts that mimic the compositional content of bone, it is preferable to produce bone graft materials from natural materials.

To imitate the structure, morphology, and mechanical properties of native bone tissues, as natural biocomposites, different methods are used, the newest of which are those that use biological or of vegetable or animal origin from agricultural wastes as raw material. For example, natural materials like bovine bones, deep-sea snails, coral seashells, eggshells etc., are sources of natural hydroxyapatite. *Unal et al.* [23] in their study they used bovine femoral and tibial cortical bones, as the best bulky parts of the bones for the extraction of hydroxyapatite bioceramic material. The processing route for obtained synthesized and bioinspired calcium phosphate composites is schematically presented in Figure 7. The use of food waste such as eggshells in the development of biomaterials has the advantages of bone mineralization and growth, treatment of osteoporosis, and therefore is used as a bone graft.

In order to improve the quality of life of patients with bone diseases, the team of Russian researchers led by *Choudhary* [129] have synthesized a bioactive polymer-ceramic composite from eggshells, for fixing implants and restoring bone defects of the skull. Synthesis process of (a) magnesium-based silicate bioceramic called diopside, of (b) calcium silicate wollastonite ( $\text{CaSiO}_3$ ) and (c) forsterite ( $\text{Mg}_2\text{SiO}_4$ ) are presented in Figure 8.

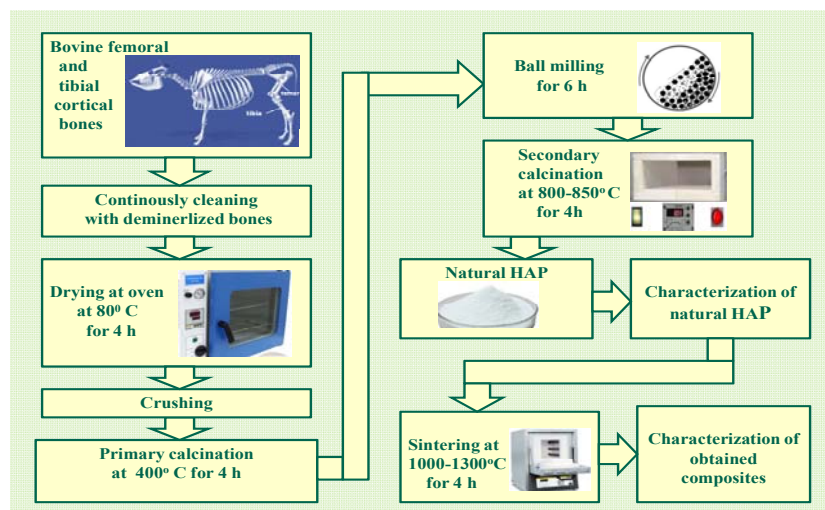


Figure 7. The processing route for obtained synthesized and bioinspired calcium phosphate composites from bovine skeleton

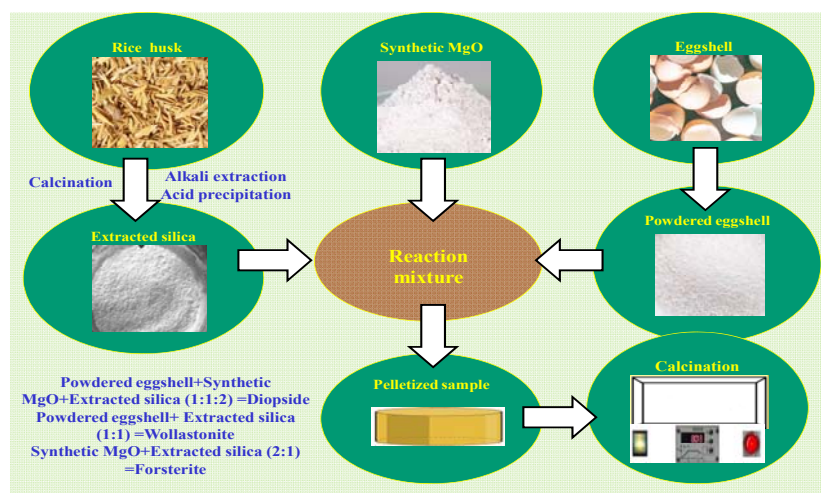


Figure 8. Schematic process route of obtaining wollastonite ( $\text{CaSiO}_3$ ), forsterite ( $\text{Mg}_2\text{SiO}_4$ ) and diopside from raw eggshell and rice husk

#### 4. CONCLUSIONS AND FUTURE PERSPECTIVES

Innovation in bone regeneration is essential to ensure fixation of artificial joints/implants and dental fixations (eg fiber reinforced cement improves stabilization of dental implants in bone [83]. In this brief review, the main characteristics of an ideal porous biomaterials used as scaffolds were presented and the characteristics of bioceramics, biopolymers metallic biomaterials and biocomposites used for medicine and tissue engineering were discussed. The requirements and main applications of metallic biomaterials and new developments of advanced materials used as scaffolds, such as 3D printed biomineral composites with bacteria-loaded ink (bactoInk), the use of plant or animal raw materials or waste, and the creation of new biomaterials that can reduce or combat the infection of scaffolds after implantation, have been also discussed. In the future, researchers are concerned with developing new strategies to design successful advanced polymeric biomaterials, such as smart (polymeric) biomaterials with self-healing and shape memory properties and other innovative, advanced type of biomaterials for regenerative medicine and tissue engineering.

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